Role of hydrogen bonding in cocrystal and coamorphous solids: Indapamide as a case study

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Electronic Supplementary Information†

Table S1 Crystallography parameters of Indapamide cocrystals.

	IDP-DPI (1:1)	IDP-BIP (1:1)	IDP-DPE-H2O (1:1:1)	IDP-PHE (1:1)	IDP-MeHP (1:1)
Empirical Formula	$C_{26}H_{24}ClN_5O_3S$	$C_{26}H_{24}ClN_5O_3S$	$C_{28}H_{28}ClN_5O_4S$	$C_{28}H_{24}ClN_5O_3S$	$C_{22}H_{23}ClN_4O_4S$
Formula weight	522.01	522.01	566.06	546.03	474.95
Crystal System	Monoclinic	Monoclinic	Triclinic	Monoclinic	Monoclinic
Space Group	$P2_1/n$	$P2_1/c$	P-1	$P2_1/c$	$P2_1/c$
T (K)	298(2)	298(2)	298(2)	298(2)	298(2)
a (Å)	7.2851 (14)	7.3151 (2)	12.2238 (2)	7.1759 (3)	7.765 (7)
b (Å)	9.0281 (17)	8.9370 (3)	14.8267 (3)	9.4074 (4)	8.741 (8)
c (Å)	38.510 (7)	38.9526 (12)	16.2328 (3)	39.0523 (17)	34.52 (3)
α (°)	90	90	93.228 (1)	90	90
β (°)	95.230 (3)	93.702 (2)	107.264 (1)	93.389 (2)	93.96 (4)
γ (°)	90	90	90.122 (1)	90	101.399(6)
V (Å^3)	2522.3 (8)	2541.21 (14)	2804.46 (9)	2631.68 (19)	90
D_{calc}(g cm^{-3})	1.375	1.364	1.341	1.378	1.349
Z	4	4	4	4	4
F(000)	1088	1088	1184	1136	992
measured reflections	23382	47789	76699	25417	32668
independent reflections	4477	4804	14012	6467	4763
R_{int}	0.030	0.160	0.060	0.027	0.045

R_1 [$I > 2\sigma(I)$]	0.042	0.080	0.072	0.053	0.061
wR_2 (all)	0.111	0.154	0.179	0.128	0.144
Goodness of fit	1.09	1.09	1.10	1.14	1.10
X-ray diffractometer	BRUKER SMART	BRUKER APEX	BRUKER APEX	BRUKER APEX	BRUKER APEX
CCDC No.	1849062	1849065	1849066	1849063	1849064

Table S2 Hydrogen bonds in IDP cocrystals (N−H, O−H, and C−H distances are neutron-normalized).

Name	D−H···A	D···A (Å)	H···A (Å)	D−H···A (°)	symmetry code
IDP-DPI(1:1)	N2−H2A···O3	2.815(2)	2.00(3)	161	3/2-x,-1/2+y,1/2-z
	N3−H3A···N4	2.973(3)	2.19(3)	151	3/2-x,-3/2+y,1/2-z
	N3−H3B···N5	3.037(3)	2.33(3)	149	1/2+x,1/2-y,1/2+z
	C13−H13···O3	3.322(4)	2.46	155	5/2-x,-1/2+y,1/2-z
	C23−H23···O1	3.405(3)	2.51	162	-1/2+x,3/2-y,-1/2+z
IDP-BIP (1:1)	N2−H2A···O3	2.798(4)	1.98(4)	172	1-x,-1/2+y,1/2-z
	N3−H3A···N4	2.973(6)	2.09(5)	158	1-x,1-y,-z
	N3−H3B···N5	3.120(6)	2.36(5)	147	x,-1+y,z
	C13−H13···O3	3.384(6)	2.49	160	2-x,-1/2+y,1/2-z
IDP-DPE-H2O (1:1:1)	N2−H2A···O8	2.9938	2.16	163	1-x,1-y,1-z
	N3−H3A···N9	2.8658	2.09	172	x,y,-1+z
	N3−H3B···O7	2.8835	2.02	165	1-x,1-y,-z
	N5−H5A···O3	2.9989	2.24	162	1-x,1-y,-z
	N6−H6A···N8	2.9957	2.23	161	x, y, z
	O7−H7A···N7	2.8854	2.08	165	1-x,1-y,1-z
	O7−H7B···O6	2.8203	2.06	168	-1+x,y,z
	O8−H8A···O2	2.9876	2.25	173	x,y,1+z
	O8−H8B···N10	2.8355	2.08	165	1-x,-y,1-z
	C6−H6···O8	3.4078	2.50	167	1-x,1-y,1-z
	C39−H39···O1	3.3674	2.50	155	1-x,1-y,-z

	C46−H46···O5	3.5189	2.60	172	2-x,-y,1-z
	C51−H51···O5	3.3837	2.54	151	2-x,-y,1-z
IDP-PHE (1:1)	N1−H1A···O1	2.864(2)	2.03	165	1-x,-1/2+y,1/2-z
	N3−H3A···N5	2.969(3)	2.17	162	1-x,1-y,-z
	N3−H3B···N4	3.166(3)	2.54	132	x,-1+y,z
	C13−H13···O1	3.394(3)	2.55	151	2-x,-1/2+y,1/2-z
	C20−H20···O3	3.174(3)	2.44	136	x, y, z
IDP-MeHP(1:1)	N2−H2A···O3	2.825(4)	1.99	152	1-x,-1/2+y,1/2-z
	N3−H3A···O4	2.973(4)	2.14	169	1-x,1-y,-z
	N3−H3B···O4	2.904(4)	2.11	164	x,-1+y,z
	N4−H4A···O4	2.814(4)	1.95	173	-x,2-y,-z
	C20−H20···O1	3.365(5)	2.52	151	-1+x,y,z
	C22−H22A···O1	3.484(5)	2.59	155	-1+x,y,z

x, y, z intramolecular hydrogen bond

Table S3 Melting point of IDP, coformers and cocrystals.

Drug/ coformer	Melting point (°C)	cocrystal	Melting point of cocrystal (°C)
IDP	168-174	-	-
DPI	112-114	IDP-DPI	200-205
BIP	70-73	IDP-BIP	134-138
DPE	148-152	IDP-DPE-H_2O	90-97
PHE	174-177	IDP-PHE	205-209
MeHP	157-159	IDP-MeHP	176-180

Table S4 Selected functional group stretching frequency in FT-IR spectra of IDP cocrystals and coamorphous compounds.

	C=O (amide) (cm^{-1})	SO2 (indapamide) (cm^{-1})	NH (cm^{-1}) sulfonamide	NH (cm^{-1}) amide
IDP	1659	1175	3507, 3432 (asym and sym)	3226

IDP−DPI (1:1)	1655	1162	-	3177
IDP−BIP (1:1)	1654	1163	3361	3169
IDP−DPE−H2O (1:1:1)	1659	1172	3458, 3369	3235
IDP−PHE (1:1)	1660	1160	3363	3192
IDP−MeHP (1:1)	1657	1159	3281	3203
IDP-PIP(1:1)	1664	1166	3224 (3454 for PIP)	3224
IDP-MPIP(1:1)	1665	1167	3245 (3425 for MPIP)	3245
IDP-EPIP(1:1)	1663	1167	3235 (3427 for EPIP)	3235
IDP-BPIP(1:1)	1669	1168	3252(3324 for BPIP)	3252
IDP-ARG(1:1)	1664	1167	3352 (3358, 3299 for ARG)	3182
IDP-LYS(1:1)	1659	1168	3375 (3342 for LYS)	3218

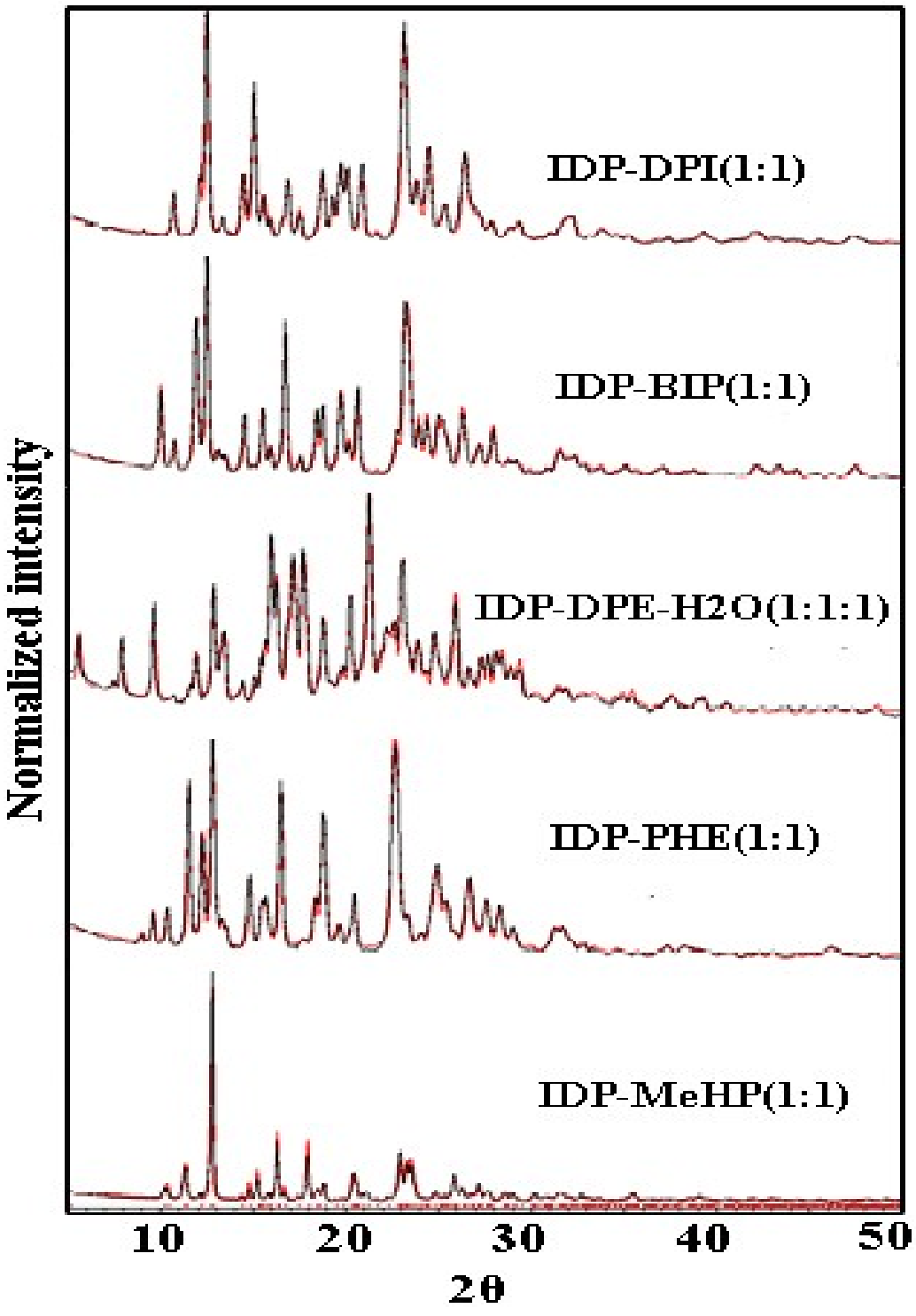


Figure S1 Overlay of experimental PXRD (black) of IDP cocrystals match with the calculated lines from the crystal structure (red).

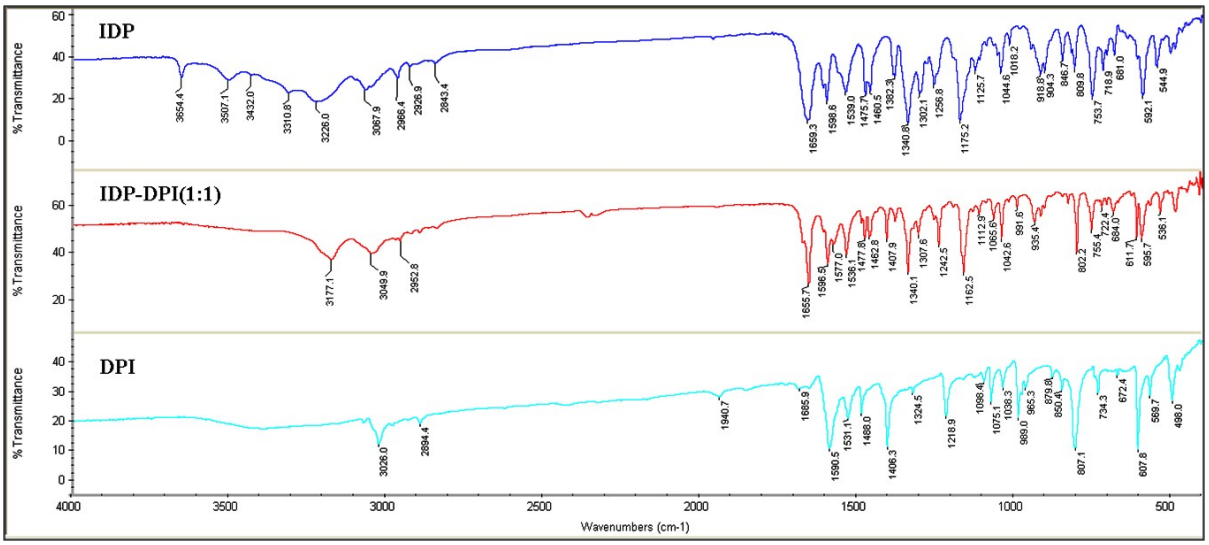


Figure S2a Overlay of IDP−DPI (1:1) cocrystal IR spectra with its starting components.

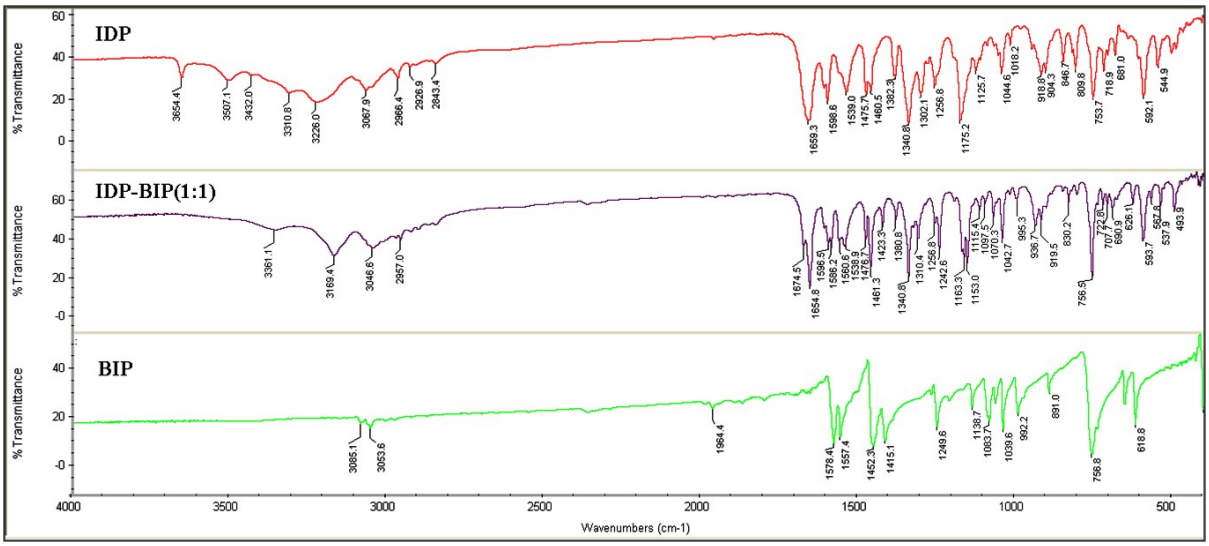


Figure S2b Overlay of IDP−BIP (1:1) cocrystal IR spectra with its starting components.

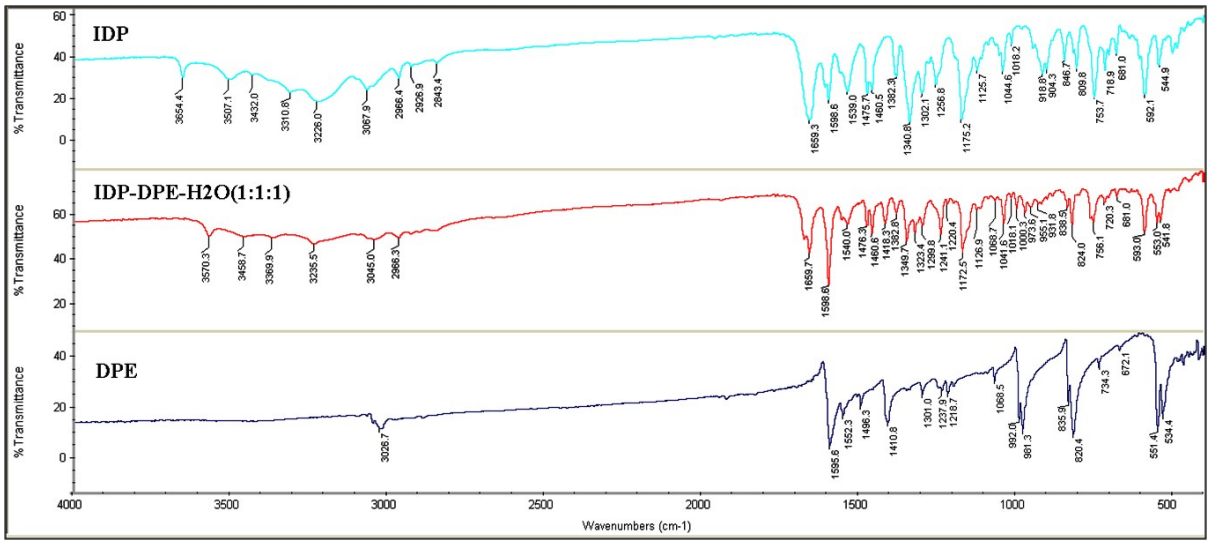


Figure S2c Overlay of IDP−DPE-H2O (1:1:1) cocrystal hydrate IR spectra with its starting components.

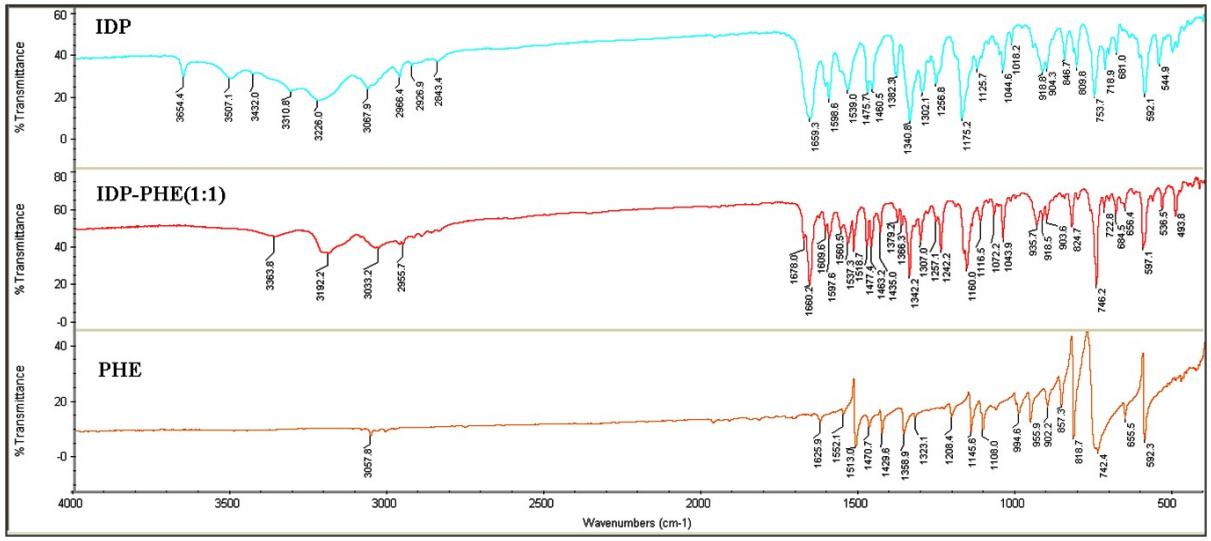


Figure S2d Overlay of IDP−PHE (1:1) cocrystal IR spectra with its starting components.

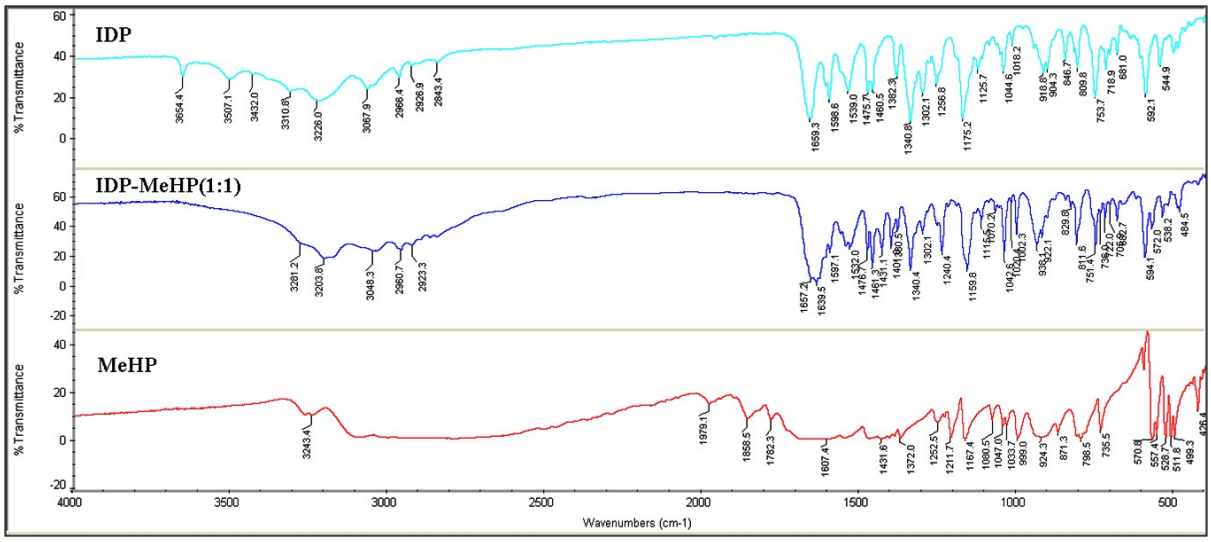


Figure S2e Overlay of IDP−MeHP (1:1) cocrystal IR spectra with its starting components.

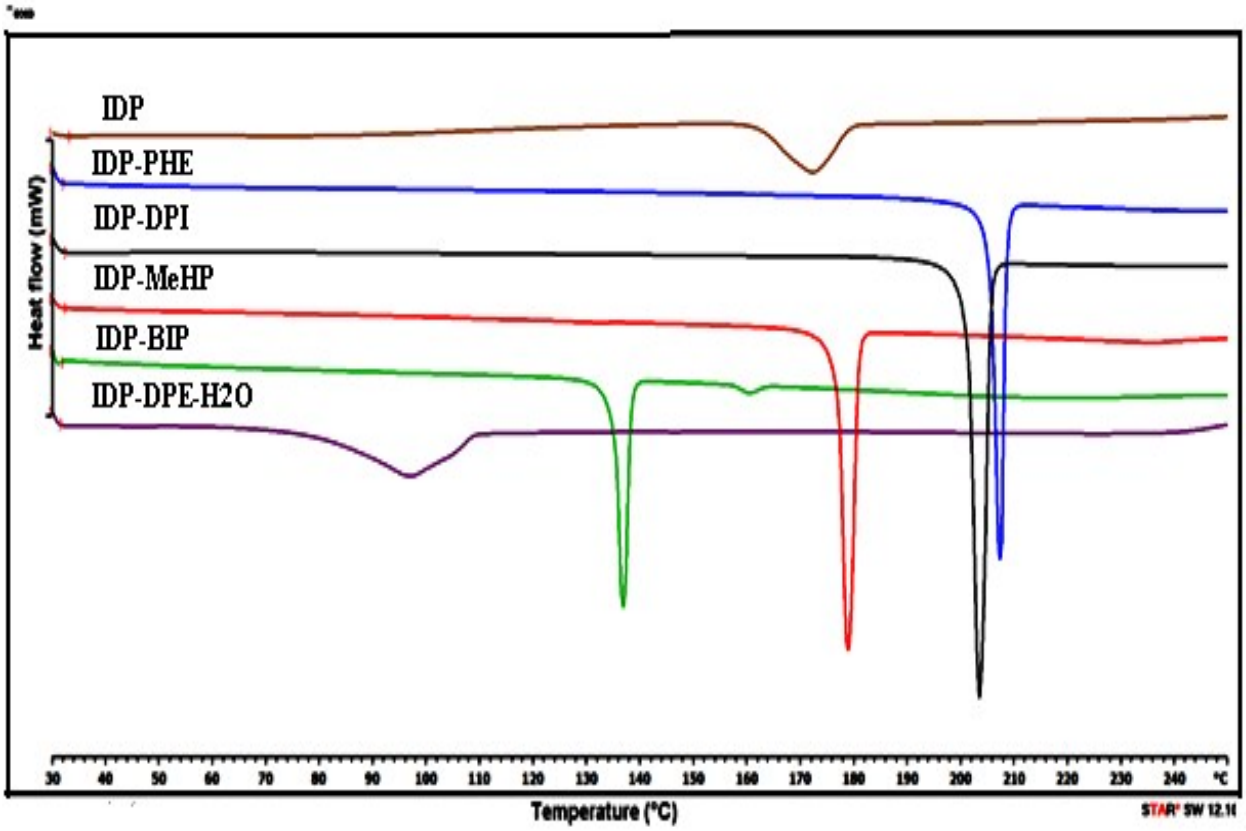


Figure S3 DSC thermogram of indapamide cocrystals.

IDP Conformations in cocrystals	Torsion angle C7-N2-N1-C11(°)
IDP-DPE-H2O	102.43
IDP-DPE-H2O	127.67
IDP-BIP	109.99
IDP-DPI	111.13
IDP-PHE	114.28
IDP-MeHP	102.29

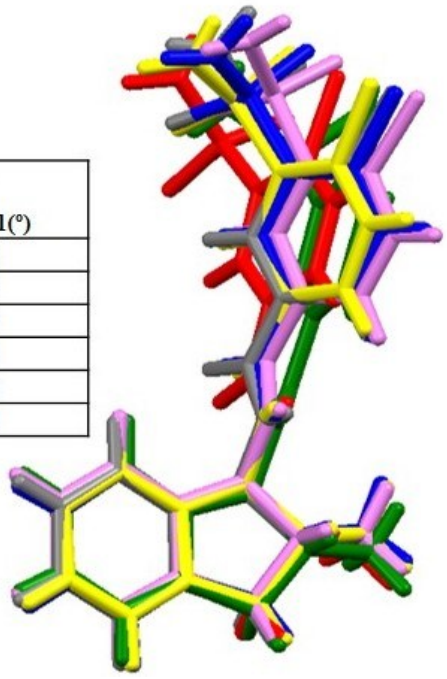


Figure S4 Overlay diagram of conformations in Indapamide (IDP).

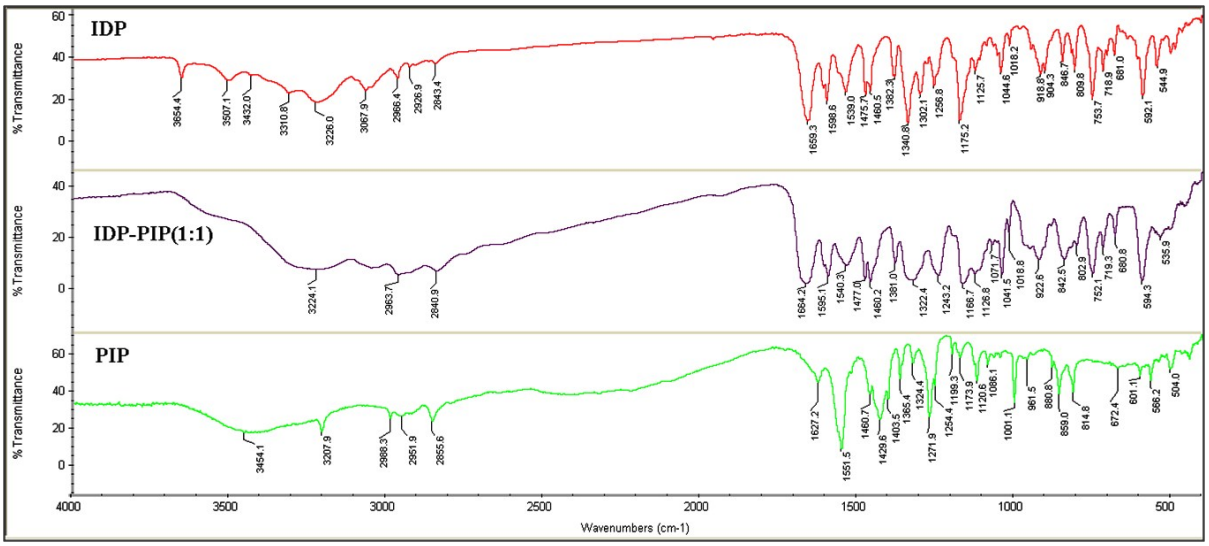


Figure S5a Overlay of IDP−PIP (1:1) coamorphous spectra with its starting components.

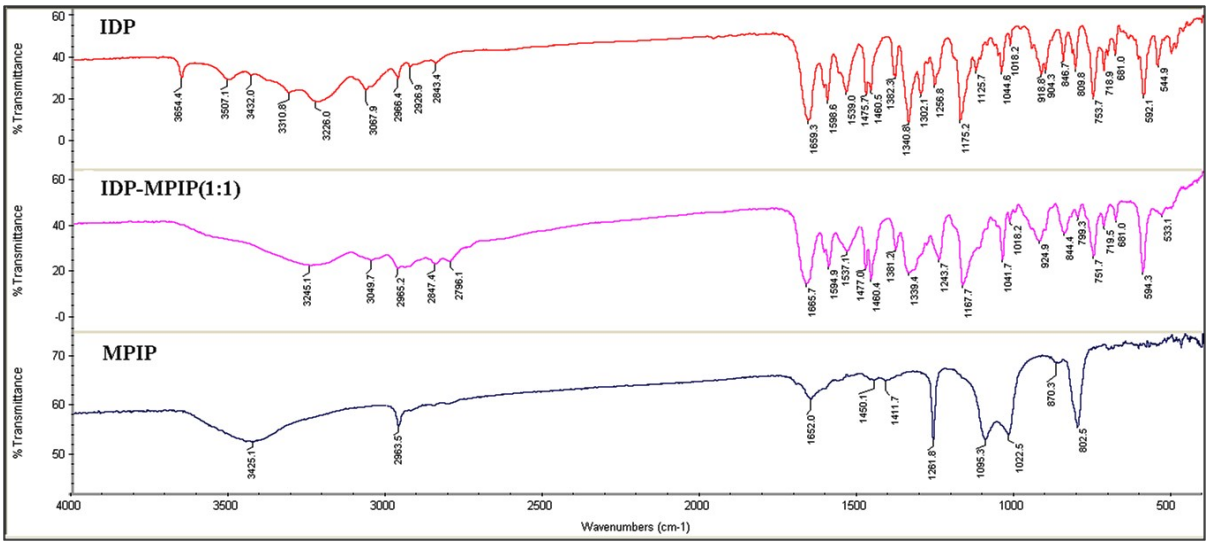


Figure S5b Overlay of IDP−MPIP (1:1) coamorphous spectra with its starting components.

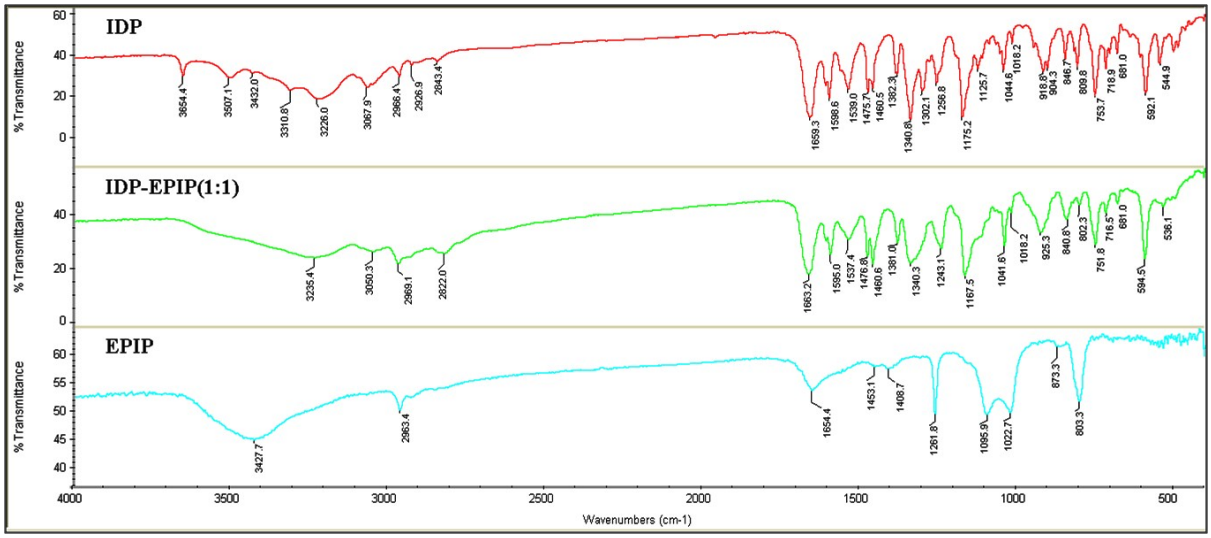


Figure S5c Overlay of IDP−EPIP (1:1) coamorphous spectra with its starting components.

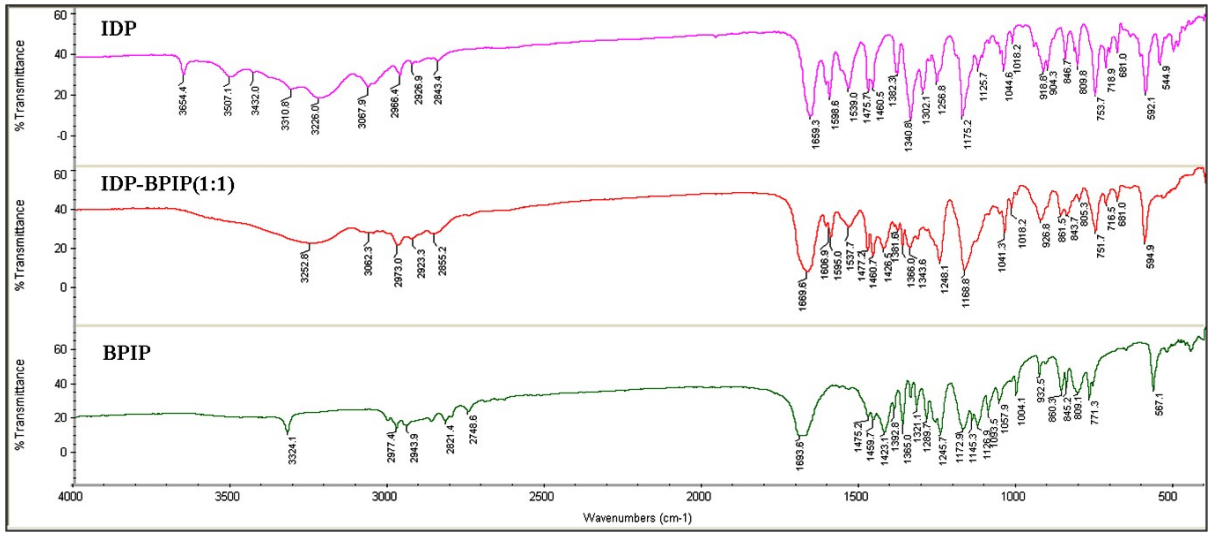


Figure S5d Overlay of IDP−BPIP (1:1) coamorphous spectra with its starting components.

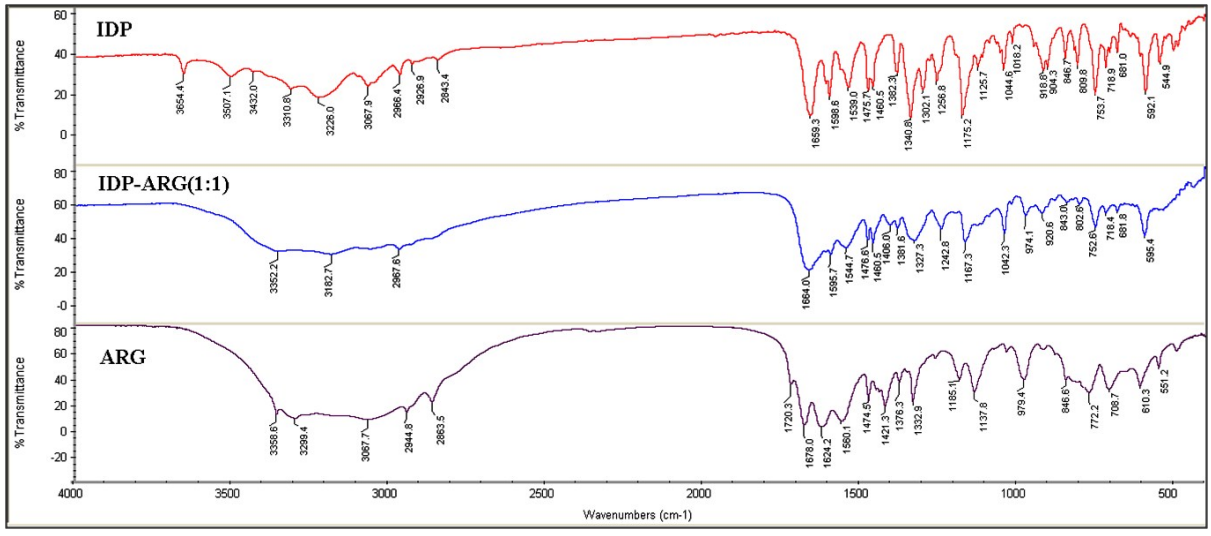


Figure S5e Overlay of IDP−ARG (1:1) coamorphous spectra with its starting components.

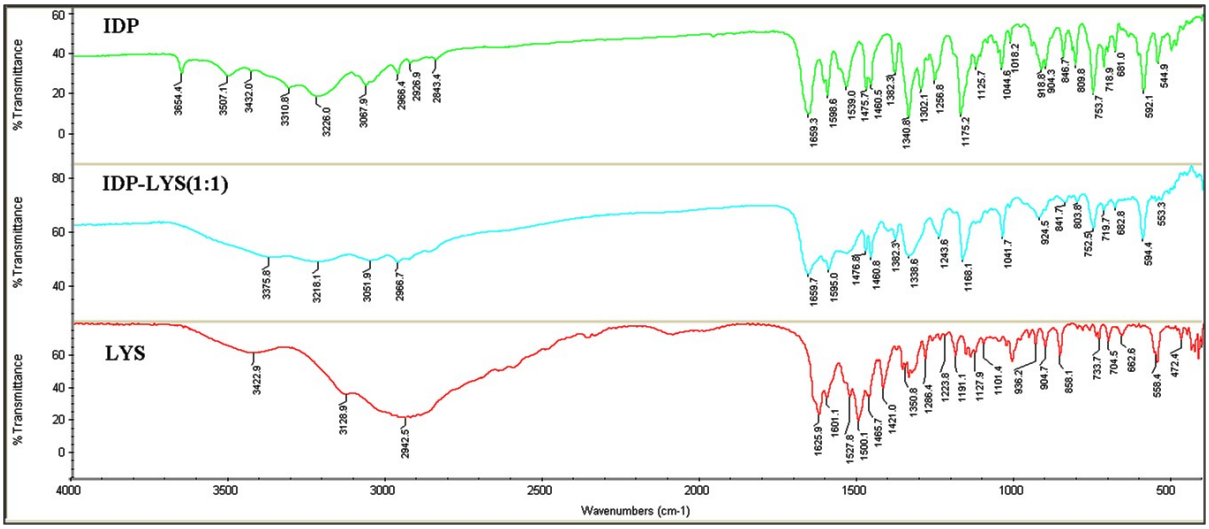


Figure S5f Overlay of IDP−LYS (1:1) coamorphous spectra with its starting components.

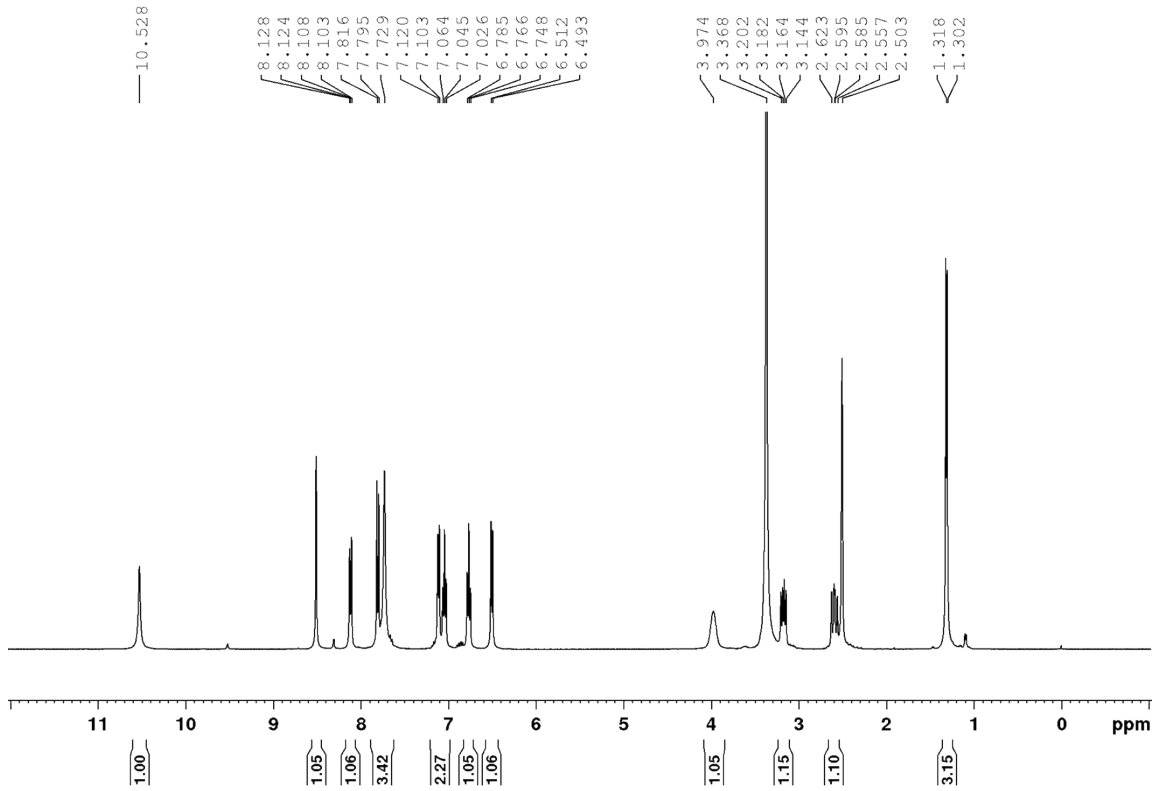


Figure S6a 1H NMR spectrum of IDP.

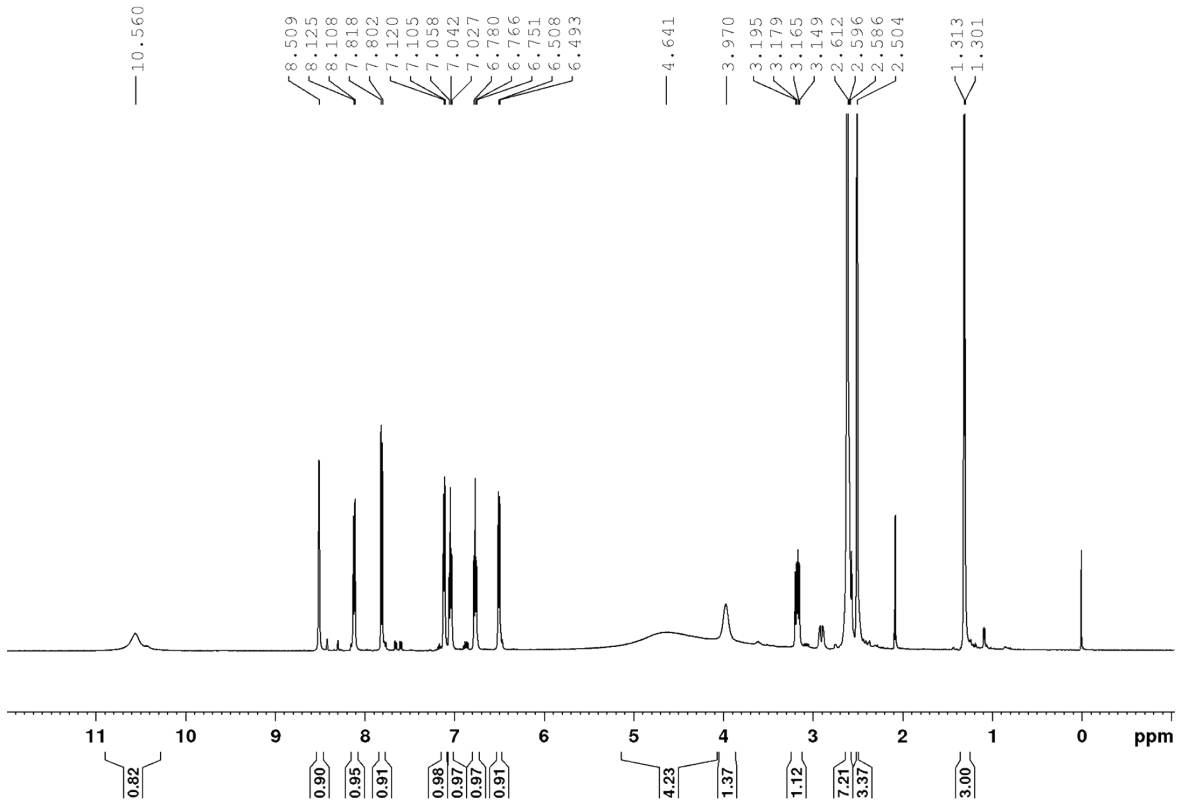


Figure S6b 1H NMR spectrum of IDP-PIP.

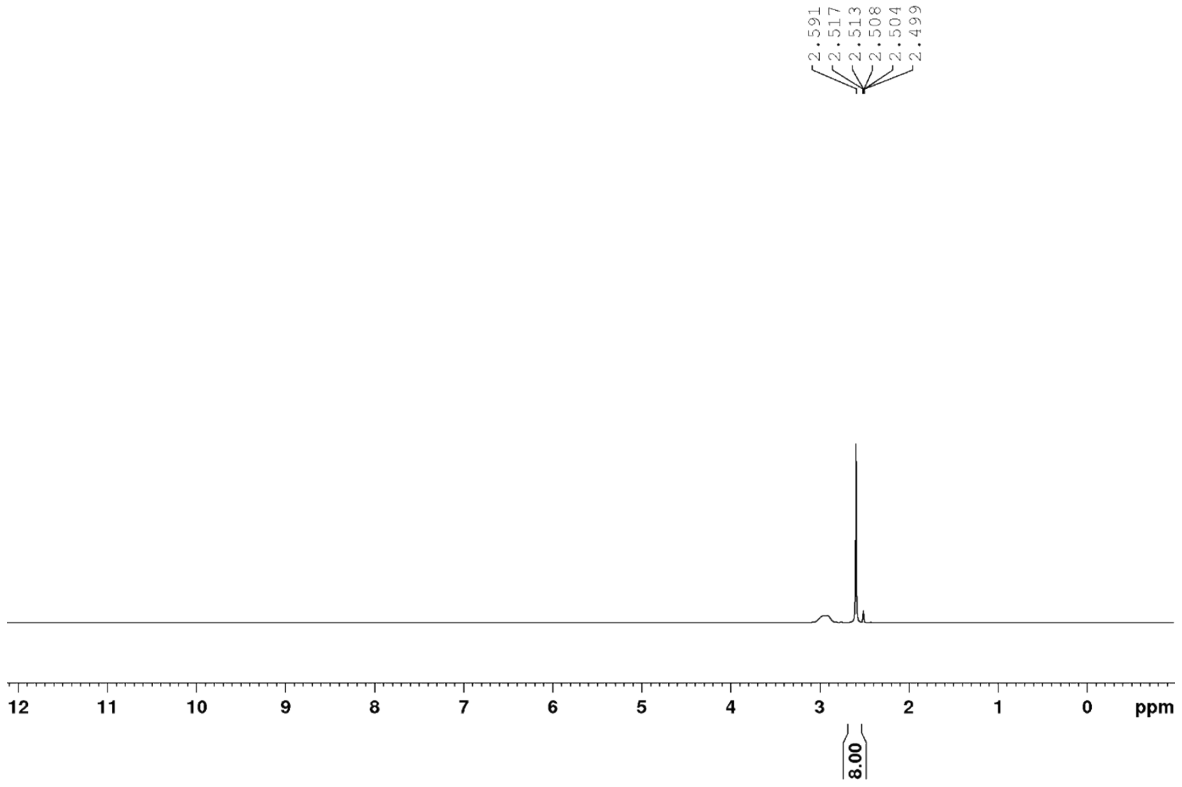


Figure S6c 1H NMR spectrum of PIP.

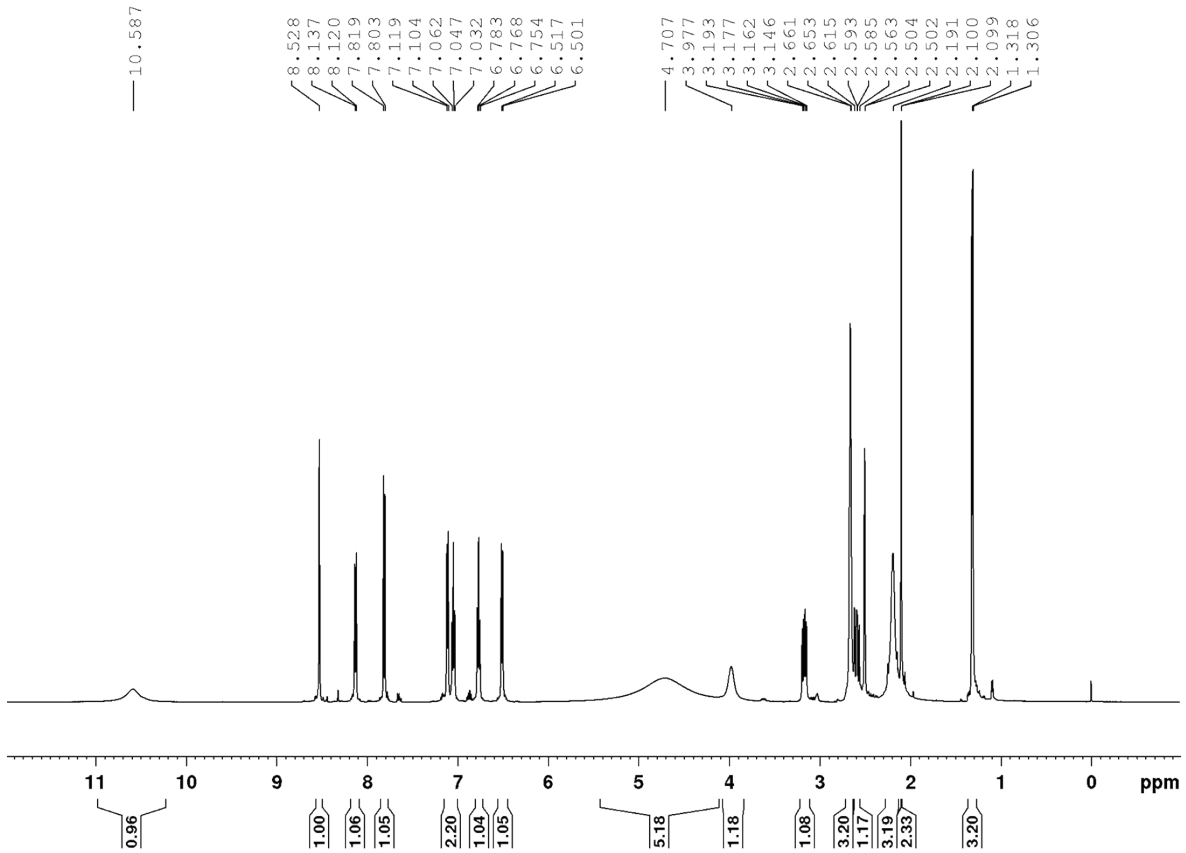


Figure S6d 1H NMR spectrum of IDP-MPIP.

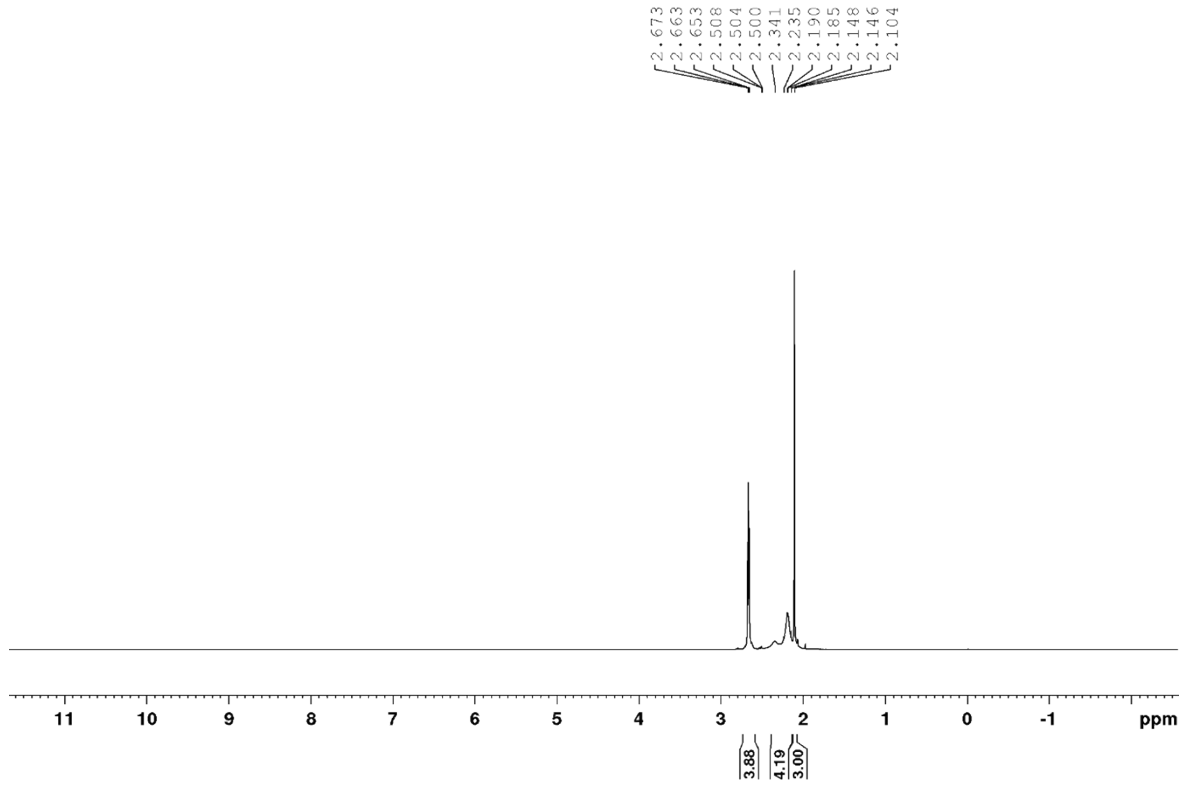


Figure S6e 1H NMR spectrum of MPIP.

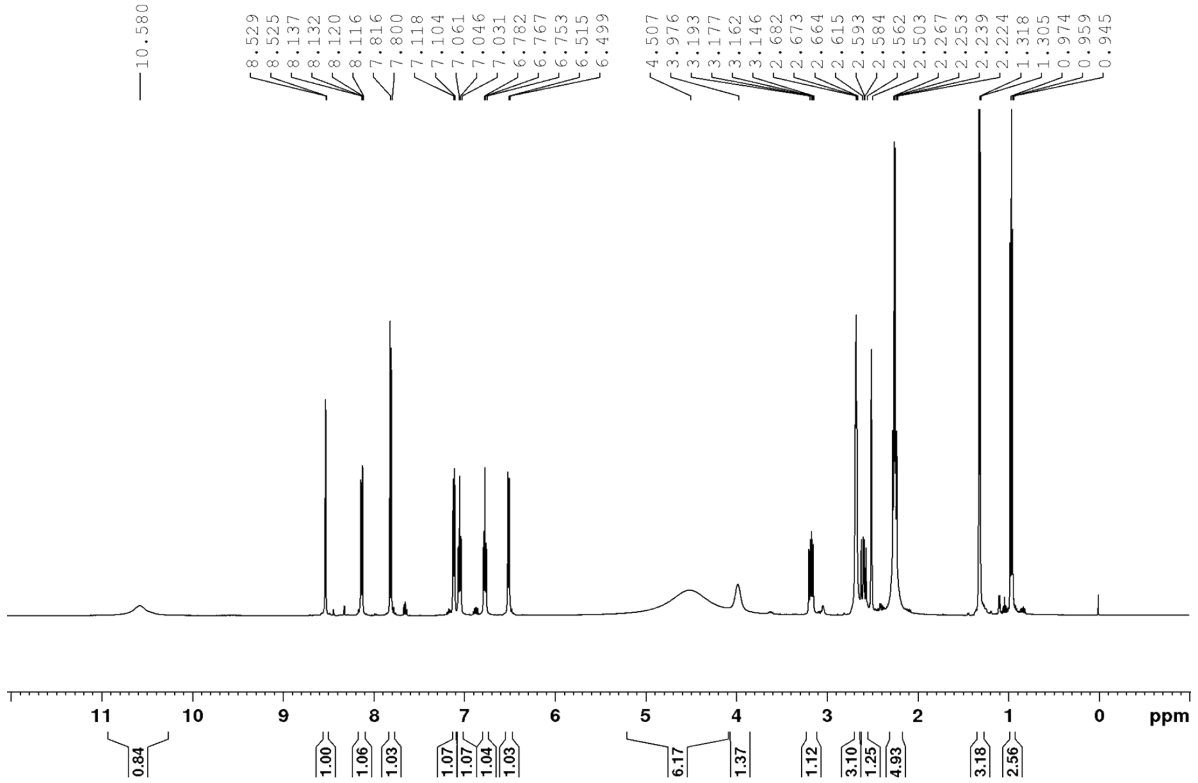


Figure S6f 1H NMR spectrum of IDP-EPIP.

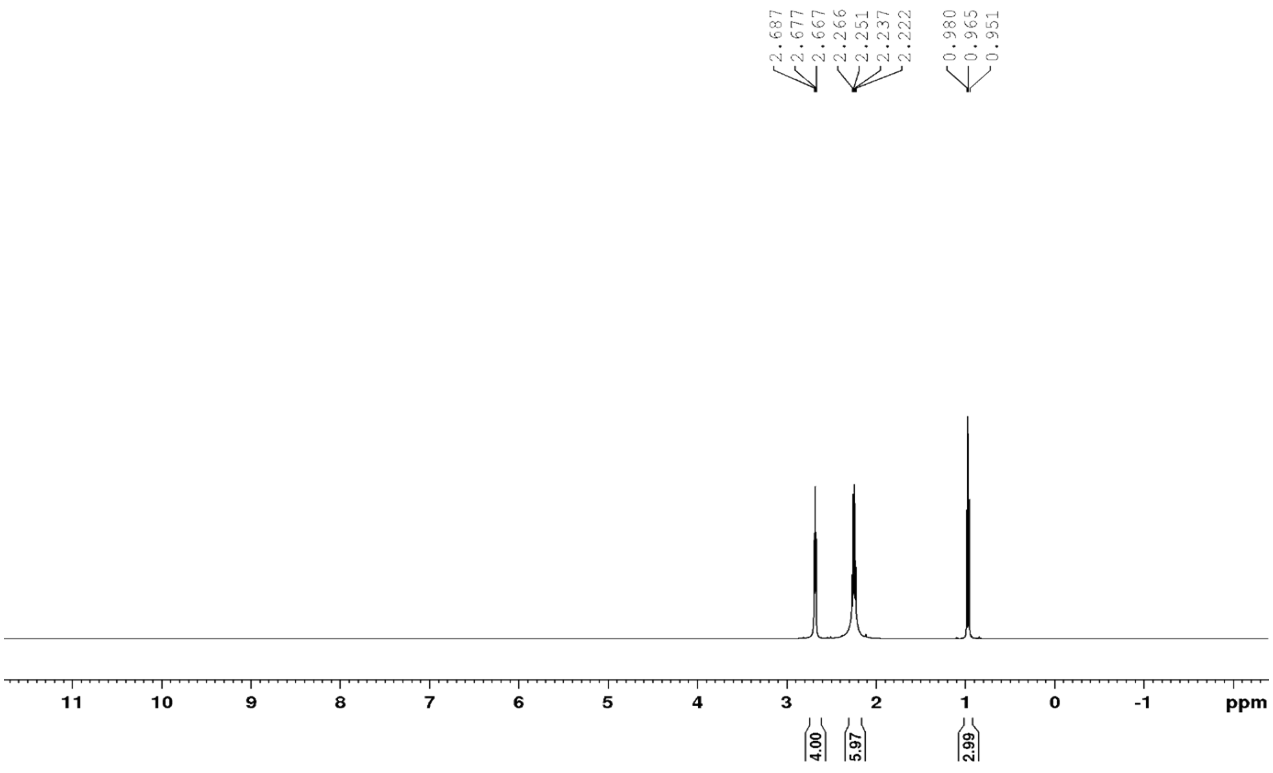


Figure S6g 1H NMR spectrum of EPIP.

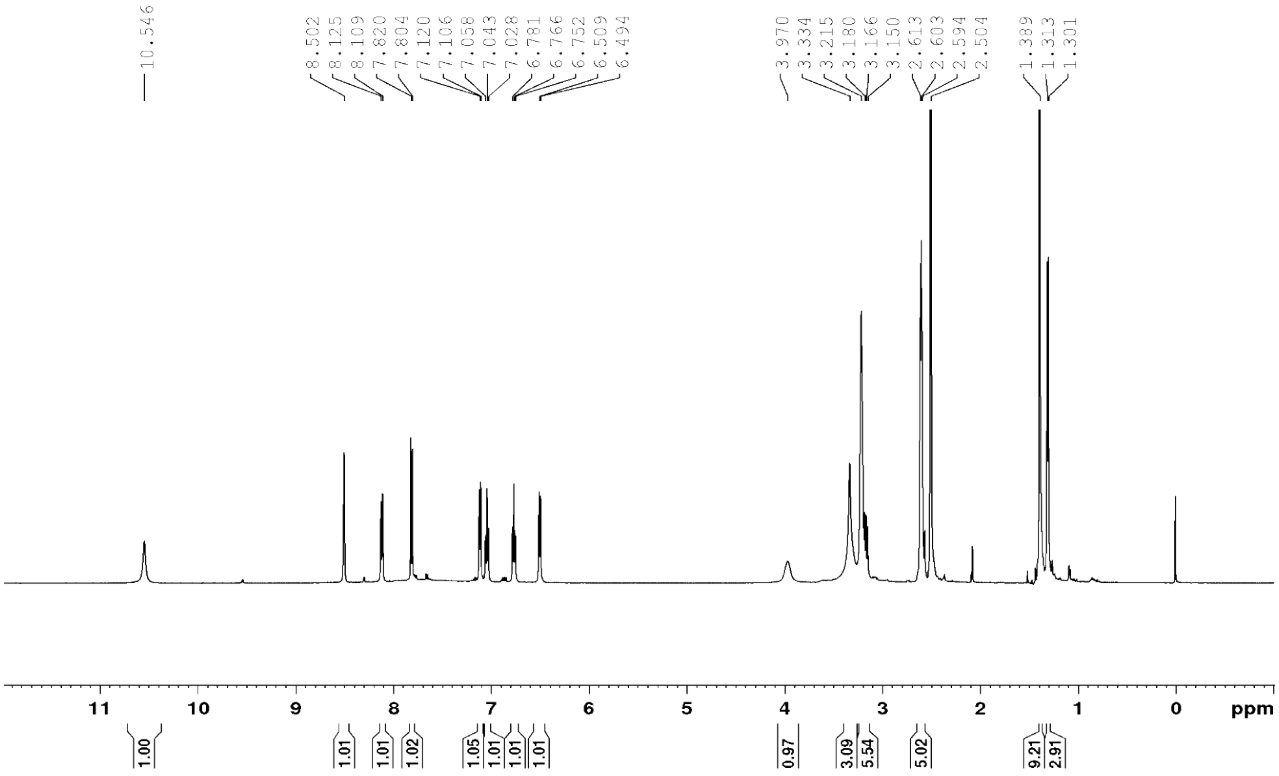


Figure S6h 1H NMR spectrum of IDP-BPIP.

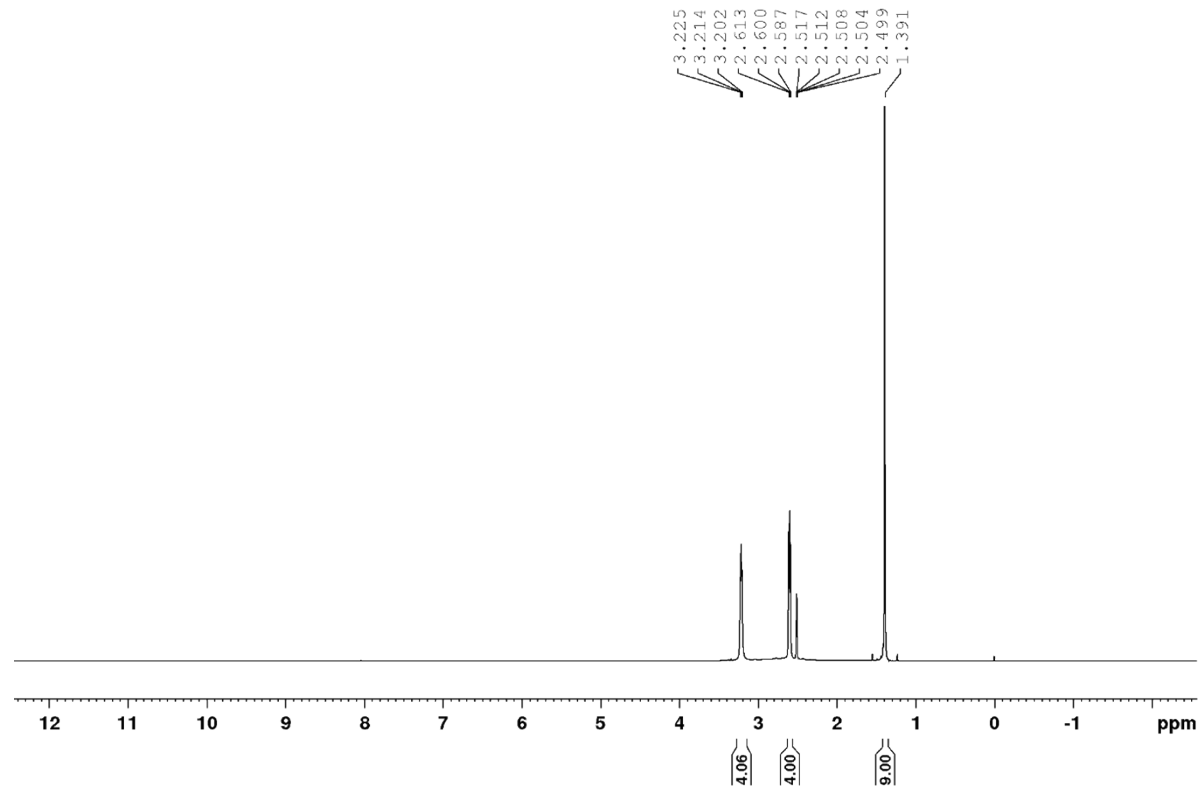


Figure S6i 1H NMR spectrum of BPIP.

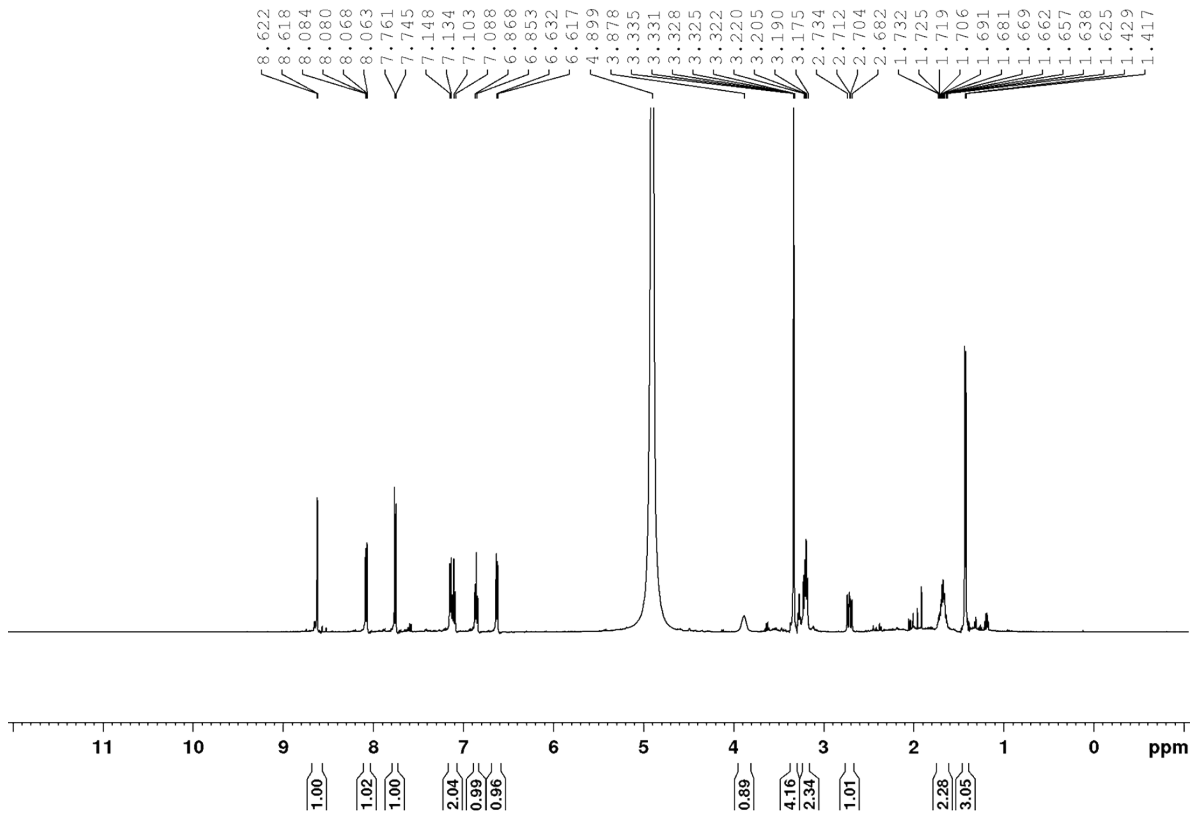


Figure S6j 1H NMR spectrum of IDP-ARG.

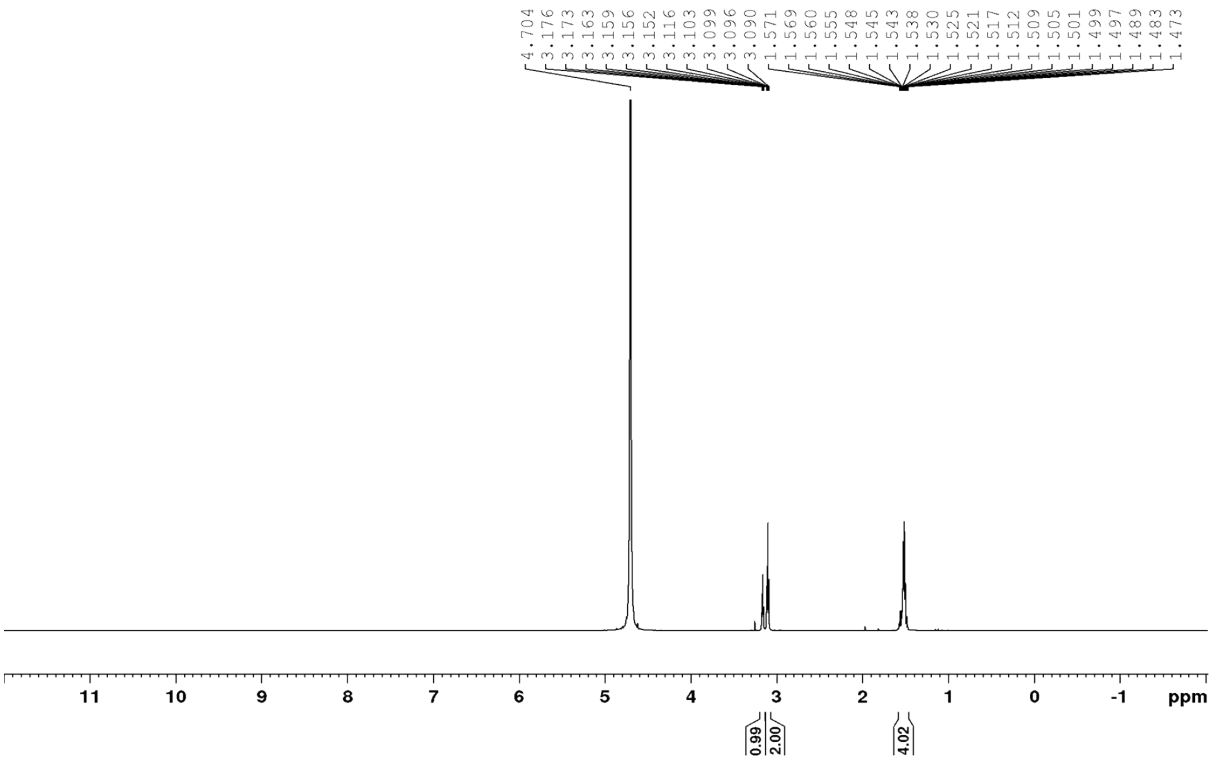


Figure S6k 1H NMR spectrum of ARG.

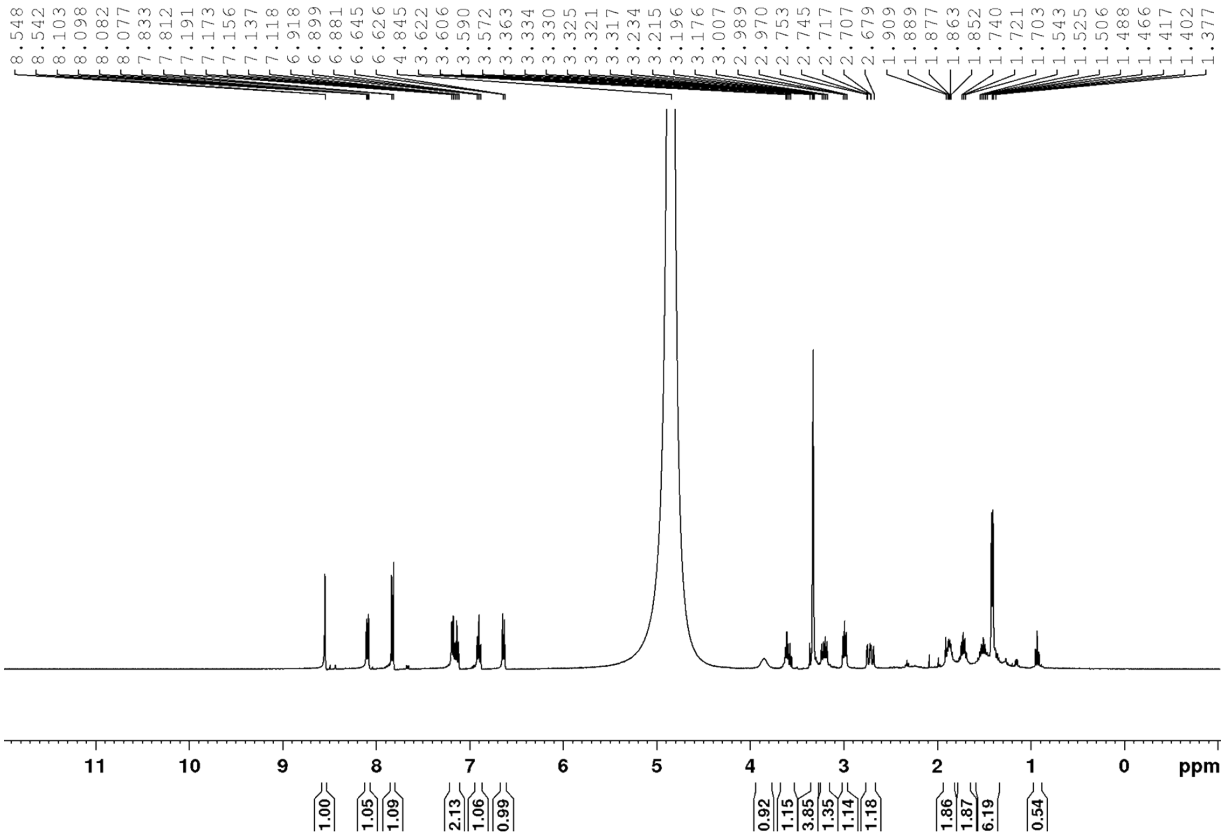


Figure S6l 1H NMR spectrum of IDP-LYS.

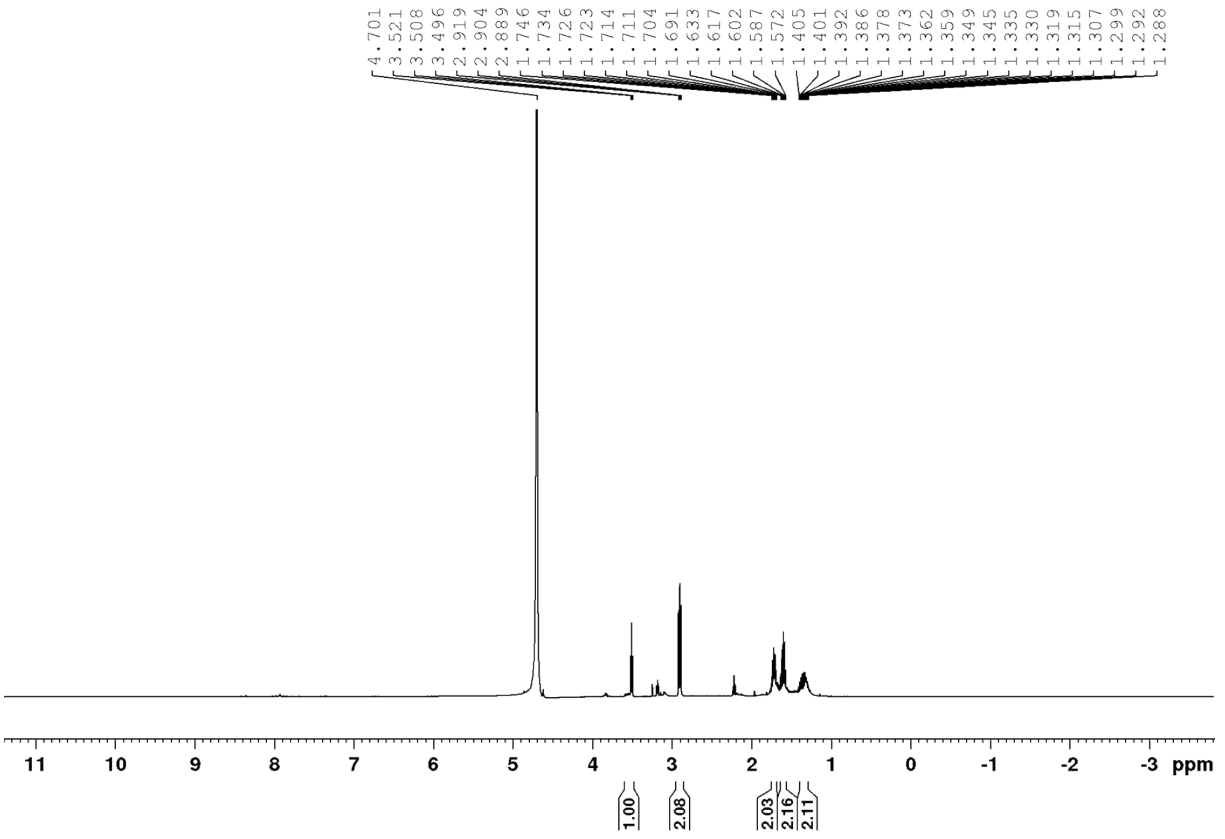


Figure S6m 1H NMR spectrum of LYS.

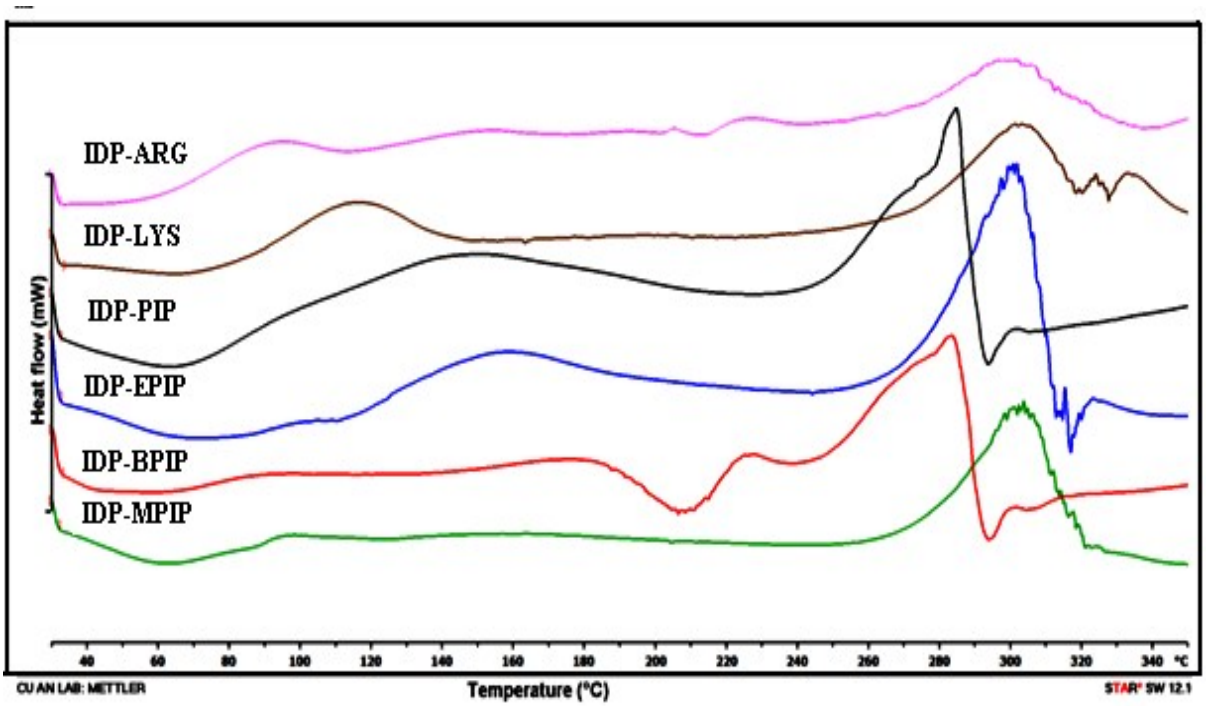
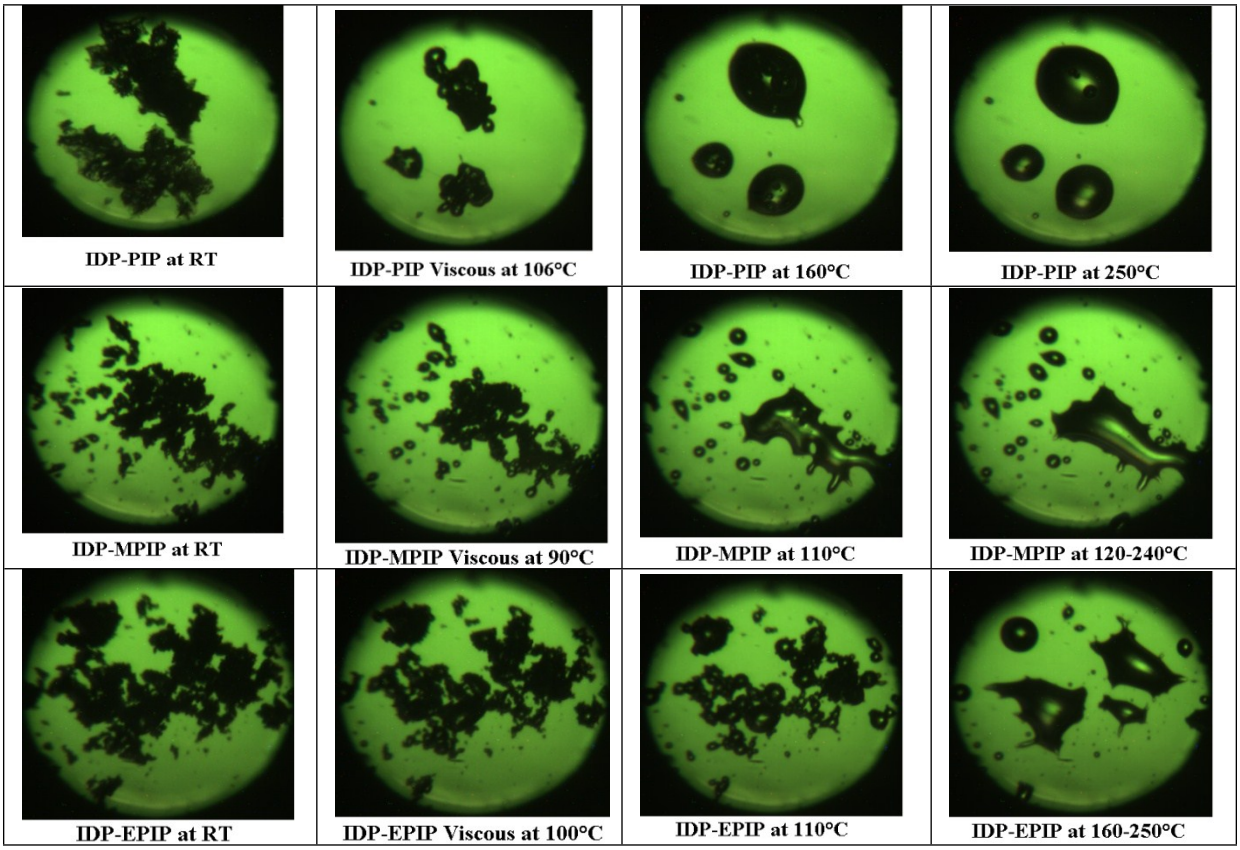


Figure S7 DSC thermogram of Indapamide coamorphus solids.



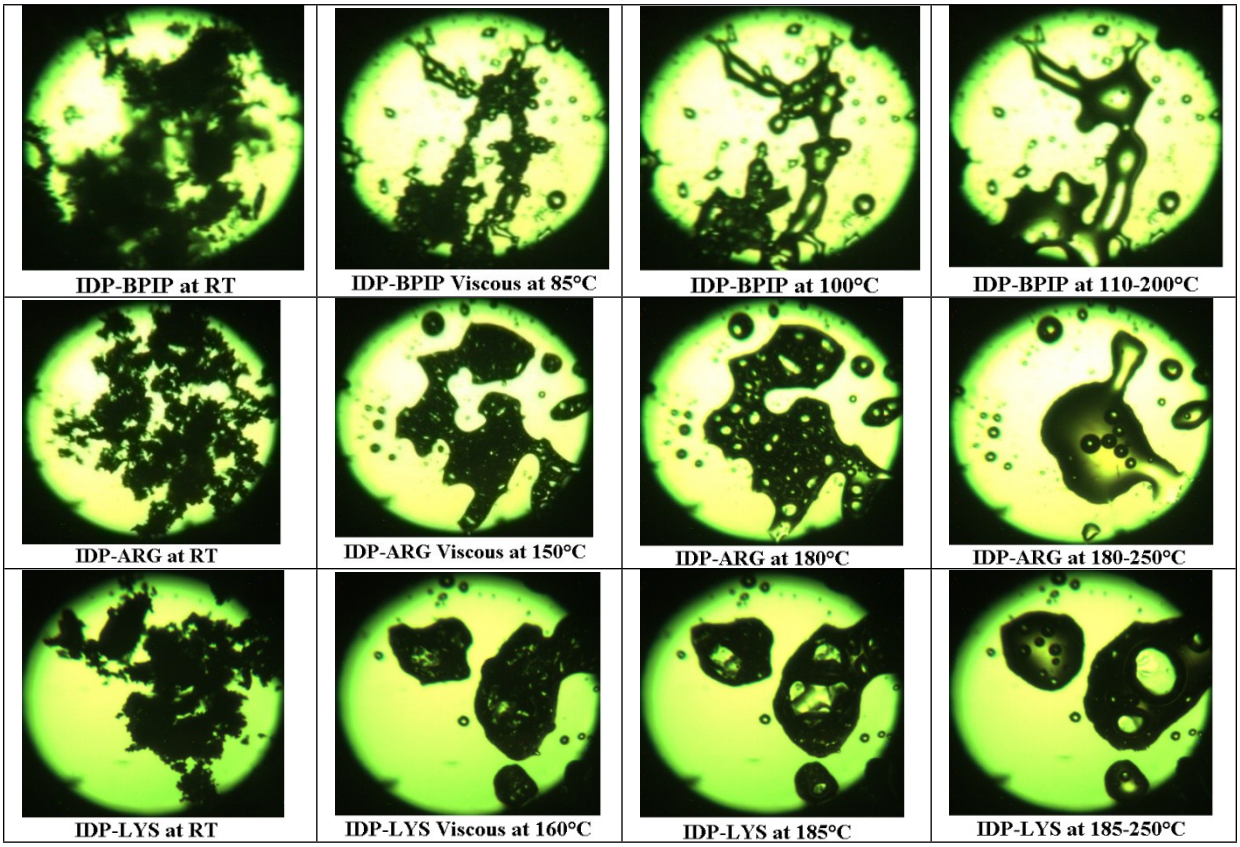


Figure S8 Hot stage microscope analaysis of amorphous materials.

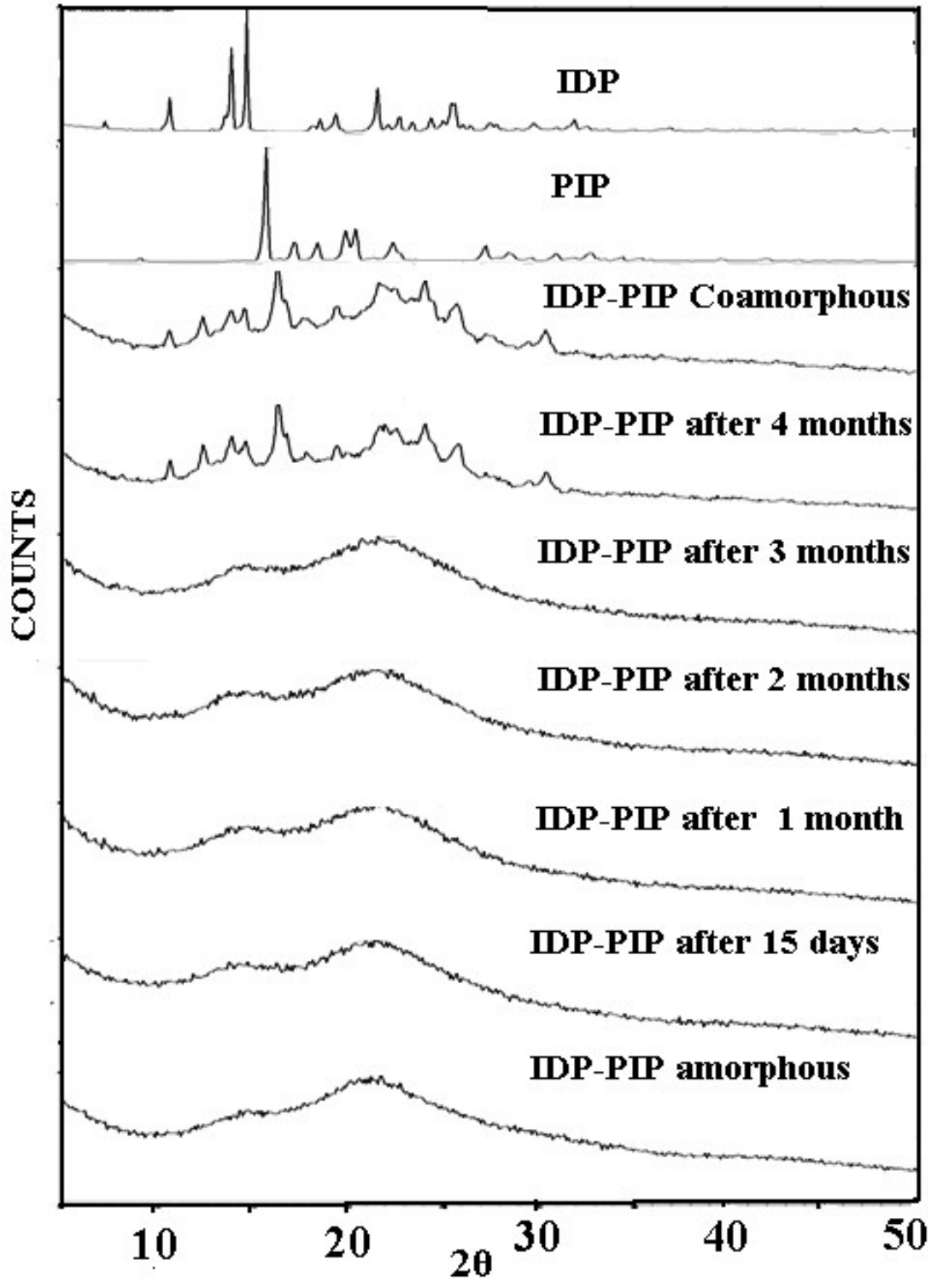


Figure S9 Stability study at 40 °C and 75% RH of IDP-PIP shows that is stable up to 3 months. It transforms to the crystalline phase.

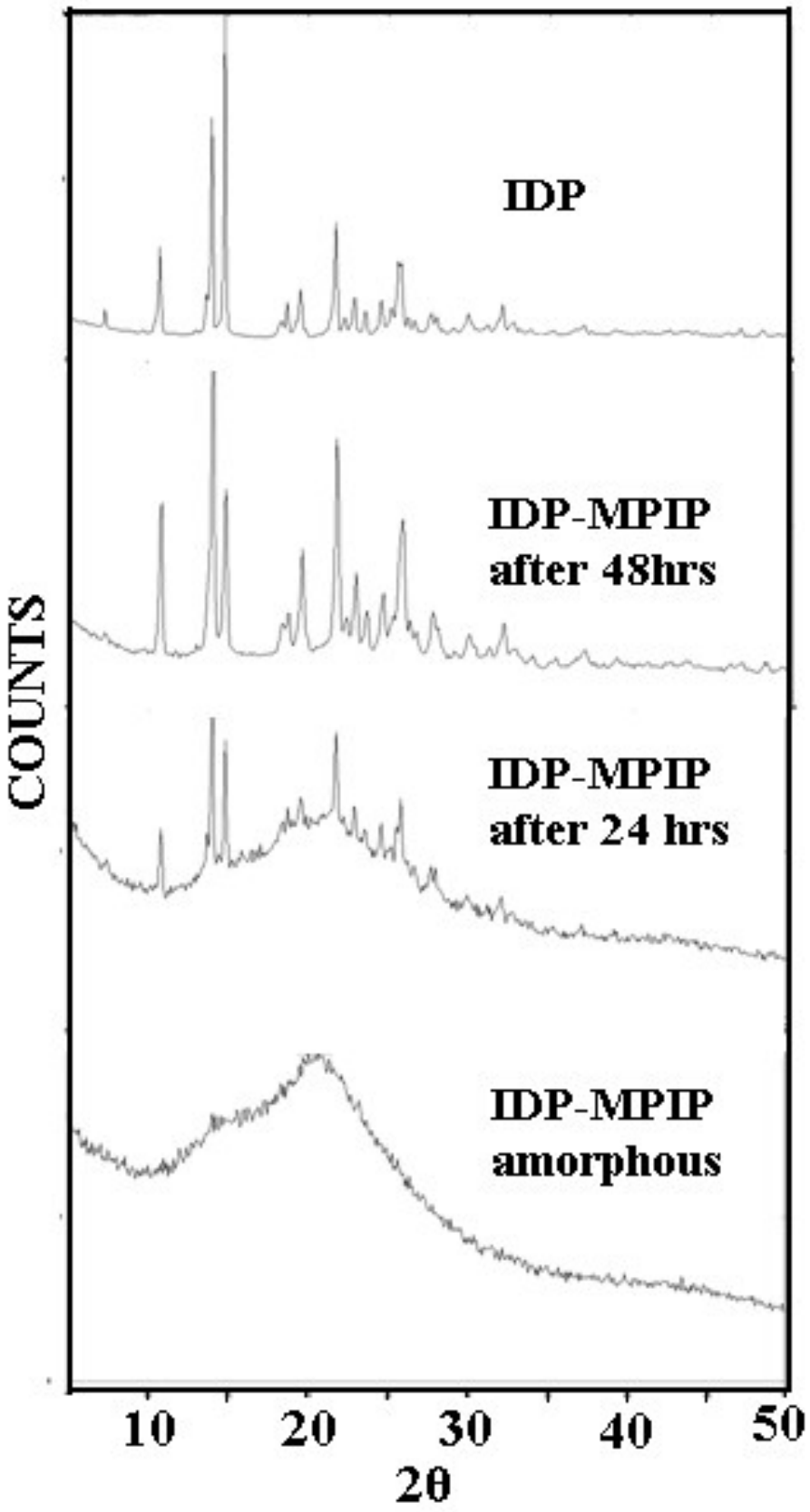


Figure S10 Stability study at 40 °C and 75% RH of IDP-MPIP amorphous form at ambient conditions shows that after 2 days it transforms to crystalline IDP.

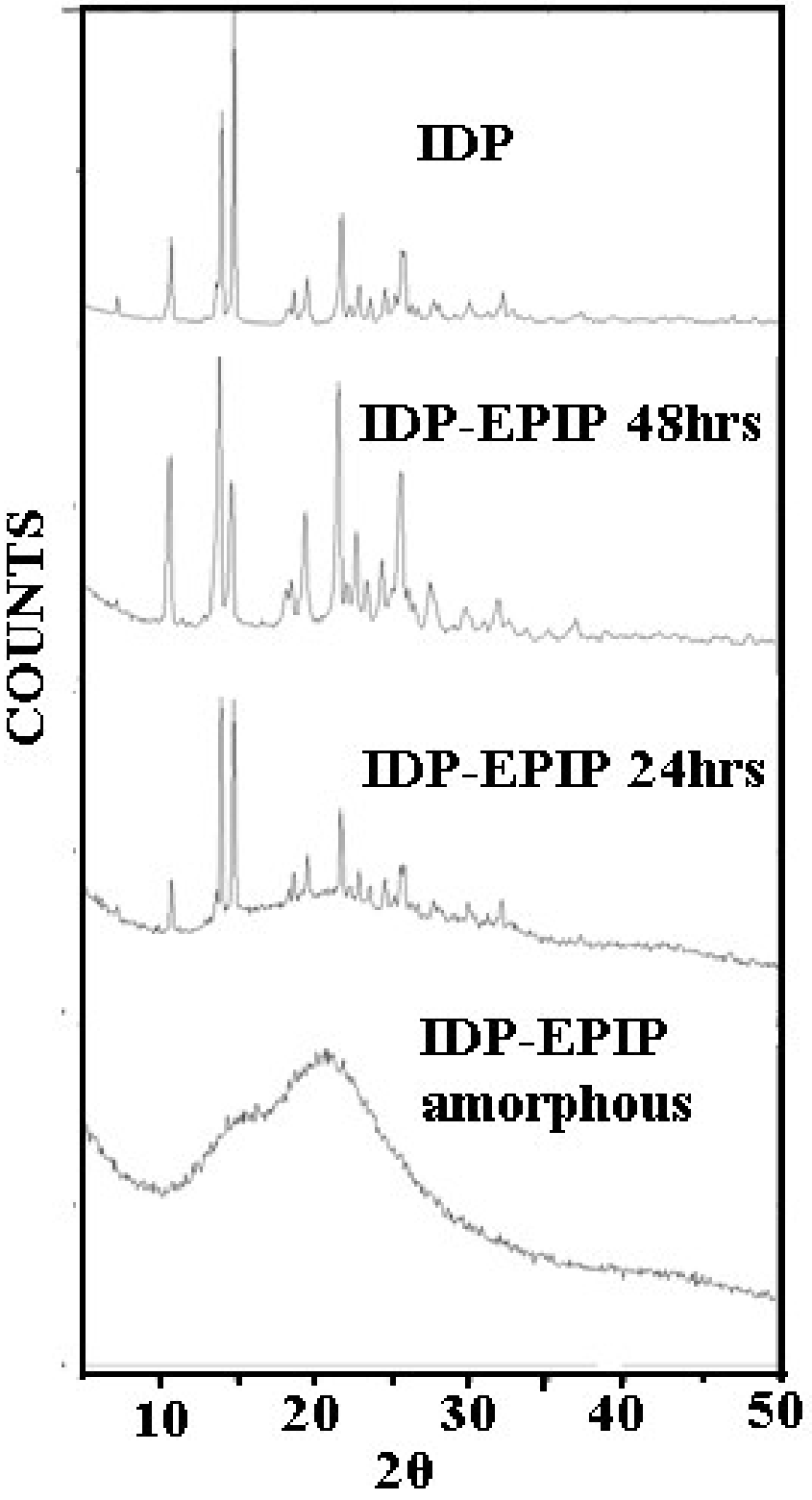


Figure S11 Stability study at 40 °C and 75% RH of IDP-EPIP amorphous form at ambient conditions shows that after 2 days it transforms to crystalline IDP.

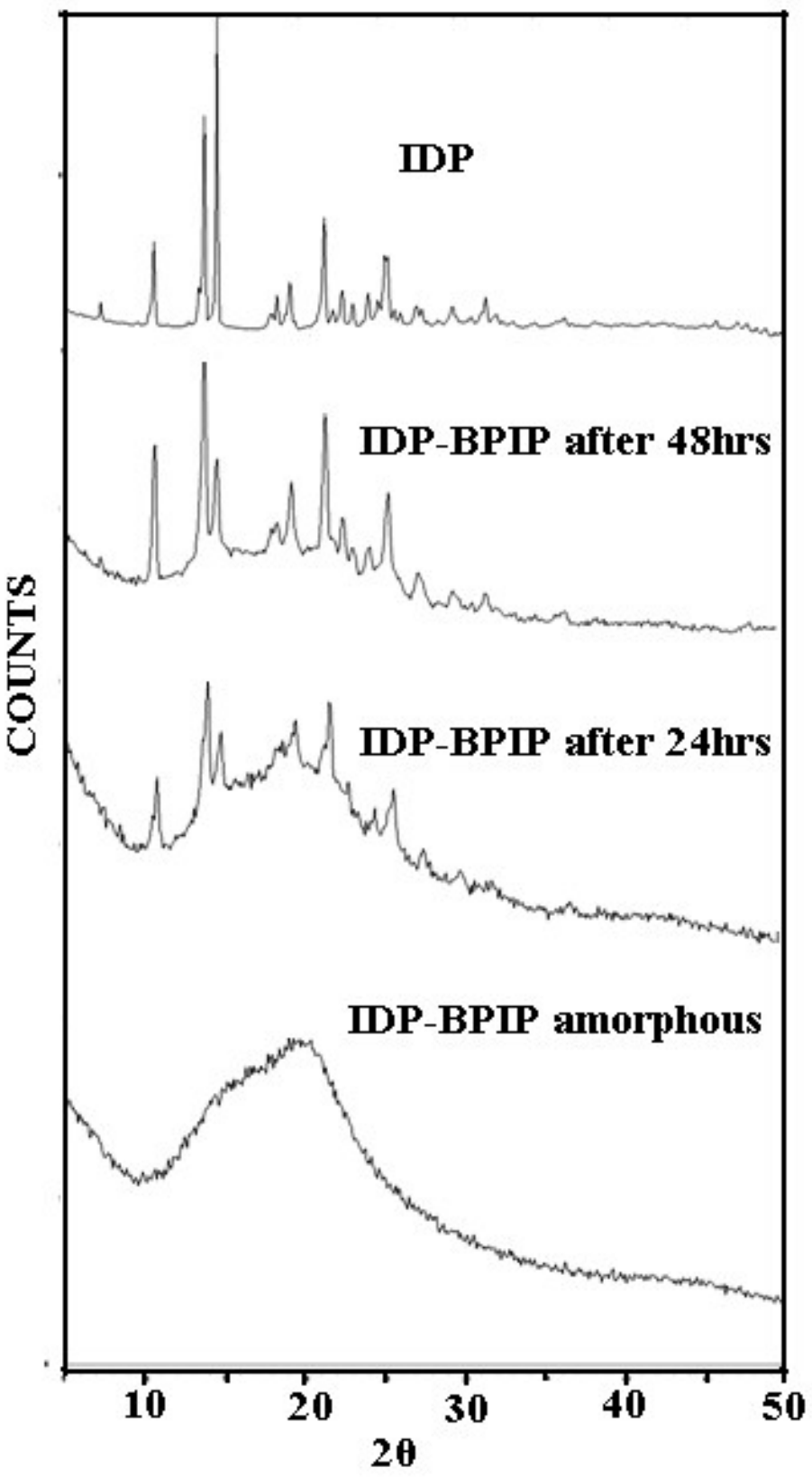


Figure S12 Stability study at 40 °C and 75% RH of IDP-BPIP amorphous form at ambient conditions shows that after 2 days it transforms to crystalline IDP.

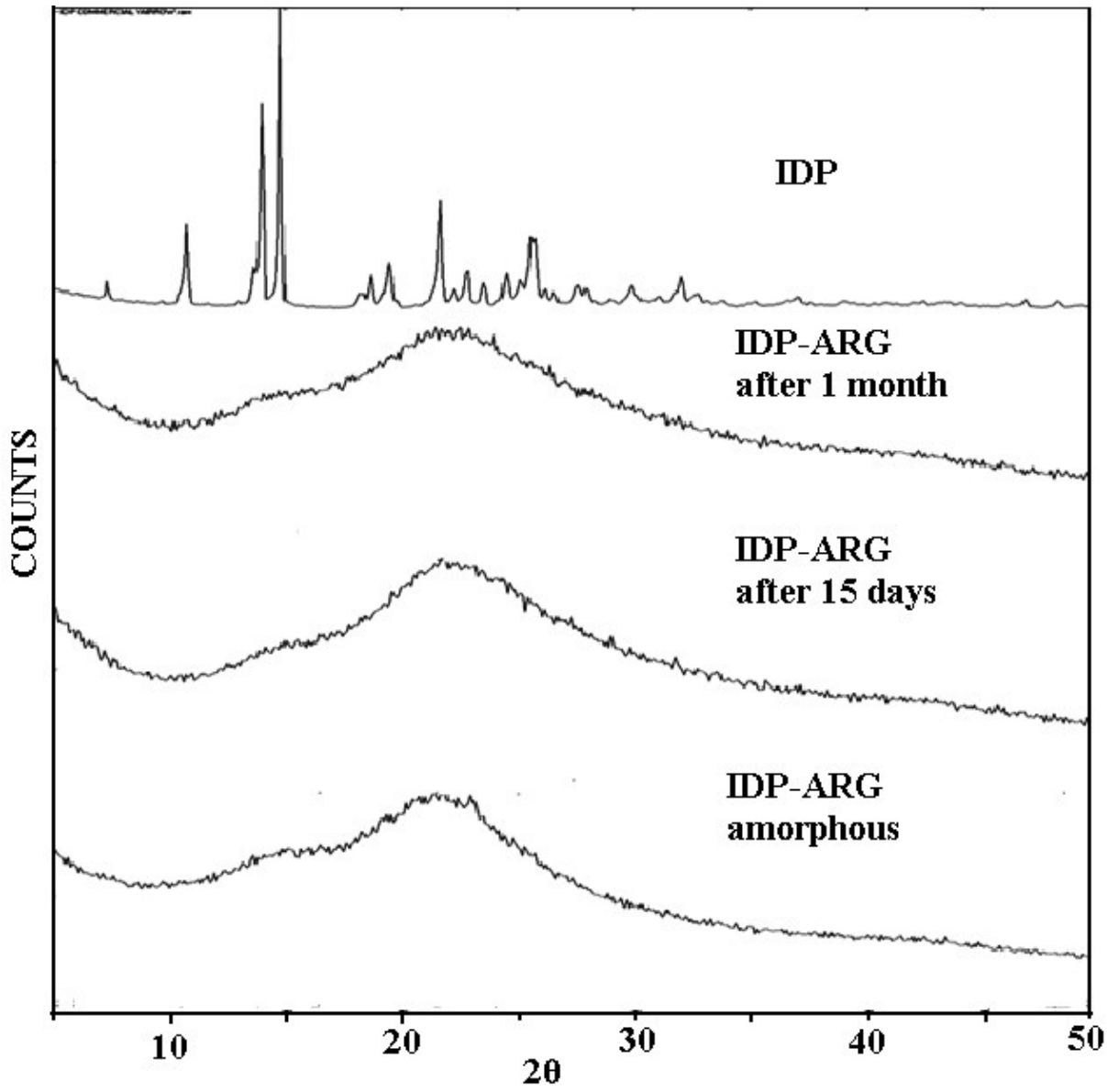


Figure S13 Stability study at 40 °C and 75% RH of IDP-ARG amorphous form at ambient conditions shows that for up to one month it stable and there is transformation to the crystalline phase.

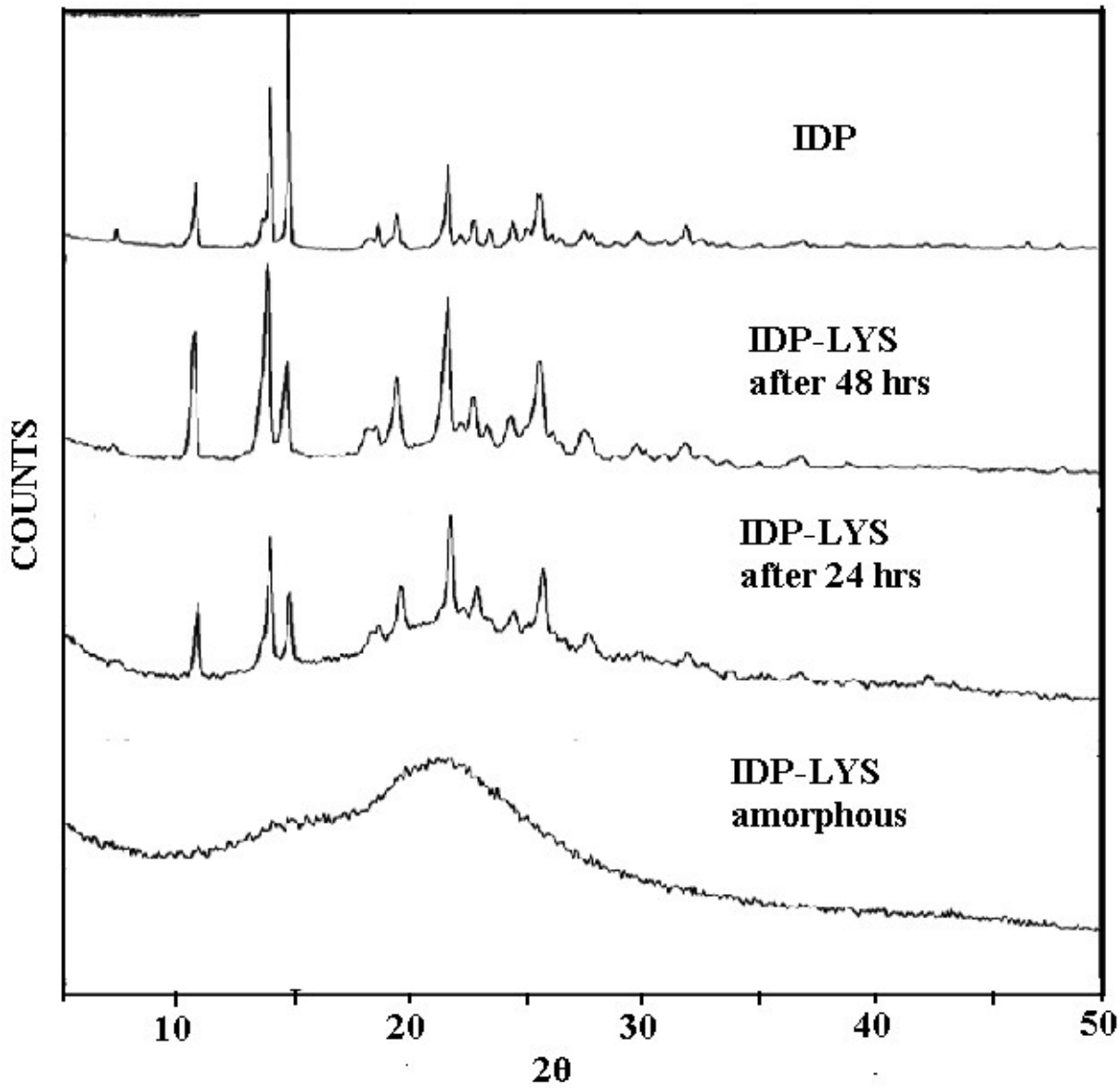


Figure S14 Stability study at 40 °C and 75% RH of IDP-LYS amorphous form at ambient conditions shows that after 2 days it transforms to crystalline IDP.

EXPERIMENTAL SECTION

Indapamide was purchased from Yarrow Chem Products (Mumbai, India). Purity of the compound was confirmed by NMR PXRD and DSC. The coformers used in this study were purchased from Sigma-Aldrich, Hyderabad, India. All chemicals are analytical and solvents are chromatographic grade.

Preparation of Cocrystals and Coamorphous

IDP−DPI (1:1): IDP (100 mg, 0.273 mmol) and DPI (42.69 mg, 0.273 mmol) were ground in a mortar and pestle for 20-25 min after adding 4-5 drops of EtOH. The ground material was kept for crystallization from solvent mixture EtOH and CH_3CN (5 mL) as well as the pure solvents in 10 mL conical at room temperature. Colorless good quality single crystals were observed by slow evaporation. M.p. 200-205 °C.

IDP−BIP (1:1): IDP (100 mg, 0.273 mmol) and BIP (42.69 mg, 0.273 mmol) were ground in a mortar and pestle for 20-25 min after adding 4-5 drops of EtOH. The ground material was kept for crystallization from EtOH and THF (5 mL) solvent mixture in 10 mL conical at room temperature. Colorless good quality single crystals were observed after slow evaporation. M.p. 134-138 °C.

IDP−DPE-HYD (1:1:1): IDP (100 mg, 0.273 mmol) and DPE (49.81 mg, 0.273 mmol) were ground in a mortar and pestle for 20-25 min after adding 4-5 drops of EtOH. The ground material was kept for crystallization from EtOH and CH_3CN (5 mL) solvent mixture in 10 mL conical at room temperature. Colorless good quality single crystals were observed by slow evaporation. M.p. 90-97°C.

IDP−PHE (1:1): IDP (100 mg, 0.273 mmol) and PHE (49.26 mg, 0.273 mmol) were ground in a mortar and pestle for 20−25 min in stoichiometric ratio by adding catalytic amount (4−5 drops) of EtOH solvent. The ground material was kept for crystallization from solvent mixture of EtOH and THF (1:1 v/v) 5ml in a 25ml conical flask at room temperature. Pale yellow green color good quality single crystals were observed by slow evaporation M.p. 205-209 ° C

IDP−MeHP (1:1): IDP (100 mg, 0.273 mmol) and MeHP (29.87 mg, 0.273 mmol) were ground in a mortar and pestle for 20-25 min after adding 4-5 drops of EtOAc. The ground material was kept for crystallization from of EtOH and EtOAc (1:1 v/v, 5 mL) mixture in a 25 mL conical flask at room temperature. Colorless good quality single crystals were observed by slow evaporation. M.p. 176-180 °C.

IDP−PIP (1:0.5): IDP (100 mg, 0.273 mmol) and PIP (23.54 mg, 0.273 mmol) were ground in a mortar and pestle for 20-25 min after adding 4-5 drops of CH3CN then it formed rubbery amorphous phase or another method is Rotavaporization dissolving the two components in a solvent and then fast evaporation under high vacuum so the product was characterized by PXRD, DSC, IR and NMR.

IDP−MPIP (1:1): IDP (100 mg, 0.273 mmol) and MPIP (27.37 mg or 30.31µl, 0.273 mmol) were ground in a mortar and pestle for 20-25 min after adding 4-5 drops of CH3CN then it formed rubbery amorphous phase or another method is Rotavaporization dissolving the two components in a solvent and then fast evaporation under high vacuum so the product was characterized by PXRD, DSC, IR and NMR.

IDP−EPIP (1:1): IDP (100 mg, 0.273 mmol) and EPIP (31.21 mg or 34.72µl, 0.273 mmol) were ground in a mortar and pestle for 20-25 min by adding 4-5 drops of CH3CN then it formed rubbery amorphous phase or another methaod is Rotavaporization dissolving the two components in a solvent and then fast evaporation under high vacuum so the product was characterized by PXRD, DSC, IR and NMR.

IDP−BPIP (1:1): IDP (100 mg, 0.274 mmol) and BPIP (50.91 mg, 0.273 mmol) were ground in a mortar and pestle for 20-25 min after adding 4-5 drops of CH3CN then it formed rubbery amorphous phase or another methaod is Rotavaporization dissolving the two components in a solvent and then fast evaporation under high vacuum so the product was characterized by PXRD, DSC, IR and NMR.

IDP−ARG (1:1): IDP (100 mg, 0.273 mmol) and ARG (47.61 mg, 0.273 mmol) were ground in a mortar and pestle for 20-25 min in stoichiometric ratio after adding 4-5 drops of EtOH then it formed rubbery amorphous phase or another methaod is Rotavaporization dissolving the two components in a solvent and then fast evaporation under high vacuum so the product was characterized by PXRD, DSC, IR and NMR.

IDP−LYS (1:1): IDP (100 mg, 0.273 mmol) and LYS (39.96 mg, 0.273 mmol) were ground in a mortar and pestle for 20-25 min after adding 4-5 drops of EtOH then it formed rubbery amorphous phase or another methaod is Rotavaporization dissolving the two components in a solvent and then fast evaporation under high vacuum so the product was characterized by PXRD, DSC, IR and NMR.

1H NMR spectra

Solution NMR spectra were recorded on Bruker Avance 500 MHzspectrometer (Bruker-Biospin, Karlsruhe, Germany) and IDP(API), IDP-LYS (1:1) recorded on Bruker Avance 400 MHz spectrometer (Bruker-Biospin, Karlsruhe, Germany).

IDP (DMSO-d_6,δ, ppm, Figure S1a): 10.52 (s, 1H); 8.5 (s, 1H); 8.11 (dd, J=6.4Hz, 8.4Hz 1H); 7.81-7.72 (m, 3H); 7.11 (d, 6.8Hz, 1H); 7.04 (t, J=7.6Hz, 1H); 6.76 (t, J=7.4Hz, 1H); 6.50 (d, J=7.6Hz, 1H); 3.97 (s, 1H); 3.20-3.14 (m, 1H); 2.62-2.5 (m, 1H); 1.31 (d, J=6.4Hz, 3H).

IDP-PIP (1:1) (DMSO-d_6, δ, ppm, Figure S1b): 10.56 (brs, 1H); 8.51 (s, 1H); 8.51 (s, 1H); 8.11 (d, J=8.5Hz, 1H); 7.81 (d, J=8.0Hz, 1H); 7.11 (d, J=7.5Hz, 1H); 7.04 (t, J=7.5Hz, 1H); 6.77 (t, J=7.5Hz, 1H); 6.50 (d, J=7.5Hz, 1H); 4.64 (s, 4H); 3.97 (s, 1H); 3.17 (dd, J= 15.0Hz,8.0Hz, 1H);2.61-2.59 (m, 7H); 2.50(s, 2H); 1.31 (d, J=6.0Hz, 3H).

IDP-MPIP (1:1) (DMSO-d_6, δ, ppm, Figure S1c): 10.59 (s, 1H); 8.53 (s, 1H); 8.13 (d, J=8.5Hz, 1H); 7.81 (d, J=8.0Hz, 1H); 6.77 (t, J=7.5Hz, 1H); 6.51 (d, J=8.0Hz, 1H); 3.17 (dd, J=15.5Hz,8.0Hz, 1H); 2.66-2.65 (m, 3H); 2.61-2.56 (m, 1H); 2.19 (brs, 3H); 2.10-2.09 (m, 2H); 1.31 (d, J=6.0Hz, 3H)

IDP-EPIP (1:1) (DMSO-d_6, δ, ppm, Figure S1d): 10.58 (brs, 1H); 8.52 (d, J=2.0Hz,1H); 8.13 (dd, J=8.0Hz, 2.0Hz, 1H); 7.81 (d,J=8.0Hz,1H); 7.11 (d,J=7.0Hz,1H); 7.05 (t,J=7.5Hz 1H); 6.77 (t, J=7.5Hz, 1H); 6.50 (d, J=8.0Hz, 1H); 4.51 (brs 6H); 3.98 (s, 1H); 3.17 (dd,J=15.5Hz,8.0Hz, 1H); 2.67 (t, J=4.5Hz, 3H); 2.59 (dd, J=15.5Hz,11.0Hz, 1H); 2.27-2.22 (m, 5H); 1.31 (d, J=6.5Hz, 3H); 0.96 (t, J=7.5Hz, 2H).

IDP-BPIP (1:1) (DMSO-d_6, δ, ppm, Figure S1e): 10.55 (s,1H); 8.50 (s, 1H); 8.11 (d, J=8.0Hz, 1H); 7.81 (d, J=8.0Hz, 1H); 7.11 (d,J=7.0Hz, 1H); 7.04 (t, J=7.5Hz, 1H); 6.77 (t, J=7.5Hz, 1H); 6.50 (d, J=7.5Hz, 1H); 3.97 (brs, 1H); 3.33 (s, 3H); 3.21-3.15 (m, 5H); 2.61-2.59 (m, 5H); 1.39 (s, 9H); 1.31-1.30 (m, 3H)

IDP-ARG (1:1) (MeOH-d_4,δ, ppm, Figure S1f): 8.62 (d, J=2Hz, 1H); 8.07 (dd, J=6,8.5Hz, 1H); 7.75 (d, J=8Hz, 1H); 7.14-7.08 (m, 2H); 6.85(t, J=7.5Hz, 1H); 6.62 (d, J=7.5Hz, 1H); 3.87 (s,1H); 3.33-3.32 (m, 4H); 3.22-3.17 (m, 2H); 2.73-2.68 (m, 2H); 1.73-1.62 (m, 2H); 1.42 (d, J=6Hz, 3H)

IDP-LYS (1:1) (MeOH-d_4,δ, ppm, Figure S1g): 8.54 (d, J=2.4Hz, 1H); 8.09 (dd, J=6.4Hz, 8.4Hz, 1H); 7.82 (d, J=8.4Hz, 1H); 7.19-7.11 (m, 2H); 6.89 (t, 7.6Hz, 1H); 6.63 (d, J=7.6Hz, 1H); 3.85 (brs, 1H); 3.62-3.55 (m, 1H); 3.33-3.31 (m, 4H); 3.23-3.17 (m, 1H); 2.98 (t, J=7.6Hz, 1H); 2.75-2.67 (m, 1H); 1.90-1.83 (m, 2H); 1.76-1.68 (m, 2H); 1.55-1.33 (m, 6H)

Stability under ICH Conditions

IDP-PIP coamorphous systems were found to be stable for up to 4 months ambient conditions of 40 °C and 75% RH exposure to humidity. (Figure S8).

Remaining coamorphous systems under 40 °C and 75% RH exposure to humidity after two days it will convert to crystalline form of IDP. (Figure S9 to S11)

Powder X-ray diffraction

Powder X-ray diffraction (PXRD) was recorded on Bruker D8 Advance diffractometer (Bruker-AXS, Karlsruhe, Germany) using Cu-Kα X-radiation (λ = 1.5406 Å) at 40 kV and 30 mA power. Diffraction patterns were collected over the 2θ range 5–50° at scan rate of 5°/min.

Vibrational spectroscopy

FT-IR spectroscopy was carried out using Thermo-Nicolet 6700 FT-IR-NIR spectrometer with NXR FT-Raman module (Thermo Scientific, Waltham, MA) with the samples dispersed in KBr pellets and Omnic software (Thermo Scientific, Waltham, MA) was utilized to analyse the data.

Thermal analysis

Differential scanning calorimetry(DSC)be present performed on Mettler-Toledo DSC 822e module, (Mettler-Toledo, Columbus, OH). Compounds were placed in sealed pin-pricked aluminium pans DSC experiments. The characteristic sample size is 3-5 mg for DSC. The temperature range for the heating curves was 30-350°C, and the sample was heated at a rate of 10 °C/ min. Samples were purged in a stream of dry nitrogen flowing at 80 mL/min.

Solution NMR spectroscopy

Solution NMR spectra were recorded on Bruker Avance 500 MHzspectrometer (Bruker-Biospin, Karlsruhe, Germany) and Bruker Avance 400 MHzspectrometer (Bruker-Biospin, Karlsruhe, Germany)

X-ray crystallography

Bruker D8 QUEST, CCD diffractometer. Mo-Kα (λ = 0.71073 Å) radiation was used to collect X-ray reflections on all crystals. Bruker D8 Quest diffractometer equipped with a graphite monochromator and Mo−Kα fine-focus sealed tube (λ = 0.71073 Å). Intensities for absorption were corrected with SADABS. Structures were solved and refined using SHELXL-97 with anisotropic displacement parameters for non-H atoms. Hydrogen atoms on O and N were experimentally located in all crystal structures. Hydrogen atoms were experimentally located through the Fourier difference electron density maps in all crystal structures. All O–H and C–H atoms were fixed geometrically with HFIX command in SHELX-TL program of Bruker-AXS. Crystal parameters (Table S1) and Hydrogen bond distances shown in Table S2 are neutron normalized to fix the D–H distance to its accurate neutron value in the X-ray crystal structures (O–H 0.983 Å, N–H 1.009 Å, and C–H 1.083 Å).A check of the final CIF file using PLATON for any missed symmetry. X-Seed was used to prepare packing diagrams. Crystallographic .cif files are available at www.ccdc.cam.ac.uk/datasuch as part of the Supporting Information.

Solubility measurements

Powder Dissolution (PD) study was carried out on USP-certified Electrolab TDT-08L dissolution tester (Mumbai, India). Standard curves for all the compounds were obtained spectrophotometrically at their respective $\lambda_{max.}$ The powder dissolution studies of IDP and coamorphous solids was done using IDP 200 mg, IDP-PIP 247 mg, IDP-MPIP 254 mg, IDP–EPIP 262 mg, IDP–BPIP 302 mg IDP–LYS 280 mg and IDP–ARG 295 mg which was directly poured into 500 mL of pH 7 phosphate buffer dissolution medium. The paddle rotation was fixed at 100 rpm and dissolution experiments were continued up to 6h at 37 ºC. At regular intervals, 5 mL of the dissolution medium was withdrawn and replaced by an equal volume of fresh medium to maintain a constant volume and the concentration of the aliquots was determined with proper dilutions from the predetermined standard curves of the respective compounds.

Diffusion studies

Diffusion studies were conducted using a glass Franz-type diffusion cell (Model JFDC-07, Orchid Scientific, Maharashtra, India) with a 20 mL volume. The membrane used was a dialysis membrane-135 [dialysis membrane-135, average flat width 33.12 mm, average diameter 23.8 mm, capacity 4.45 mL/cm] obtained from HiMedia, India. The dialysis membrane was placed between the two compartments and held by a stainless steel clamp with an effective mass transfer area of 3.14 cm^2. The receptor compartment was filled with PBS solution, and air bubbles were removed. Afterwards, the donor compartment was loaded with pure crystalline API and its coamorphous in equimolar ratio powders and 2 mL of PBS were added. The temperature of diffusion medium was thermostatically maintained at 37±1 °C throughout the experiment and the IDP and its coamorphous was then allowed to stir at 600 rpm and diffuse through the membrane towards the receptor compartment. Aliquots of 1 mL were withdrawn from the receptor compartment at predetermined time periods (15, 30, 45, 60, 90, 120, 150, 180, 240, 270, 300, 360 min) and fresh PBS was added to replenish volume. The determination of IDP diffused was performed by UV spectroscopy (Thermo Scientific EVOLUTION 300 UV-VIS). The cumulative concentration of drug which diffuses into the receptor compartment at each interval was determined taking into consideration the replacement of aliquots with PBS and the dilution derived from the addition of PBS buffer.