Supporting information

Solid State NMR Characterization of Ibuprofen:Nicotinamide Cocrystals and New Idea for Controlling of Release of the Drugs Embedded into Mesoporous Silica Particles.

by

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KEYWORDS Drug Delivery Systems, Cocrystal, Mesoporous Silica Nanoparticles, Solid State NMR, Multidirectional Treatment, Nonsteroidal Anti-inflammatory Drug

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^{13}C CP MAS NMR

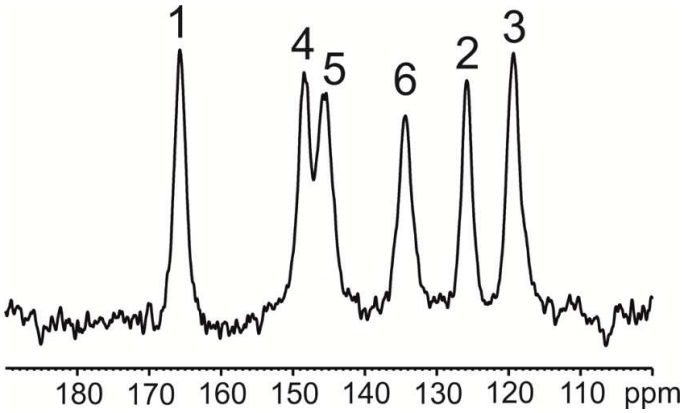


Figure S1. The ^{13}C CP MAS NMR spectrum of nicotinamide recorded with a spinning rate of 8 kHz

DSC analysis

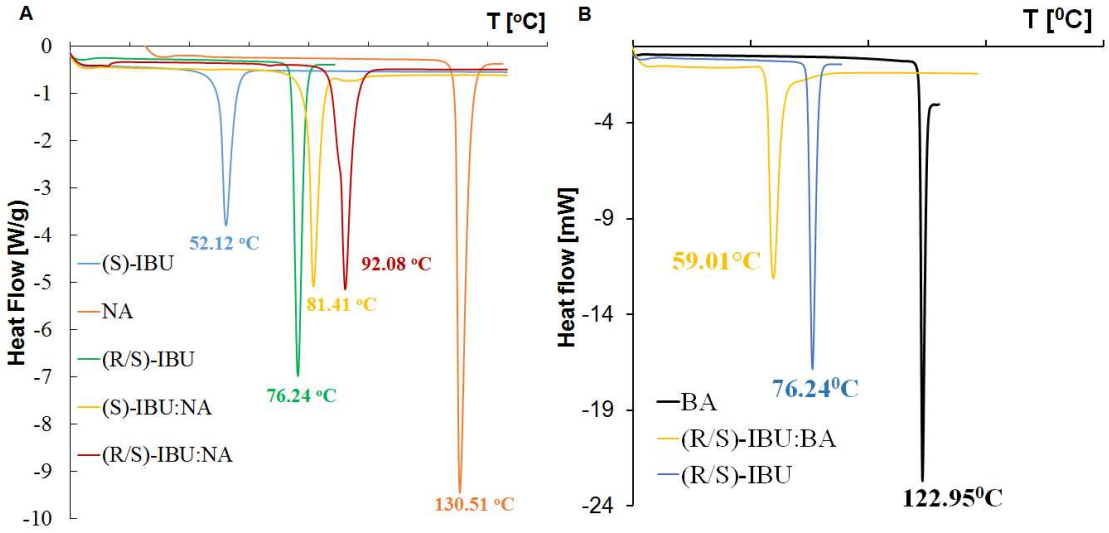


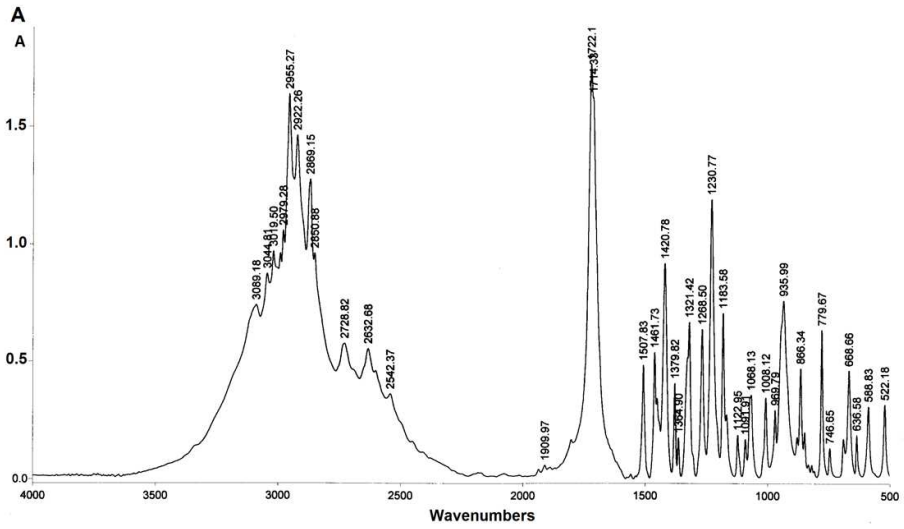
Figure S2. DSC plots of A) bulk commercial nicotinamide, (S)-ibuprofen, (R/S)-ibuprofen, (S)-ibuprofen:nicotinamide cocrystal and (R/S)-ibuprofen:nicotinamide cocrystal; B) bulk commercial benzoic acid, (R/S)-ibuprofen and (R/S)-ibuprofen:benzoic acid cocrystal.

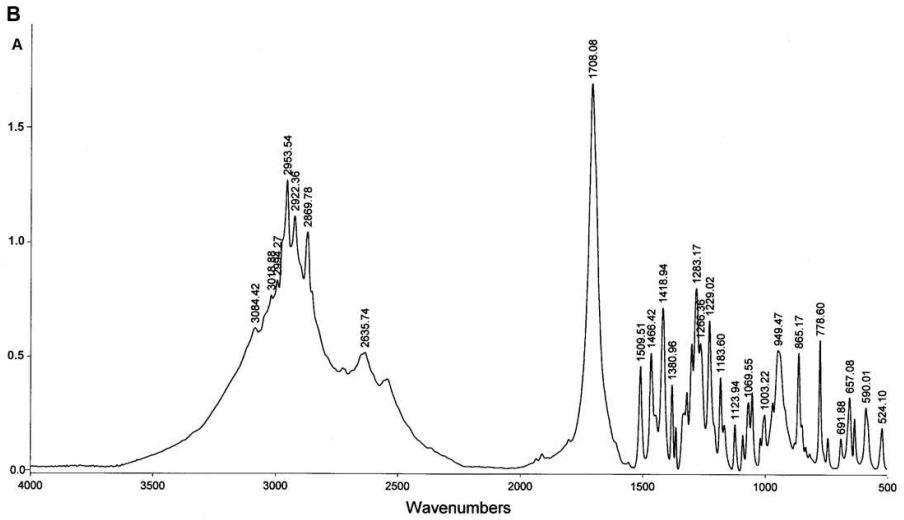
FT-IR data

Further information providing details related to hydrogen bonding pattern for cocrystals was obtained from FT-IR measurements. For the (S)-IBU:NA cocrystal this analysis has not been previously described in the literature. The FT-IR spectrum for **3a** cocrystal was already analyzed by Oberoi et al.[1] Similarly to the authors we received a ν(C=O) stretching band at 1706 cm^{-1} in both cocrystals and δ(NH2) 1624 cm^{-1} and 1627 cm^{-1} in **3a** and **3b**, respectively which are shifted as compared to pure components (Figure S4A−E). The symmetric stretching bands of the amine group at 3165 cm^{-1} in nicotinamide is shifted to 3175 cm^{-1} and 3180 cm^{-1} in cocrystals **3a** and **3b**, respectively. It is worth to mentioned that asymmetric bands of this motif are also shifted, but in both systems, are different. On the FT-IR spectrum of **3a** is shown only one absorption band, and in the case of the crystal **3b** in this spectral range is observed two bands which may result from different types of ibuprofen molecules and interaction of hydrogen-bonding in the cocrystals. Formations at 2480 cm^{-1} and 1981 cm^{-1} corresponding to new hydrogen bonds ($O\text{-}H^{\cdots}N_{aromatic}$) were also observed. The appearance of these characteristic absorption bands was observed in previous studies of NPX:PA cocrystal.[2] Furthermore, FT-IR analysis clearly indicated the existence of intermolecular $O^{\cdots}H\text{-}N_{amide}$ hydrogen bond in both cocrystals (band at 3316 cm^{-1}). The all FT-IR data were collected in Table 1.

Table 1. FT-IR data obtained for (R/S)-ibuprofen, (S)-ibuprofen, nicotinamide and cocrystals **3a** and **3b**.

	(R/S)-Ibuprofen (cm^{-1})	(S)-Ibuprofen (cm^{-1})	Nicotinamide (cm^{-1})	cocrystal 3a (cm^{-1})	cocrystal 3b (cm^{-1})
v C=O	1722	1708	1678	1706	1706
v N-H	-	-	3361 3165	3400 3180	3399 and 3384 3175
v O-H	2500-3090	2500-3090	-	-	-
v $C\text{-}N_{amide}$	-	-	1396	1402	1401
$O^{\cdots}H\text{-}N$	-	-	-	3316	3319
$O\text{-}H^{\cdots}N$	-	-	-	2479 1981	2479 1980
Fingerprint region	-	-	-	857, 795, 716	857, 795, 716


A
A
1.5
1.0
0.5
0.0
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers
3089.18
2955.27
2922.26
2869.15
2728.82
2632.68
2542.37
1909.97
1722.1
1507.83
1461.73
1420.78
1379.82
1321.42
1268.50
1230.77
1183.58
1068.13
1008.12
935.99
866.34
779.67
746.65
668.66
636.58
588.83
522.18


B
A
1.5
1.0
0.5
0.0
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers
3084.42
2953.54
2922.36
2869.78
2635.74
1708.08
1509.51
1466.42
1418.94
1380.96
1283.17
1229.02
1183.60
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865.17
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691.88
657.08
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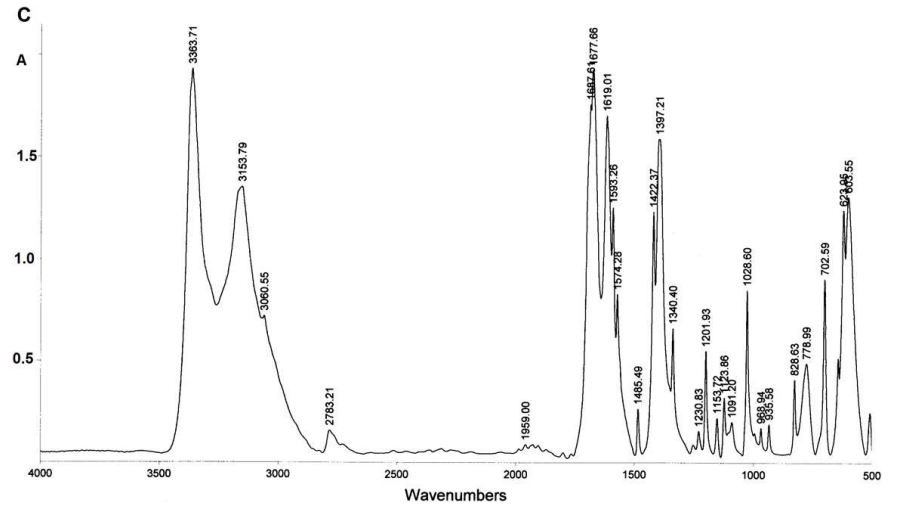
524.10


C
A
1.5
1.0
0.5
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers
3383.71
3153.79
3060.55
2783.21
1959.00
1677.66
1619.01
1593.26
1574.28
1485.49
1422.37
1397.21
1340.40
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1201.93
1153.72
1123.86
1091.20
1028.60
828.63
778.99
702.59

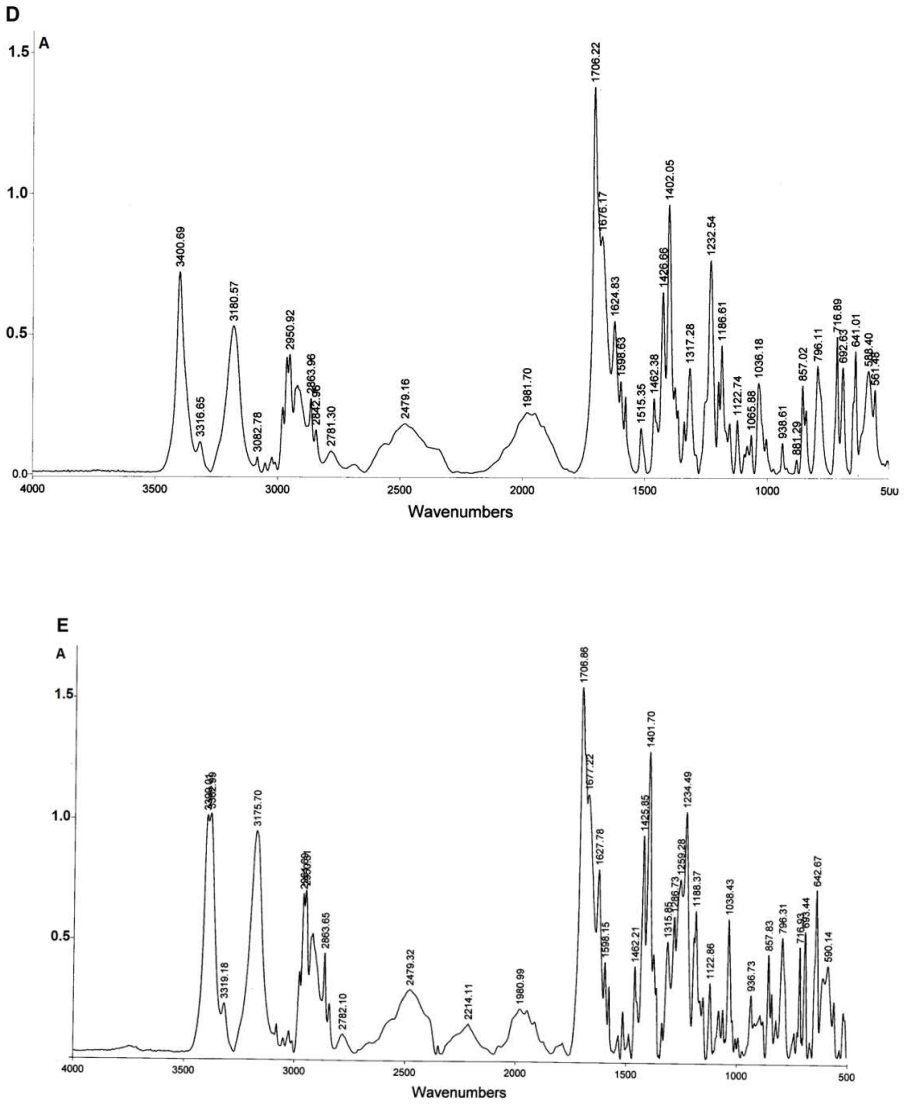


Figure S3. The FT-IR spectra of A) (R/S)-ibuprofen, B)-(R)-ibuprofen, C)- nicotinamide, D)-(R/S)-IBU:NA, E)-(S)-IBU:NA

2D VF MAS NMR experiment

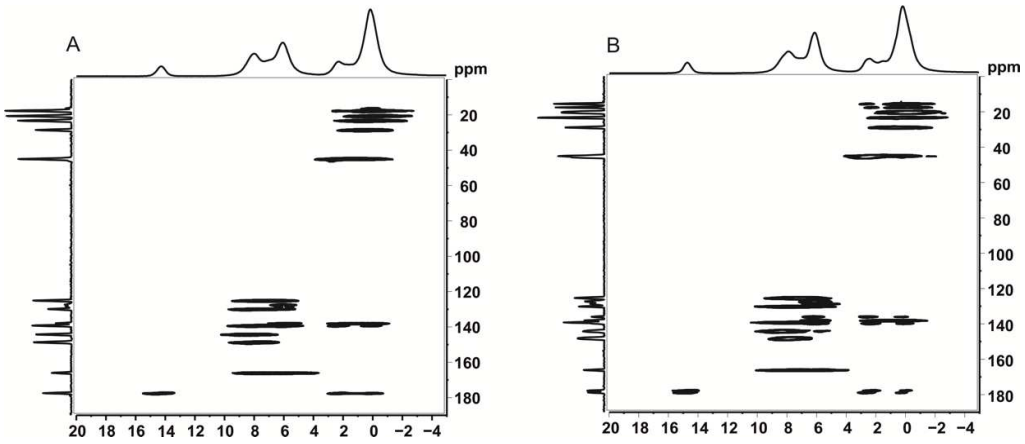


Figure S4. ^{1}H-^{13}C HETCOR experiment recorded with a spinning rate of 60 kHz of A-(R/S)-ibuprofen:nicotinamide cocrystal, B-(S)-ibuprofen:nicotinamide cocrystal.

X-ray data

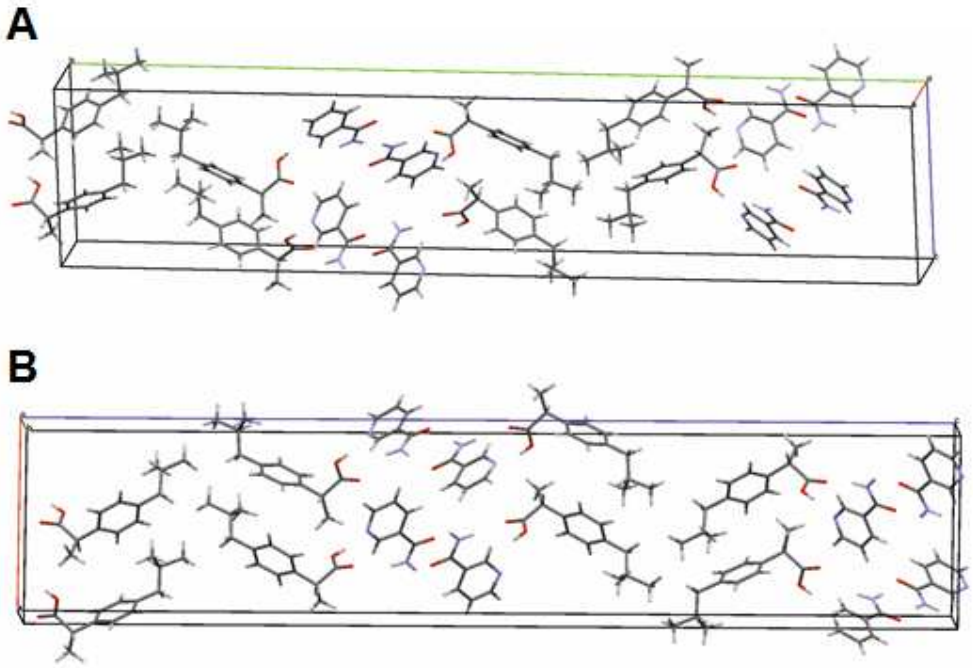
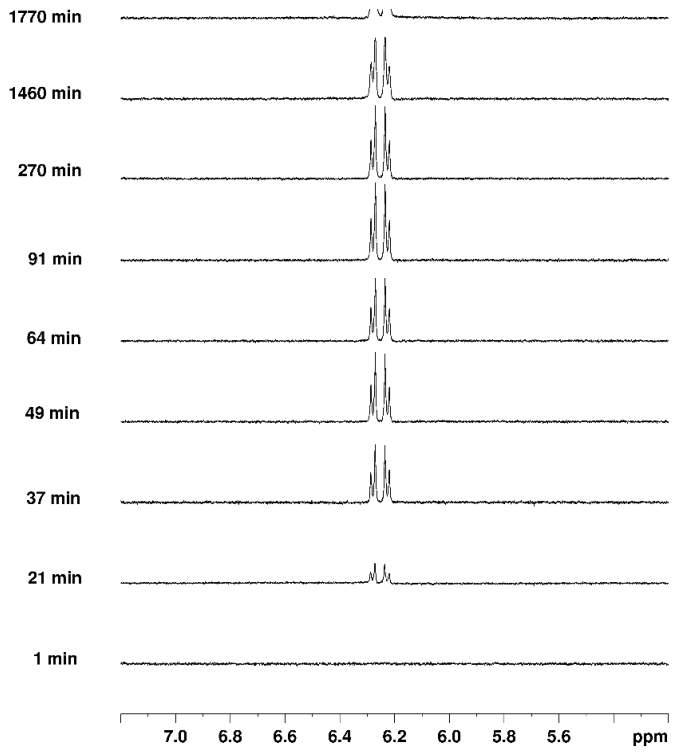


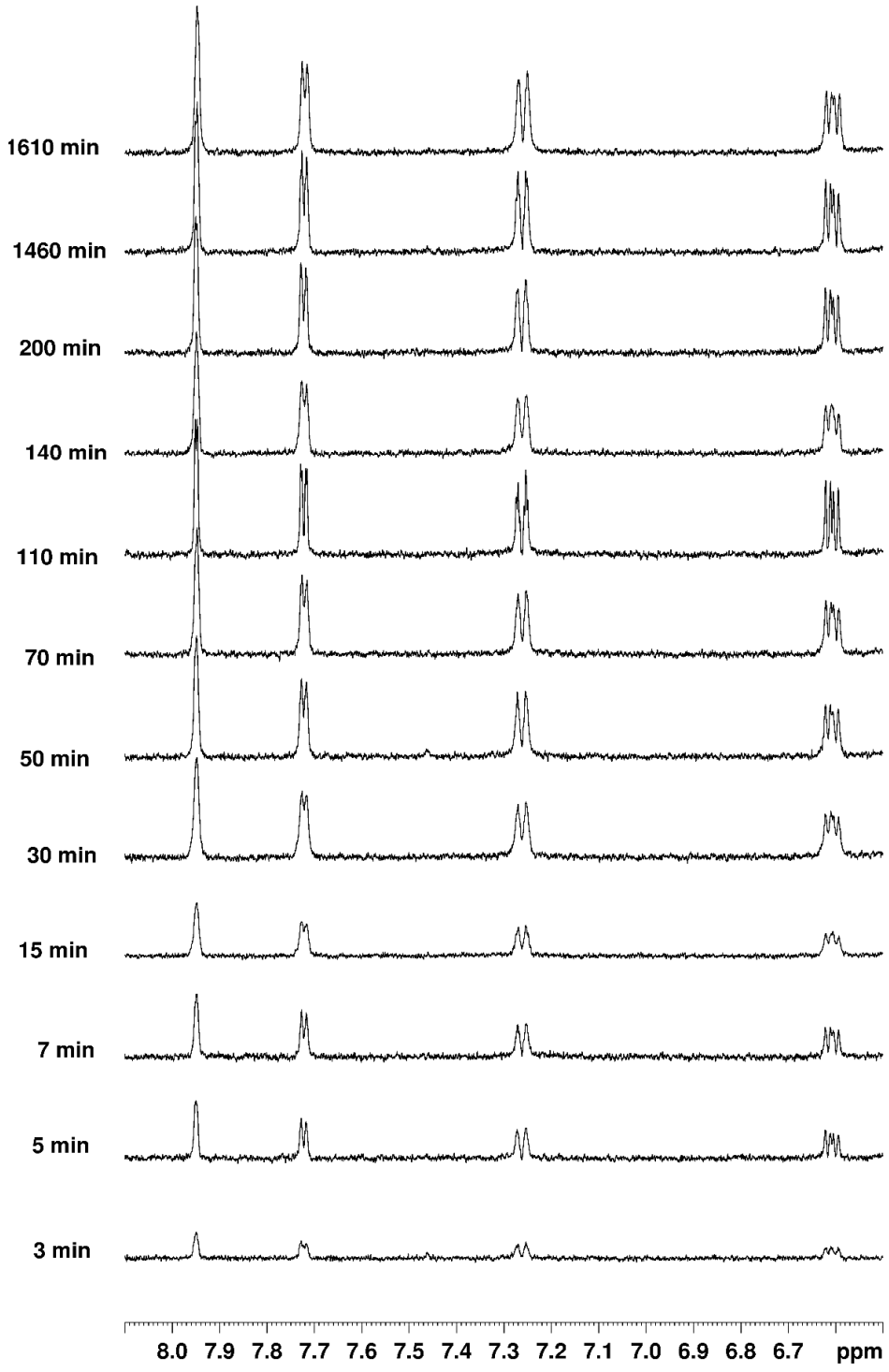
Figure S5. X-ray data of A – (S)-IBU:NA and B – (R/S)-IBU:NA[3]

^{1}H NMR spectra

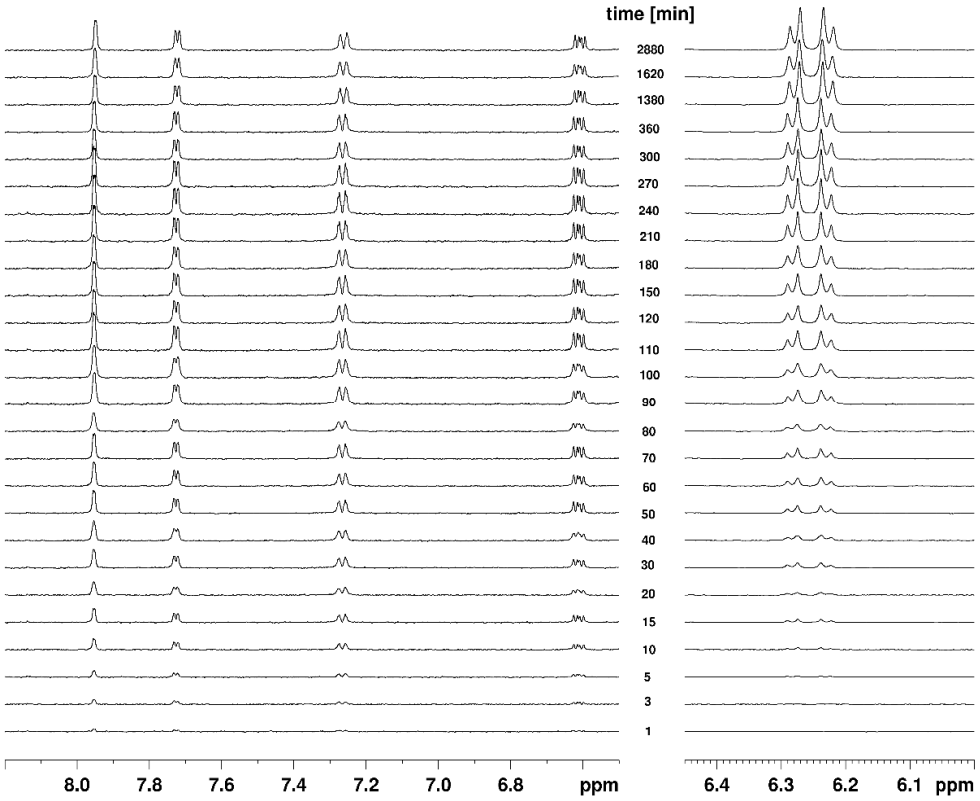
A



B


1610 min
1460 min
200 min
140 min
110 min
70 min
50 min
30 min
15 min
7 min
5 min
3 min
8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 ppm

C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2880
1620
1380
360
300
270
240
210
180
150
120
110
100
90
80
70
60
50
40
30
20
15
10
5
3
1
8.0
7.8
7.6
7.4
7.2
7.0
6.8
ppm
6.4
6.3
6.2
6.1
ppm

D

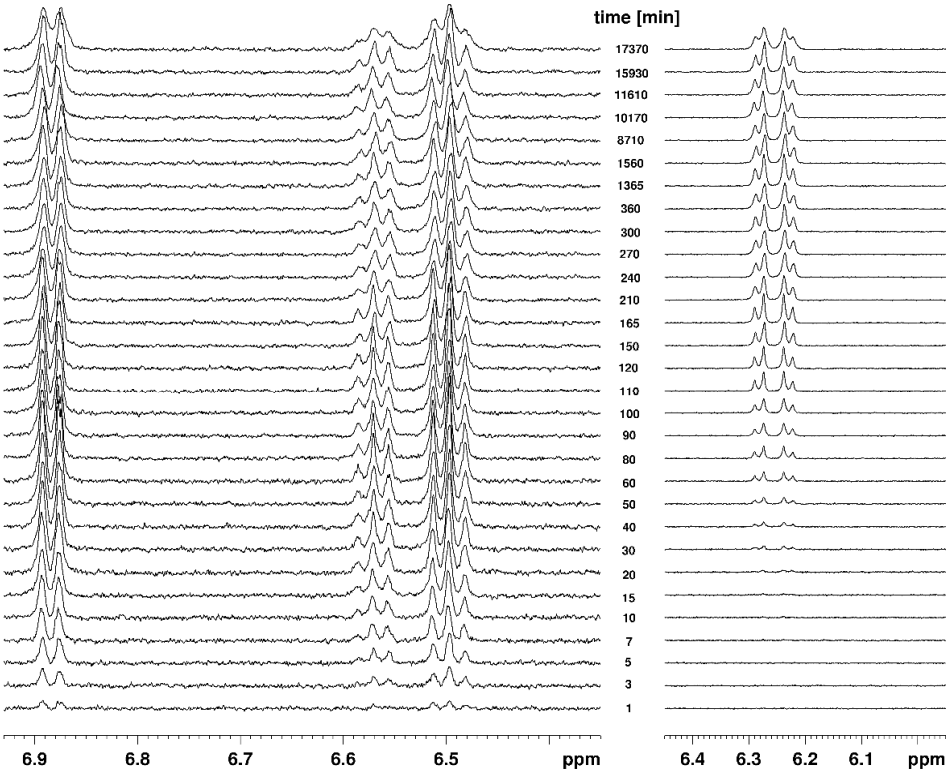

Figure S6. ^{1}H NMR spectra with water suppression of A) IBU/MCM-41, B) NA/MCM-41; C) (S)-IBU:NA/MCM-41; D) (R/S)-IBU:BA/MCM-41 in acetone d-6 (external solvent).

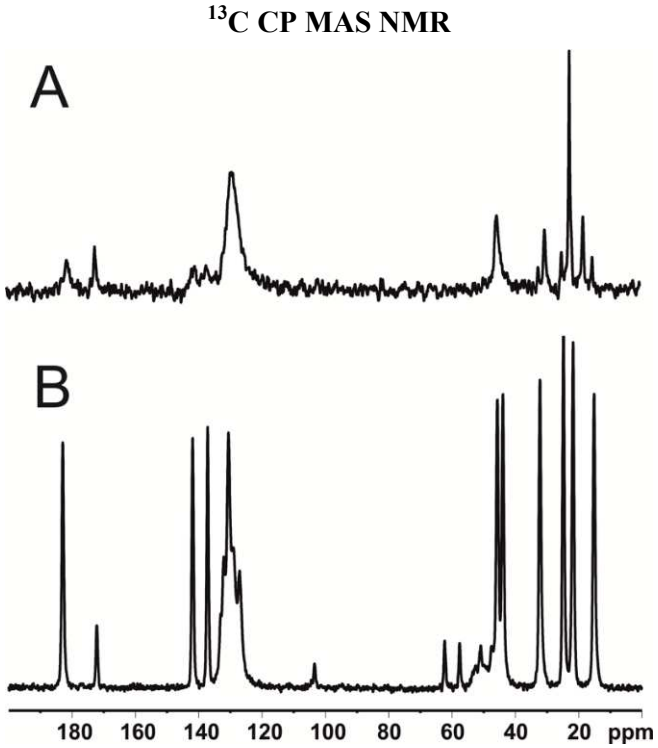

Figure S7. The ^{13}C CP MAS NMR spectrum of A) (R/S)-IBU:BA in MCM-41 (1:1) B) (R/S)-IBU:BA recorded with a spinning rate of 12 kHz

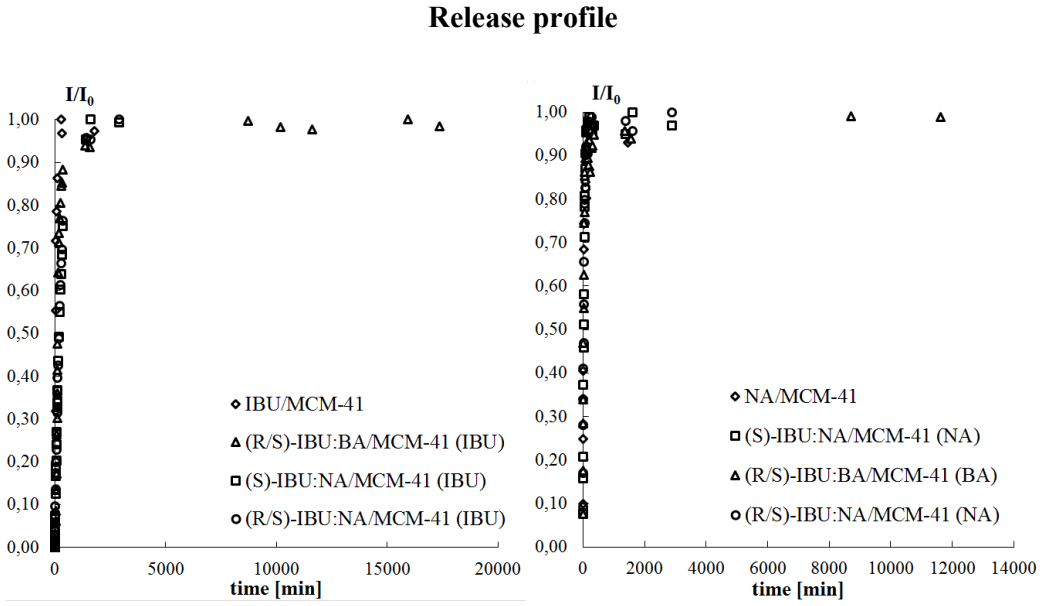

Figure S7. Release profile for A) ibuprofen form (R/S)-IBU:NA/MCM-41, (S)-IBU:NA/MCM-41 and (R/S)-IBU:BA/MCM-41 samples, B) coformers (benzoic acid, nicotinamide) form (R/S)-IBU:NA/MCM-41, (S)-IBU:NA/MCM-41 and (R/S)-IBU:BA/MCM-41 samples.

[1] Oberoi, L. M.; Alexsander, K. S.; Riga, A. T. Study of Interaction between Ibuprofen and Nicotinamide Using Differential Scanning Calorimetry, Spectroscopy, and Microscopy and Formulation of a Fast-Acting and Possibly Better Ibuprofen Suspension for Osteoarthritis Patients *J. Pharm. Sciences*, **2005**, *94 (1)*, 93-101

[2] Skorupska, E.; Jeziorna, A.; Potrzebowski, M. J. Thermal Solvent-Free Method of Loading of Pharmaceutical Cocrystals into the Pores of Silica Particles: A Case of Naproxen/ Picolinamide Cocrystal. *J. Phys. Chem*. C. **2016**, *120*, 13169−13180

[3] Berry, D. J.; Seaton, C. C.; Clegg, W.; Harrington, R. W.; Coles, S. J.; Horton, P. N.; Hursthouse, M. B.; Storey, R.; Jones, W.; Friščć, T.; Blagden, N. Applying Hot-Stage Microscopy to Co-Crystal Screening: A Study of Nicotinamide with Seven Active Pharmaceutical Ingredients. *Cryst. Growth Des*. **2008**, *8*, 1697-1712