Electronic Supplementary Information (ESI)

A sildenafil cocrystal based on acetylsalicylic acid exhibits an enhanced intrinsic dissolution rate

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1. Materials

Sildenafil of 98% purity was obtained from an in-house source and used without further purification. Acetylsalisylic acid (98%, Merck) and 2-propanol were used as received.

2. Crystallographic studies

2.1. Powder X-ray diffraction

X-ray powder diffraction patterns were obtained by using a *Phillips X'Pert Pro* diffractometer equipped with an *X'celerator RTMS* detector using Ni-filtered CuK_α radiation (λ = 1.5406 Å) generated at 45 kV and 40 mA. The sample (~150 mg) was placed on a circular sample holder (16 mm diameter, PW1811/16, PW1811/00). Data collection was conducted at ambient conditions using the *X'Pert Data Collector* program[1] (v. 2.2h). The scans were performed in the continuous mode (gonio scan axis) in the 3-40° 2θ range with a step size of 0.017° and a step time of 40 s. The acquired data was analysed using the *XPertDataView* program.[1]

2.2 Single-crystal X-ray diffraction

Single crystal diffraction data was collected using a *Nonius KappaCCD* diffractometer (being equipped with a 95mm CCD camera on a κ-goniostat) and monochromated CuK_α radiation (λ = 1.54184 Å, graded mirrors). The diffraction data of **1** was collected at 293 K.

Data collection, cell refinement and data reduction were performed using *Collect*[2] and *HKL Scalepack*/*Denzo*,[3] respectively. The structures were solved by direct methods and refined on F^2 by weighted full-matrix least squares. SHELX[4] was used to solve and refine the crystal structures. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms belonging to C(sp^2) and C(sp^3) carbon atoms were placed in geometrically idealized positions with isotropic displacement parameters and fixed at 1.2 times of U_{eq} for methylene carbon atoms and 1.5 times *Ueq* for methyl groups. Hydrogen atoms belonging to O and N atoms were placed in geometrically idealized positions with isotropic displacement parameters and fixed at 1.5 times of U_{eq} of the corresponding atoms.

The investigated single crystal of compound **1** was a small-sized, brittle and poorly diffracting needle. Numerous datasets were collected on single crystals from different batches, whereof the one of the highest quality is reported herein. Attempts to collect a dataset of higher quality at low temperatures failed, as the fine needles tend to crack under the N_2 flow.

3. Thermal analyses

3.1. Thermogravimetric analysis

TGA profiles were generated in range of 25-420 °C using *TA Instruments Hi-Res TGA 2950*. About 10 mg of the sample was placed in an open platinum pan. The mass loss of the sample was determined as a function of temperature. The resulting data were analyzed using the *TA Instruments Universal Analysis 2000* software (v. 4.7A). The TGA thermograms of solids **1** and **2** are shown on Figures S1 and S2, respectively.

3.1. Differential-scanning calorimetry (DSC)

DSC thermograms was acquired in the temperature range of 25−250 °C using a *TA Q1000* instrument. About 2-5 mg of the sample was encapsulated in a pierced Al pan. The same empty pan was used as reference. A nitrogen purge at 50 mL/min was employed. The obtained data was examined using the *TA Instruments Universal Analysis 2000* software (v. 4.7A). The DSC thermograms of solids **1** and **2** are shown on Figures S1 and S2, respectively.

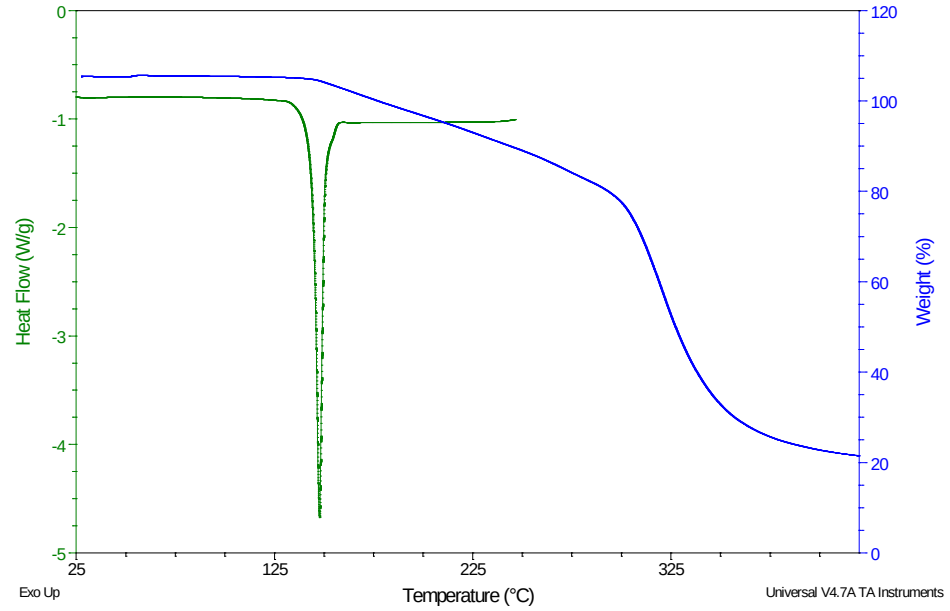

Figure S1. DSC (blue) and TG (green) thermograms of solid **1** ($t_{melting}$ = 148.0 °C).

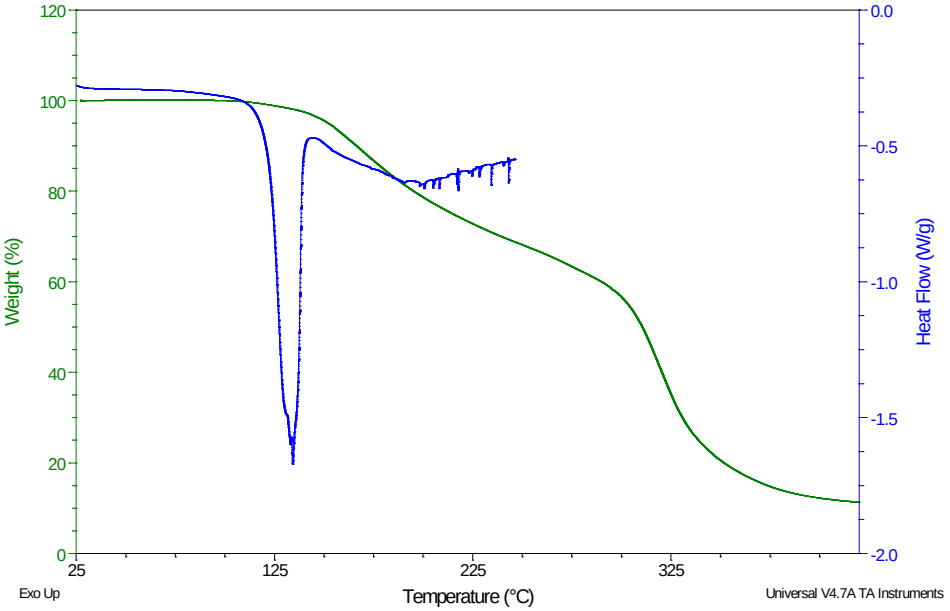

Figure S2. DSC (blue) and TG (green) thermograms of solid **2** ($t_{melting}$ = 134.3 °C).

4. Spectroscopic studies

4.1. FT-IR spectroscopy

FT-IR of solids **1** and **2** were recorded on a *Nicolet 6700* spectrophotometer and measured in the range of 4000-400 cm^{-1} using the KBr-pellet technique (sample concentration: 1 mg in 10 mg of KBr). The data analysis was performed using the *Omnic* program (v. 8.0).

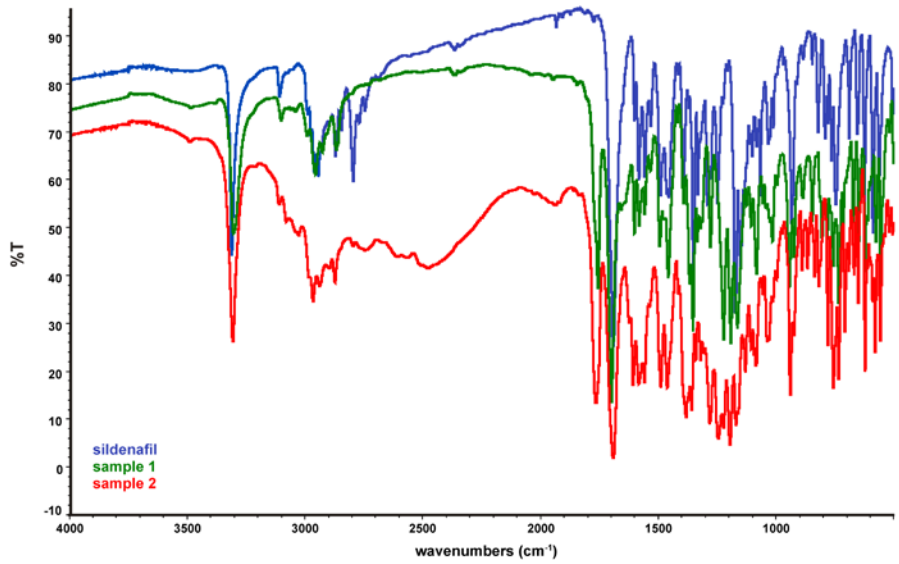

Figure S3. FT-IR spectra of sildenafil (blue), solid **1** (green) and solid **2** (red).

4.1. ^{1}H, ^{13}C and ^{15}N CP-MAS NMR spectroscopy

The ^{1}H and ^{13}C NMR spectra of samples **1** and **2** were recorded on an *Agilent Technologies* NMR System 600 MHz NMR spectrometer equipped with a 3.2 mm NB Double Resonance HX MAS Solids Probe. The Larmor frequencies of proton and carbon nuclei were 599.62 and 150.77 MHz, respectively. The ^{1}H MAS NMR spectra were externally referenced using adamantine. The ^{13}C CP-MAS NMR spectra were externally referenced using hexamethylbenzene. Samples were spun at the magic angle with 20 kHz during ^{1}H measurement and with 16 kHz during ^{13}C measurement. The ^{1}H spectra were acquired within 16 scans using a spin echo sequence with a repetition delay of 10 s. The pulse sequence used for acquiring the ^{13}C spectra was a standard cross-polarization MAS pulse sequence with high-power proton decoupling during acquisition. The repetition delay in all ^{13}C data acquisitions was 5 s and the number of scans was between 500 and 13770, depending on the sample.

The ^{15}N NMR spectra of solids **1** and **2** were also recorded on an *Agilent Technologies* NMR System 600 MHz NMR spectrometer, which was equipped with a 3.2 mm NB Double Resonance HX MAS Solids Probe. The Larmor frequencies of proton and nitrogen nuclei were 599.62 and 60.77 MHz, respectively. The ^{15}N CP-MAS NMR spectra were externally referenced using ammonium sulphate (δ -355.7 ppm, as compared to nitromethane at δ 0.0 ppm). The samples were spun at the magic angle with 10 kHz during all ^{15}N measurement. The pulse sequence used for ^{15}N data acquisition was a standard cross-polarization MAS pulse sequence with high-power proton decoupling during acquisition. The repetition delay in all ^{15}N experiments was 5 s and the number of scans was between 4430 and 27400, depending on the sample.

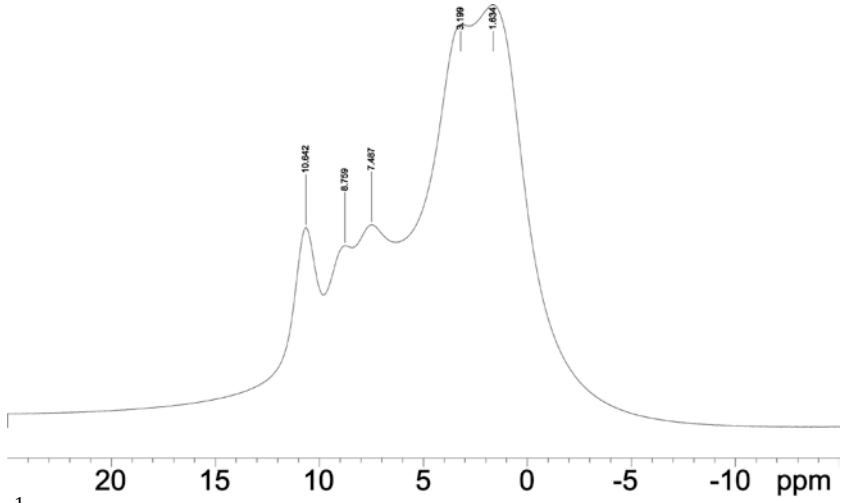

Figure S4. ^{1}H MAS NMR spectrum of sildenafil.

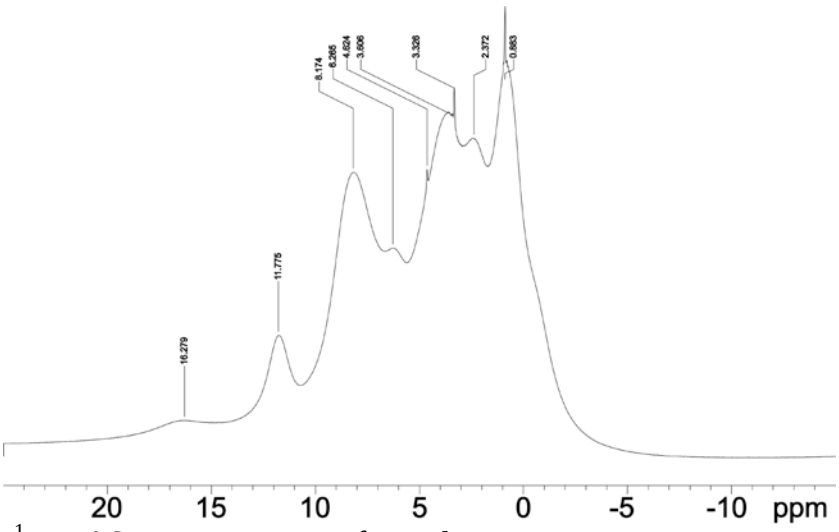

Figure S5. ^{1}H MAS NMR spectrum of sample **1**.

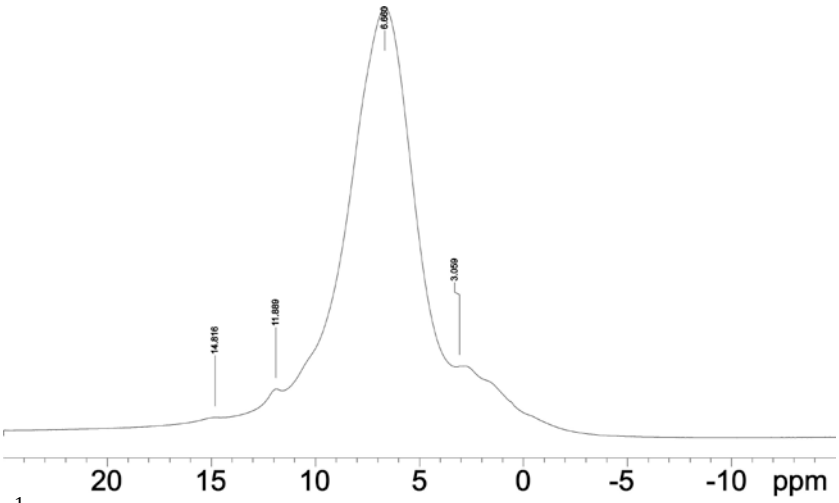

Figure S6. ^{1}H MAS NMR spectrum of sample **2**.

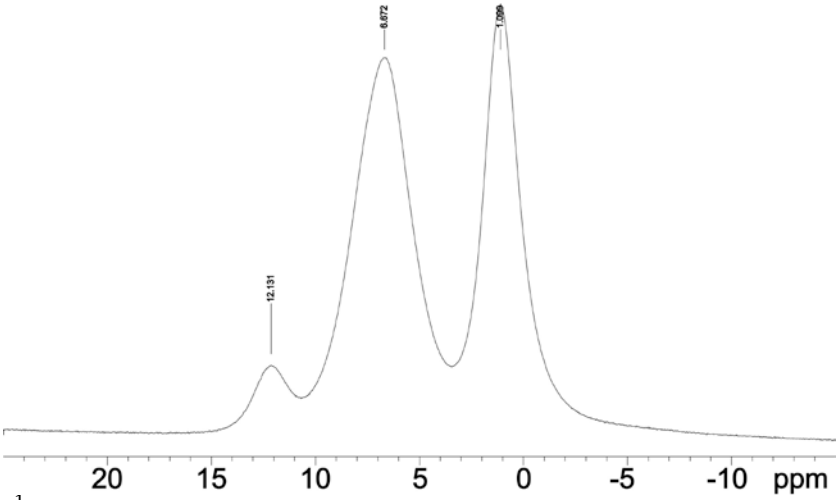

Figure S7. [1]H MAS NMR spectrum of acetilsalicylic acid.

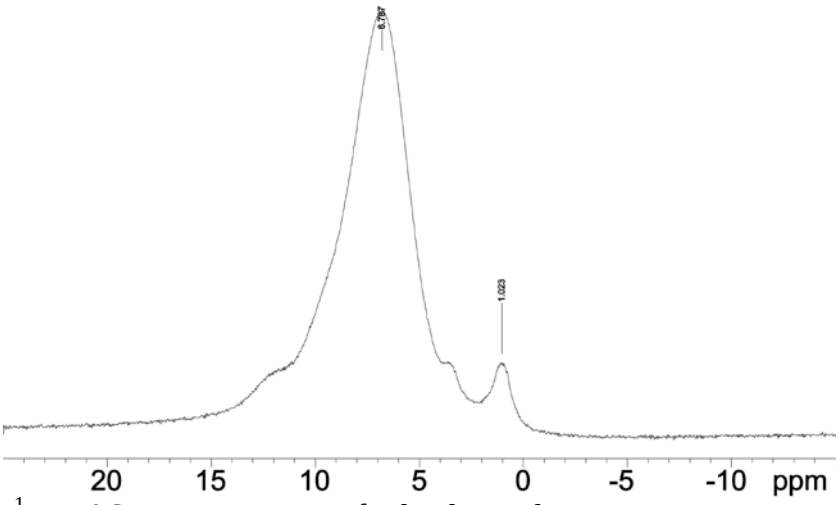

Figure S8. [1]H MAS NMR spectrum of salicylic acid.

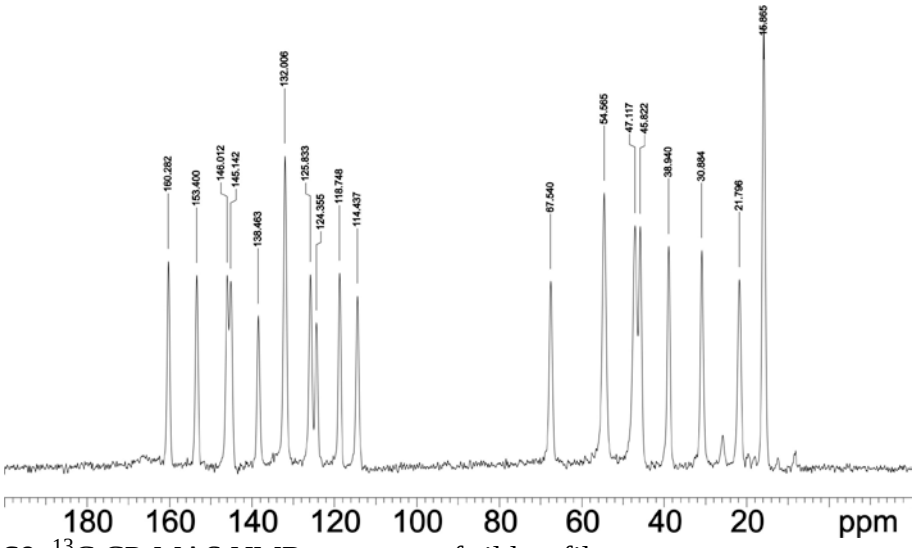

Figure S9. [13]C CP-MAS NMR spectrum of sildenafil.

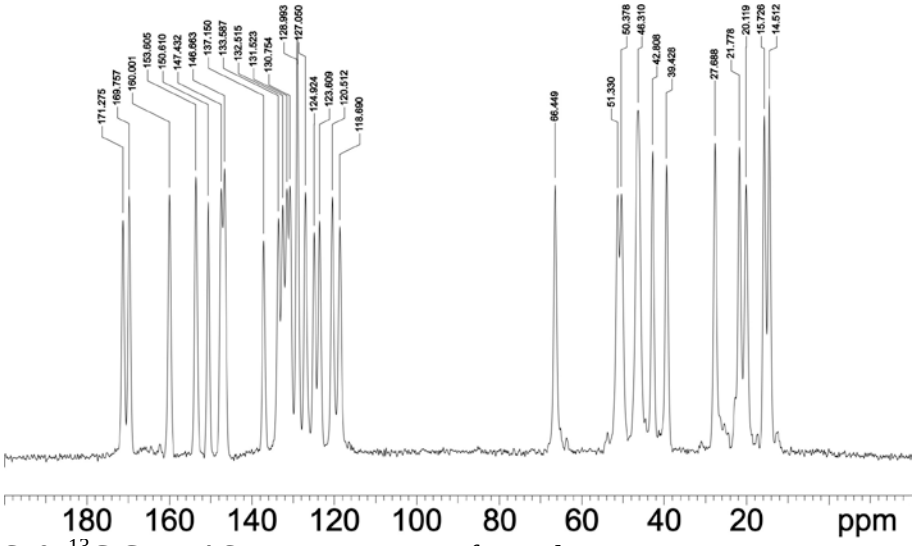

Figure S10. ^{13}C CP-MAS NMR spectrum of sample **1**.

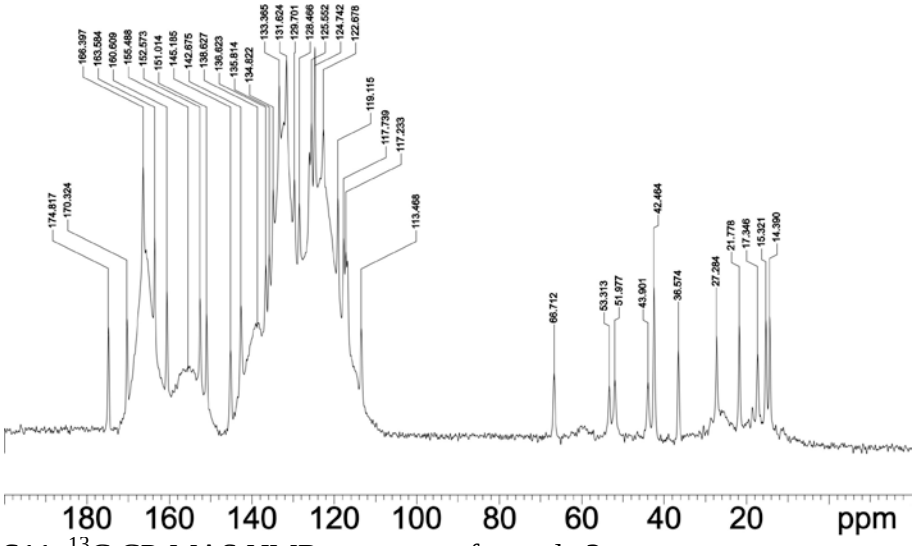

Figure S11. ^{13}C CP-MAS NMR spectrum of sample **2**.

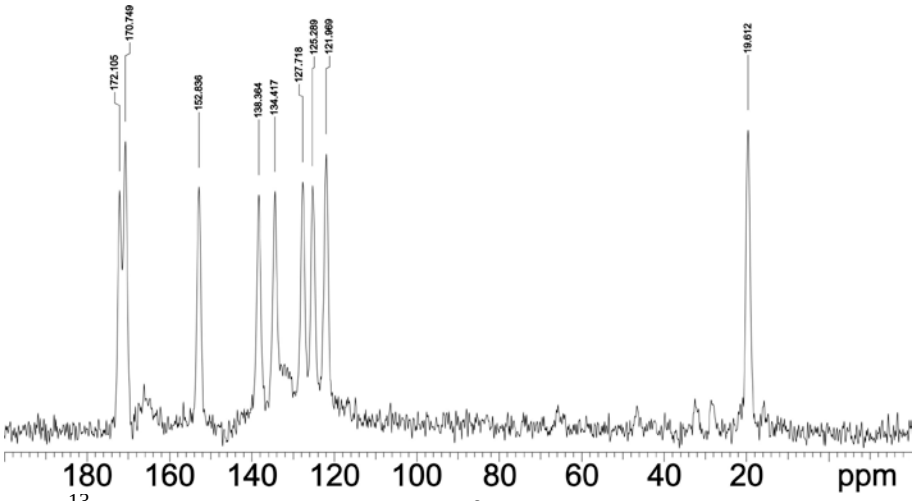

Figure S12. ^{13}C CP-MAS NMR spectrum of acetilsalicylic acid.

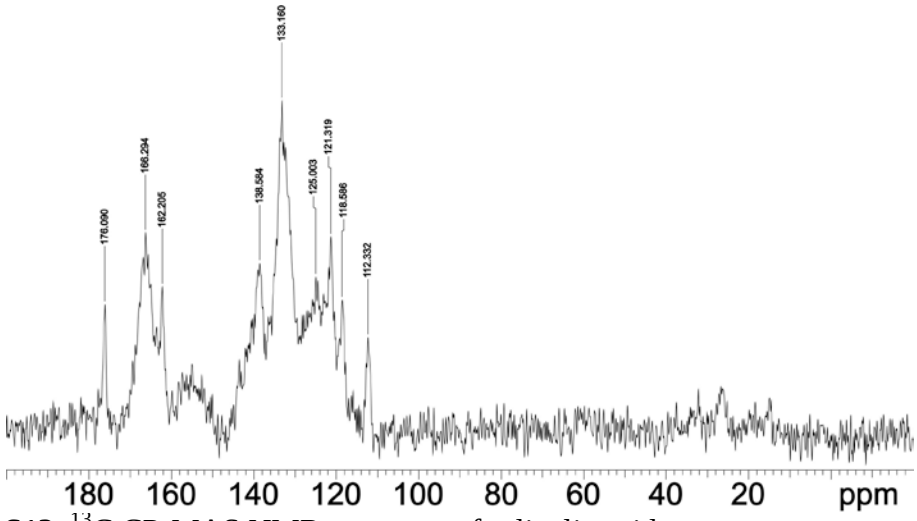

Figure S13. ^{13}C CP-MAS NMR spectrum of salicylic acid.

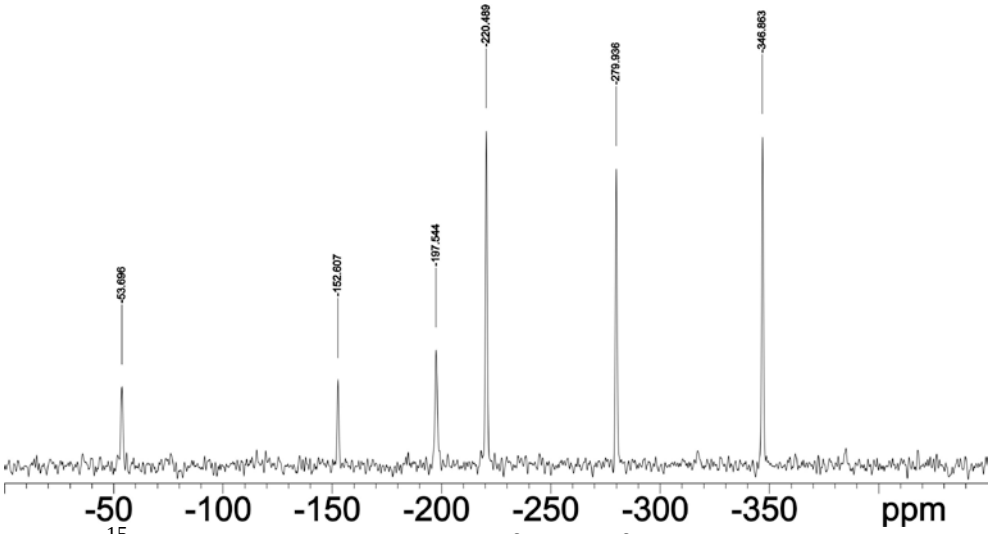

Figure S14. ^{15}N CP-MAS NMR spectrum of sildenafil.

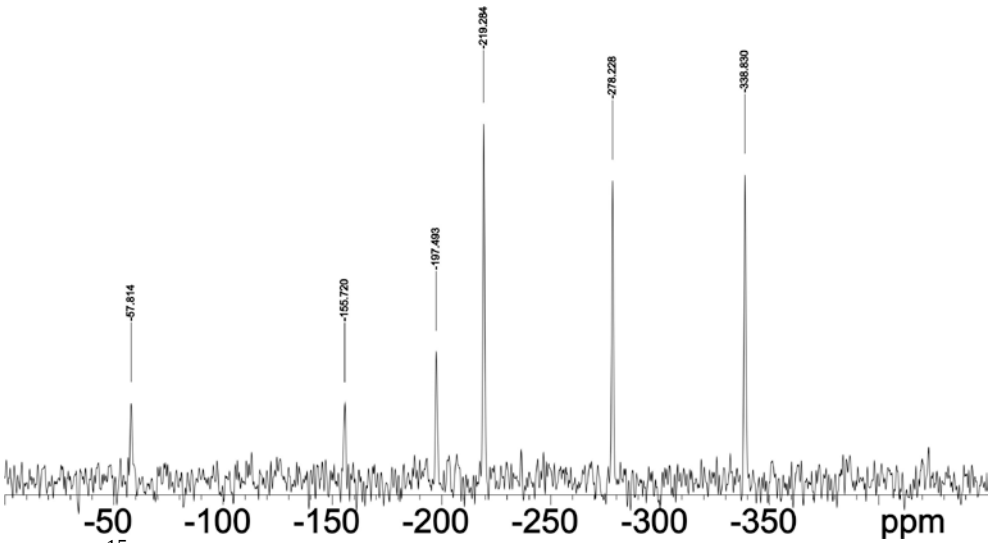

Figure S15. ^{15}N CP-MAS NMR spectrum of sample **1**.

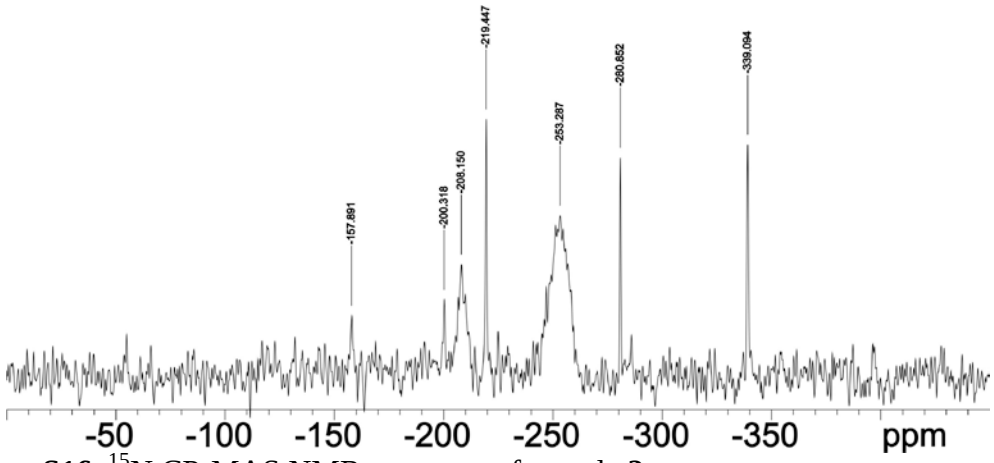

Figure S16. ^{15}N CP-MAS NMR spectrum of sample **2**.

5. Intrinsic dissolution rate studies

Intrinsic dissolution rates were examined on PHARMA TEST dissolution apparatus (*VanKel* intrinsic dissolution apparatus) at 100 rpm. In a typical experiment, 100 mg of the solid sample was pressed into a pellet at 1.5 MT for 1 min. IDRs were examined in three different media, namely degassed water, degassed water with 1.2% NaCl and a pH=1.2 buffer. The volume of the dissolution media was 900 mL. The obtained solutions were collected in five-minute intervals, and analyzed using a *Carry* 50 spectrophotometer at 292 nm.

6. HPLC analyses

The HPLC analysis of compound **2** was performed on an *Agilent* (1100 Series) instrument that was fitted with a *Phenomenex Intersil ODS-3* column (150x4.60mm, 5 μm particle size). The mobile phase was composed of a KH_2PO_4 buffer (pH=2.3; 65%) and acetonitrile (35%). The components of solid **2** were eluted over 8 min at rate of 1 mL min^{-1}. The column was kept at a temperature of 40°C. The separation of the solid's components was monitored in real time by a *Carry* 50 spectrophotometer at 292 nm.

The composition of solid **2** was determined by calculating retention factors for acetyilsalicylic acid and salicylic acid. A typical HPLC chromatogram for solid **2** is shown in Fig. S17, while the data used to determine the composition of solid **2** is shown in Table S1. and S2.

Table S1. Standard solution of sildenafil, acetylsalicylic acid and salicylic acid used to determine the composition of solid **2** *via* HPLC analyses.

compound	m/mg	V/mL	c/mg mL^{-1}	area	RF
sildenafil	51.22	50	1.024	4610.06	**4500.25**
acetylsalicylic acid	53.23	50	1.065	2665.56	**2503.81**
salicylic acid	50.37	50	1.007	6498.41	**6450.67**

Table S2. Composition of solid **2**, as determined *via* HPLC analyses.

batch	m/mg	V/mL	c/mg mL^{-1}	compound	area	RF	assay*/%
1	31.36	25	1.25	acetylsalicylic acid	794.90	633.69	**25.3**
				salicylic acid	1556.74	1241.03	**19.2**
2	26.91	25	1.08	acetylsalicylic acid	682.65	634.20	**25.3**
				salicylic acid	1316.57	1223.13	**19.0**
3	21.04	25	0.84	acetylsalicylic acid	499.82	593.89	**23.7**
				salicylic acid	1017.29	1208.75	**18.7**
4	27.98	25	1.12	acetylsalicylic acid	745.83	666.39	**26.6**
				salicylic acid	1240.61	1108.48	**17.2**
5	25.74	25	1.03	acetylsalicylic acid	627.40	609.36	**24.3**
				salicylic acid	1318.43	1280.53	**19.9**

* theoretical *w*/*w*%: sildenafil – 59.9%, **acetylsalicylic acid – 22.7%**, **salicylic acid – 17.4%**

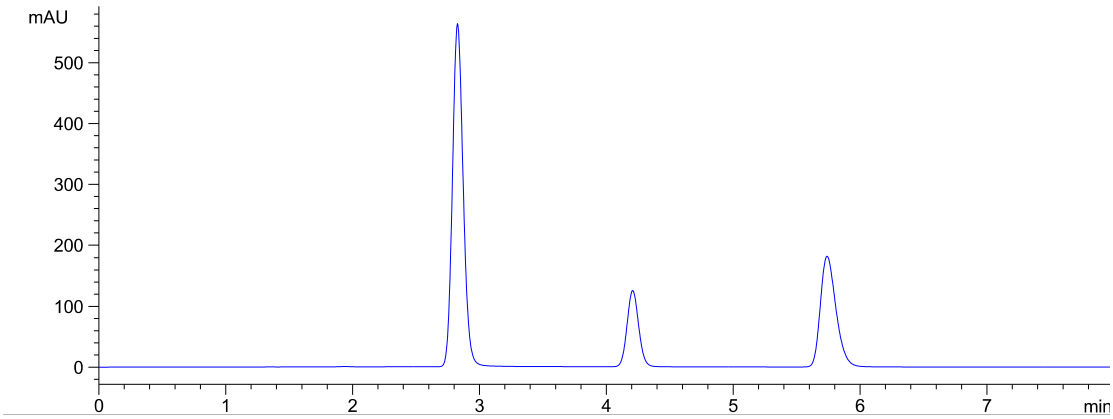

Figure S17. A typical HPLC chromatogram of solid **2**.

7. References

1. PANalytical B. V., Almelo, The Netherlands, 2006.
2. R. W. W. Hooft, Nonius BV, Delft, The Netherlands, 1998.
3. Z. Otwinowski, W. Minor in *Methods in Enzymology*, ed. C. W. Carter Jr and R. M. Sweet , 1997, Vol. 276 (*Macromolecular Crystallography*, Part A), pp. 307-326.
4. G. M. Sheldrick, *Acta Cryst.*, 2008, **A64**, 112-122.