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 CuKα 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 CuKα 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 \(U_{eq}\) 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 \textit{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 \textit{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.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure_s1.png}
\caption{DSC (blue) and TG (green) thermograms of solid 1 ($t_{\text{melting}} = 148.0$ °C).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure_s2.png}
\caption{DSC (blue) and TG (green) thermograms of solid 2 ($t_{\text{melting}} = 134.3$ °C).}
\end{figure}
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).](image)

1H, 13C and 15N 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 adamantane. 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 (\(\delta\) -355.7 ppm, as compared to nitromethane at \(\delta\) 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.
Figures S7, S8, and S9. 

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.
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 KH₂PO₄ 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 acetylsalicylic 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.

<table>
<thead>
<tr>
<th>compound</th>
<th>m/mg</th>
<th>V/mL</th>
<th>c/mg mL⁻¹</th>
<th>area</th>
<th>RF</th>
</tr>
</thead>
<tbody>
<tr>
<td>sildenafil</td>
<td>51.22</td>
<td>50</td>
<td>1.024</td>
<td>4610.06</td>
<td>4500.25</td>
</tr>
<tr>
<td>acetylsalicylic acid</td>
<td>53.23</td>
<td>50</td>
<td>1.065</td>
<td>2665.56</td>
<td>2503.81</td>
</tr>
<tr>
<td>salicylic acid</td>
<td>50.37</td>
<td>50</td>
<td>1.007</td>
<td>6498.41</td>
<td>6450.67</td>
</tr>
</tbody>
</table>
Table S2. Composition of solid 2, as determined via HPLC analyses.

<table>
<thead>
<tr>
<th>batch</th>
<th>m/mg</th>
<th>V/mL</th>
<th>c/mg mL^-1</th>
<th>compound</th>
<th>area</th>
<th>RF</th>
<th>assay*/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31.36</td>
<td>25</td>
<td>1.25</td>
<td>acetylsalicylic acid</td>
<td>794.90</td>
<td>633.69</td>
<td>25.3</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>salicylic acid</td>
<td>1556.74</td>
<td>1241.03</td>
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<tr>
<td>2</td>
<td>26.91</td>
<td>25</td>
<td>1.08</td>
<td>acetylsalicylic acid</td>
<td>682.65</td>
<td>634.20</td>
<td>25.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>salicylic acid</td>
<td>1316.57</td>
<td>1223.13</td>
<td>19.0</td>
</tr>
<tr>
<td>3</td>
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<td>25</td>
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<td>499.82</td>
<td>593.89</td>
<td>23.7</td>
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<td></td>
<td></td>
<td></td>
<td>salicylic acid</td>
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<td>1208.75</td>
<td>18.7</td>
</tr>
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<td>4</td>
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<td>25</td>
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<td>745.83</td>
<td>666.39</td>
<td>26.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td>salicylic acid</td>
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<td>1108.48</td>
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<tr>
<td>5</td>
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<td>25</td>
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<td>acetylsalicylic acid</td>
<td>627.40</td>
<td>609.36</td>
<td>24.3</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>salicylic acid</td>
<td>1318.43</td>
<td>1280.53</td>
<td>19.9</td>
</tr>
</tbody>
</table>

* 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