

A rational approach to screen for hydrated forms of the pharmaceutical derivative magnesium naproxen using liquid-assisted grinding

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EXPERIMENTAL

All reagents and solvents were purchased from Sigma-Aldrich Chemical Co. and were used without further purification, except for magnesium oxide which was heated to 600 °C before use and kept in a desiccator over P₄O₁₀.

All LAG reactions were performed by placing 200 mg of a mixture of solid reactants MgO (16 mg) and **Hnap** (194 mg) into a 10 mL stainless steel jar, along with 50 µL of the grinding liquid and two 7 mm diameter stainless steel balls. The mixture was then ground for 30 min in a Retsch MM200 grinder mill operating at 30 Hz. During grinding the temperature of the jars increased by approximately 4 °C.

Solution synthesis of magnesium naproxen

The solution synthesis of magnesium naproxen was conducted by vigorously mixing 5 mmol (1.02 g) of MgCl₂·6H₂O and 10 mmol of naproxen (2.30 g) with 40 mL of a 1:1 mixture (v/v) of ethanol and water. To the vigorously stirred suspension was then added a solution of 10 mmol (0.40 g) of NaOH in 10 mL of a 1:1 (v/v) mixture of ethanol and water. Upon the addition of NaOH and gentle heating up to 60 °C the suspension turned into a colourless solution. After cooling and slow evaporation over 12 hours was obtained the product as fine white needles. The needles were separated by filtration, washed with small amount of ethanol and dried in air. Yield: 1.50 g

Mechanochemical synthesis of magnesium naproxen hydrate forms.

Compounds **1**, **2** and **3** were synthesised mechanochemically, by grinding 0.016 g of magnesium oxide with 0.194 g of naproxen in the presence of a suitable liquid for 30 minutes. For the synthesis of **1**, 75 µL of water was used as the grinding liquid. For the synthesis of **2** the grinding liquid was 50 µL of an 8:2 or 9:1 (v/v) mixture of ethanol and water, while for the synthesis of **3** 50 µL of a 6:4 or 1:1 (v/v) mixture of *i*-propanol and water were used.

SOLID-STATE NMR SPECTROSCOPY

Solid-state ¹³C NMR experiments on compounds **1** and **3** were performed on a standard-bore Bruker Avance III spectrometer operating at 500.13 MHz using a Bruker 4 mm double-resonance probe with MAS at 12 kHz. The spectra were referenced using the chemical shift of the carbonyl carbon of glycine at 174.1 ppm with respect to TMS. A recycle delay of 5 s was used with a SPINAL-64 proton decoupling at 100 kHz. The spectrum of **1** was acquired in 256 scans using a CP contact time of 2 ms and a recycle delay of 5 s while one spectrum of **3** was acquired in 32 scans using a CP contact time of 2 ms using a recycle delay of 10 s and the other was acquired in 32 scans using a CP contact time of 100 µs and a recycle delay of 5 s.

FTIR-ATR SPECTROSCOPY

Reflectance FTIR spectra of all samples were recorded on a ThermoNicolet NEXUS spectrometer equipped with the Golden Gate ATR accessory, in the range 3600-600 cm⁻¹.

THERMOGRAVIMETRIC ANALYSIS (TGA)

Thermogravimetric measurements were performed on a Mettler Toledo TGA/SDTA851^e thermobalance, using samples of 8-20 mg weight placed in 70 µL open aluminium oxide pans. Measurements were performed in a dynamic atmosphere (50 cm³/min) of either nitrogen or air, and at a heating rate of either 5 or 10 K min⁻¹.

POWDER X-RAY DIFFRACTION

PXRD data for screening experiments was collected on a laboratory Philips X'Pert Pro diffractometer, equipped with an X'celerator RTMS detector, using Ni-filtered CuK α radiation, using a flat plate configuration. Data were typically collected in the 2θ range 5–40°.

Synchrotron experiments were performed on the High Resolution Powder Diffractometer ID31 at the ESRF with an energy of about 40 keV (wavelength 0.30659 Å). The samples were spinning while acquiring the data. The detection system is composed of a bank of 9 detectors, each one preceded by a Si(111) analyser crystal. Separation between detectors is about 2 degrees. Four patterns were collected at a speed of 1 degree/minute for the first two scans and 2 degrees/min for the scans 3 and 4. Total data collection time was 110 minutes. Scans were merged to obtain the final pattern with binning of 0.001. No corrections were applied to the pattern.

STRUCTURE DETERMINATION OF COMPOUND 3

The powder pattern was indexed using an orthorhombic unit cell. Likely systematic extinctions suggested the $P2_12_12_1$ space group. Structure solution was then attempted by simulated annealing (SA) with the naproxen moiety (geometry taken from the crystal structure of the monohydrate **2**) treated as a rigid body and oxygen and magnesium atoms treated with no restraints. Occupancies of magnesium and oxygen atoms and the torsion angles determining orientations of the substituents on the naphthalene ring of naproxen moiety were also included in SA. Position and orientation of the naproxen moiety was found quickly after which it became clear that the coordinates of oxygen and magnesium atoms along the a axis can be forced to remain in the range from 0.2 to 0.3. After the likely coordination chain was recognised and with the occupancy of the magnesium atom around 0.5, the structural model was introduced into Rietveld refinement and distance and bond angle restraints on the coordination chain were included. The naproxen moiety was refined as a rigid body. All calculations (indexing, SA and Rietveld refinement) were undertaken using the program Topas (version 4.1, Bruker-AXS, Karlsruhe, Germany). Structure determination starting from synchrotron data led to essentially the same structure (Figure S1).

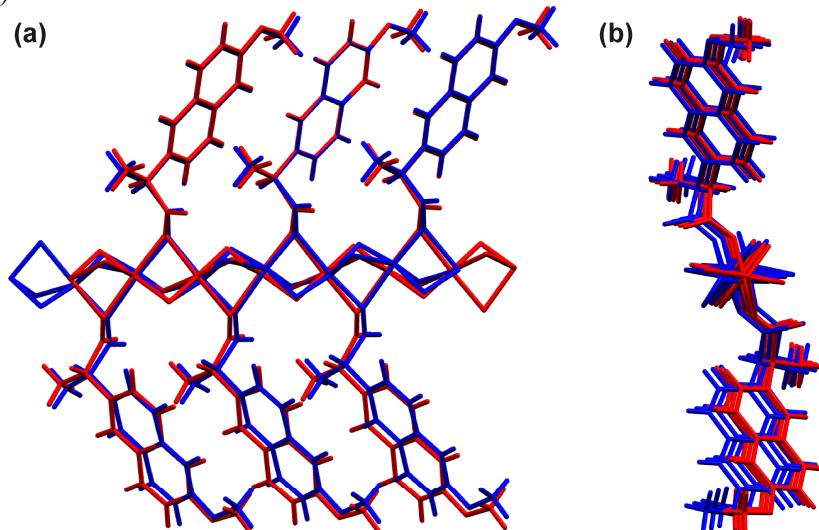


Figure S1. Overlay of fragments from the structure of **3** determined using laboratory (red) and synchrotron (blue) data: (a) viewed along the crystallographic b -direction and (b) viewed along the crystallographic c -direction

ATTEMPTED STRUCTURE DETERMINATION OF COMPOUND 1

The powder pattern was indexed using an orthorhombic unit cell. Likely systematic extinctions suggested the $P2_12_12_1$ space group. Unit cell and the space group of **1** were confirmed using a Le Bail type fit. Since the material contained small amounts of **Hnap** and MgO, they were included into refinement using the Rietveld method (Figure S2). Structure solution was then attempted by simulated annealing (SA) with the naproxen moiety (geometry taken from the crystal structure of the monohydrate **2**) treated as a rigid body but with torsion angles determining orientations of the substituents on the naphthalene ring of naproxen moiety also included in SA in order to determine the correct conformation of **nap**⁻. To determine the nature of the hydrated magnesium ion, various structural fragments were tested. These ranged from a hexacoordinated magnesium atom with a more or less restrained geometry to optimisations using independently one magnesium atom and 6 to 9 oxygen atoms, occupancies of which were also included in SA constrained to remain in the range from 0.1 to 1.5. Position, orientation and likely conformation of the naproxen moiety were found quickly but the arrangement of magnesium and oxygen atoms did not yield a convincingly good model with the laboratory data at hand (Figure S3). All calculations (indexing, Le Bail refinement, SA) were undertaken using the program Topas (version 4.1, Bruker-AXS, Karlsruhe, Germany).

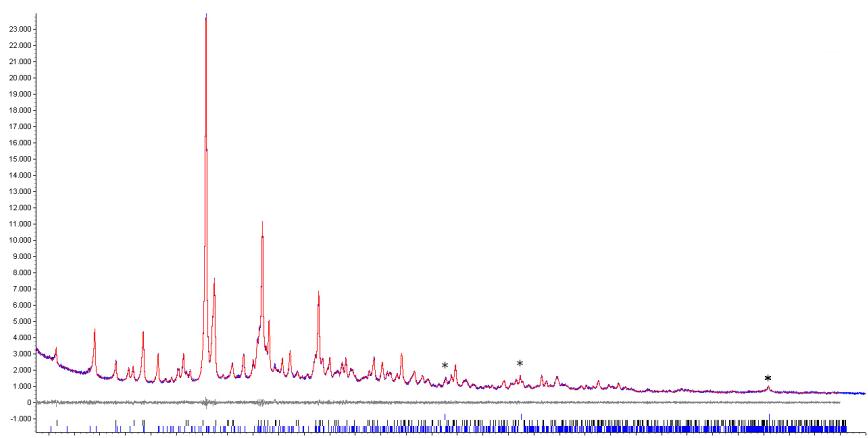


Figure S2. Le Bail-type fit for **1** with small amounts of **Hnap** and MgO. Whereas the fit is very good, the positions of all water molecules could not be determined. Asterisks mark reflections belonging to MgO, while black tick marks designate **Hnap** and blue designate **1**. Colour code: blue – measured, red – calculated, grey – difference.

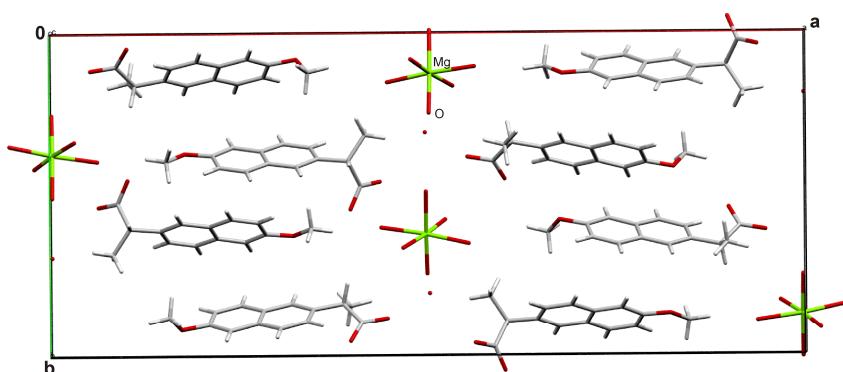


Figure S3. Preliminary model of the structure of **1**, viewed along the crystallographic *c*-direction. The model corresponds to the composition $Mg(nap)_2 \cdot 7H_2O$.

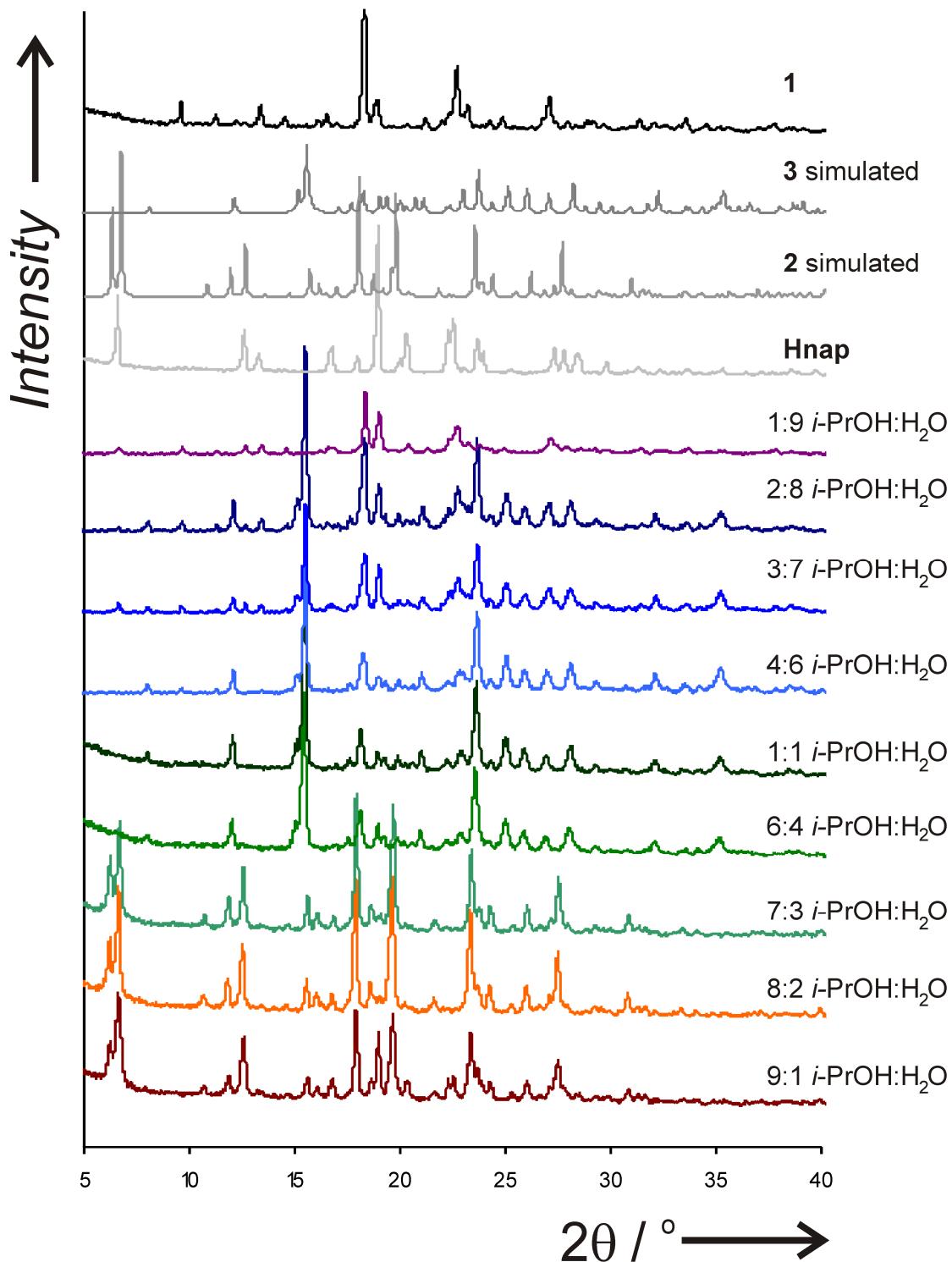


Figure S4. PXRD patterns of (top to bottom): measured pattern for **1**; simulated pattern for **3**; simulated pattern for **2**; PXRD pattern of **Hnap**; patterns of a mixture of MgO and **Hnap** after grinding with mixtures of *i*-PrOH and water in ratios 1:9; 2:8; 3:7; 4:6; 1:1; 6:4; 7:3; 8:2 and 9:1.

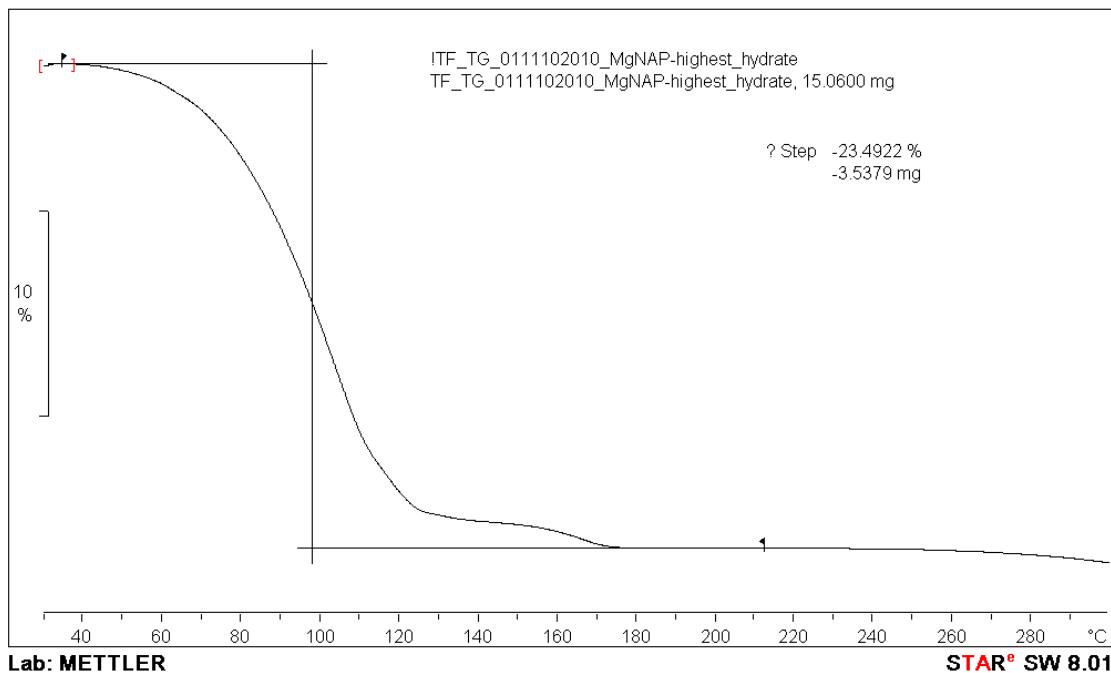


Figure S5. Example TGA curve for compound **1**, measured in a dynamic atmosphere of nitrogen ($50 \text{ cm}^3 \text{ min}^{-1}$) with a heating rate of 10 K min^{-1} . Calculated fraction of water for composition $\text{Mg(nap)}_2 \cdot 8\text{H}_2\text{O} = 23.0\%$; measured loss of weight upon heating = 23.5% .

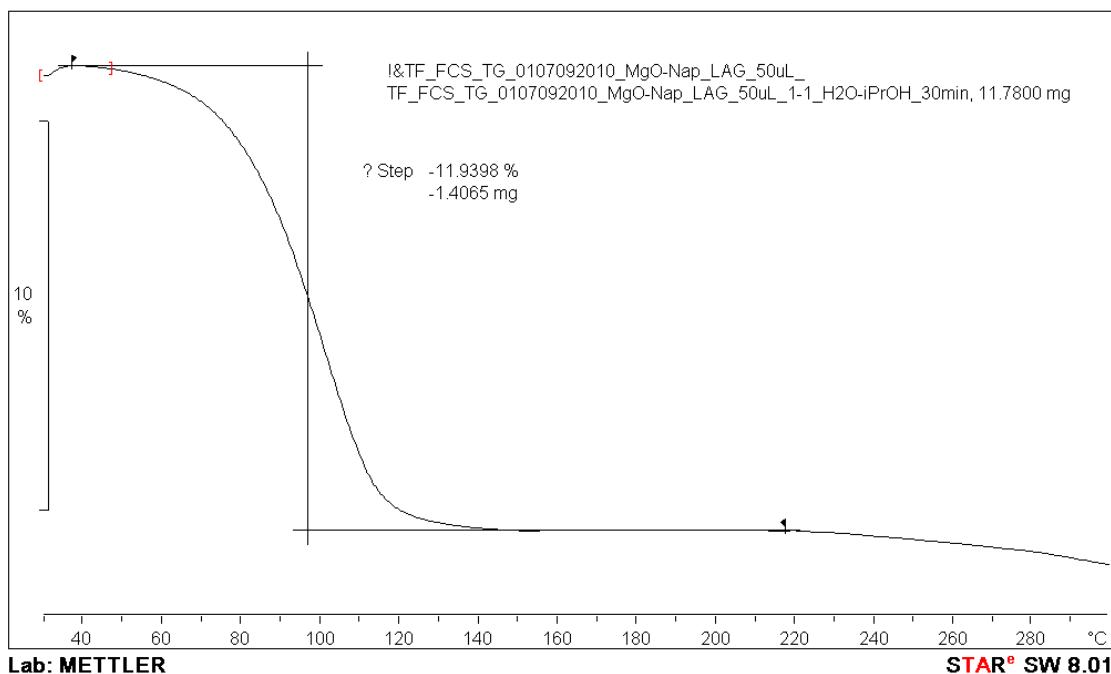


Figure S6. Example TGA curve for compound **3**, measured in a dynamic atmosphere of nitrogen ($50 \text{ cm}^3 \text{ min}^{-1}$) with a heating rate of 5 K min^{-1} . Calculated fraction of water for composition $\text{Mg(nap)}_2 \cdot 4\text{H}_2\text{O} = 13.0\%$; measured loss of weight upon heating = 11.9% .

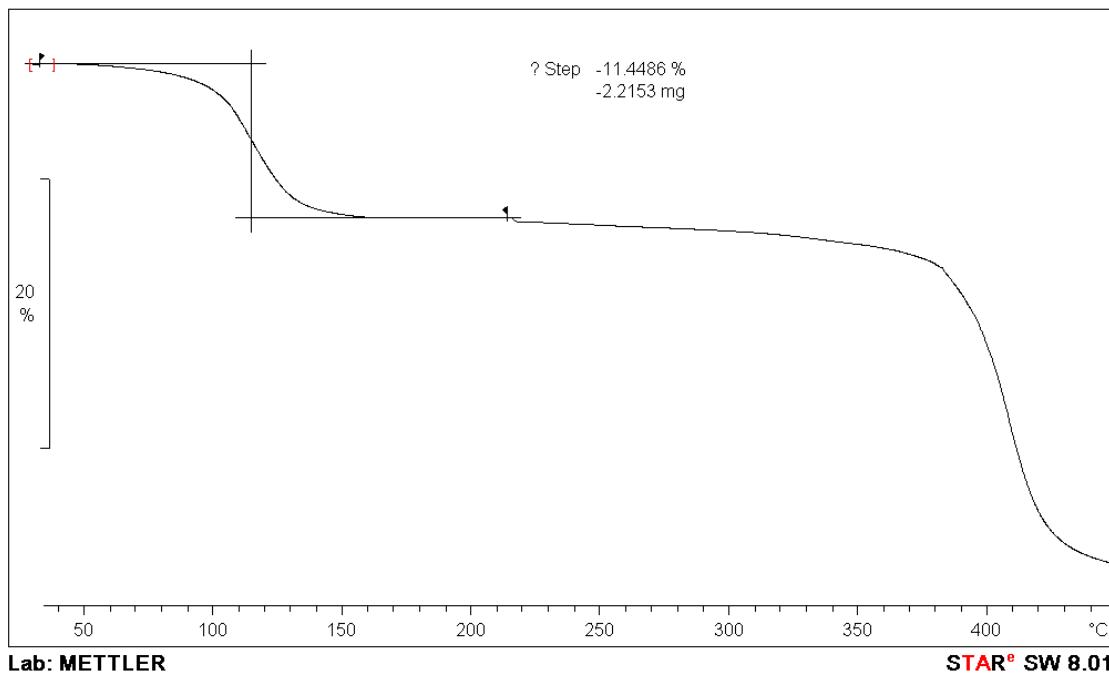


Figure S7. Example TGA curve for compound **3**, measured in a dynamic air atmosphere ($50 \text{ cm}^3 \text{ min}^{-1}$) with a heating rate of 10 K min^{-1} . Calculated fraction of water for composition $\text{Mg(nap)}_2 \cdot 4\text{H}_2\text{O} = 13.0\%$; measured loss of weight upon heating = 11.4%.

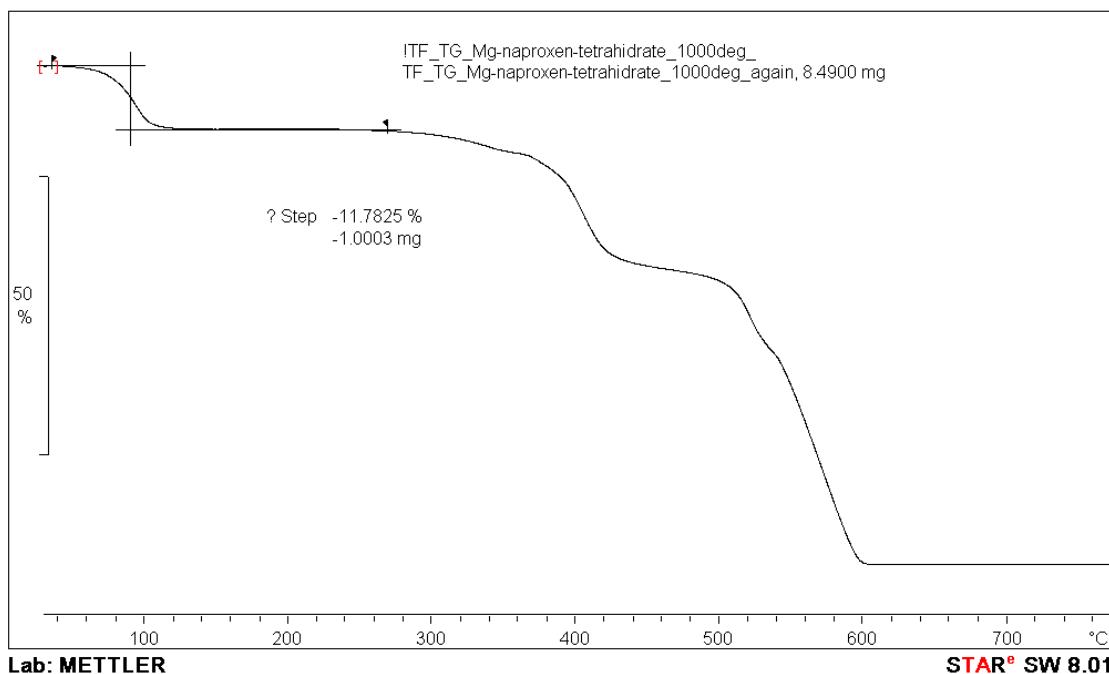


Figure S8. Example TGA curve for compound **3**, measured in a dynamic air atmosphere ($50 \text{ cm}^3 \text{ min}^{-1}$) with a heating rate of 10 K min^{-1} . Calculated fraction of water for composition $\text{Mg(nap)}_2 \cdot 4\text{H}_2\text{O} = 13.0\%$; measured loss of weight upon heating = 11.8%.

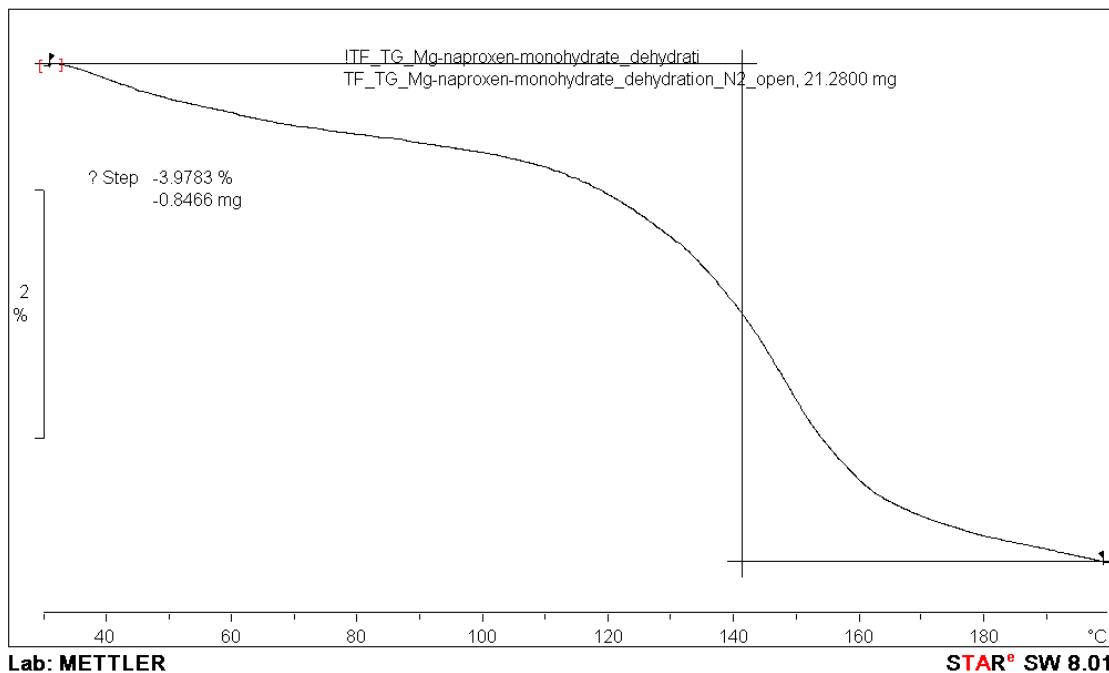


Figure S9. Example TGA curve for compound **2**, measured in a dynamic nitrogen atmosphere ($50 \text{ cm}^3 \text{ min}^{-1}$) with a heating rate of 10 K min^{-1} . Calculated fraction of water for composition $\text{Mg}(\text{nap})_2 \cdot \text{H}_2\text{O} = 3.6\%$; measured loss of weight upon heating = 4.0%.

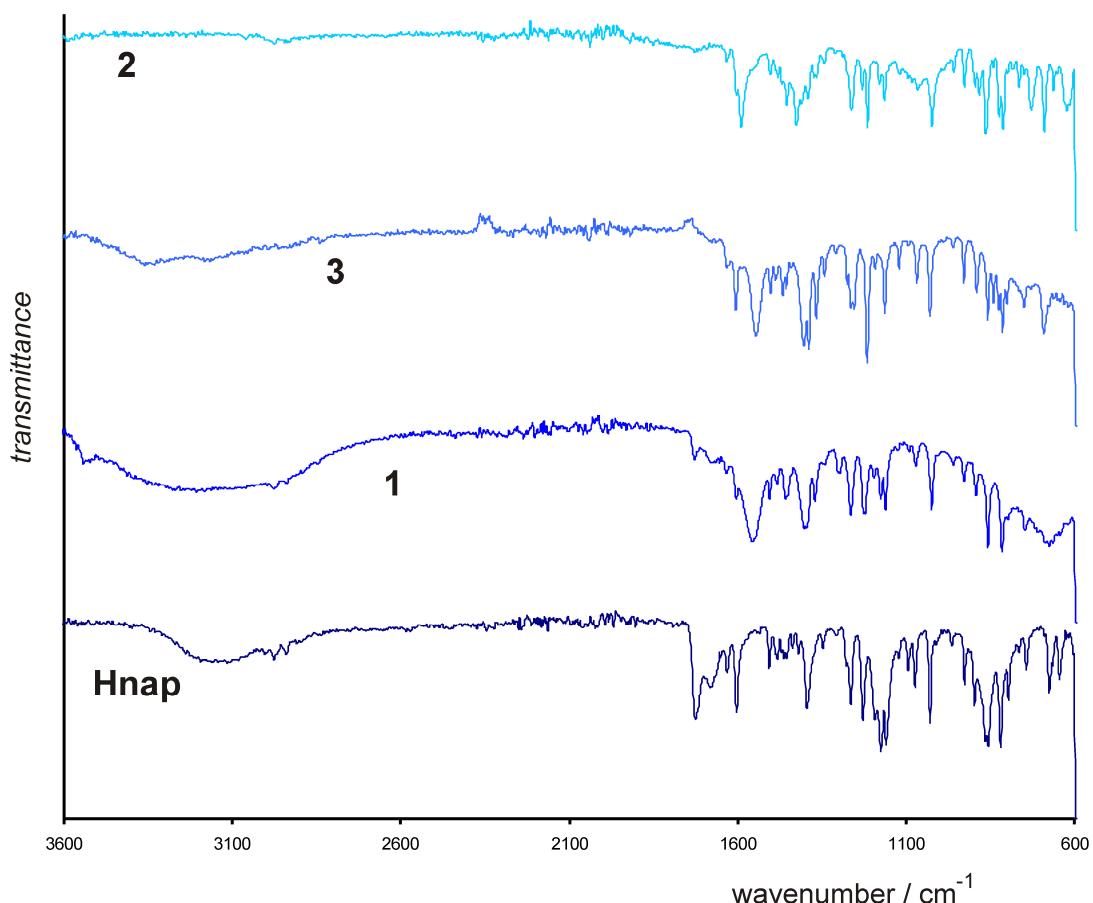


Figure S10. FTIR-ATR spectra (top to bottom) for compounds **2**; **3**; **1** and naproxen.