Supporting Information
Improvement of the water solubility of tolfenamic acid by new multiple component crystals produced by mechanochemical methods

Figures S1: Raman spectra of all prepared compounds.

a) Raman spectrum of HTA Form I.

b) Raman spectrum of HTA Form II.
c) Raman spectrum of NaTA·0.5 H₂O.

d) Raman spectrum of NaTA HT Form

e) Raman spectrum of NaTA·HTA·H₂O/NaHCO₃.
f) Raman spectrum of NaTA·HTA·0.5NaAc·2H₂O.

g) Raman spectrum of IMH-TA·HTA.

Figures S2: IR-ATR spectra of all prepared compounds

a) IR (KBr) spectrum of HTA Form I.
b) IR (KBr) spectrum of HTA Form II.

c) IR (KBr) spectrum of NaTA·0.5H₂O.

d) IR (ATR) spectrum of NaTA HT Form.
e) IR (KBr) spectrum of NaTA·HTA·H₂O/NaHCO₃.

f) IR (KBr) spectrum of NaHCO₃.

g) IR (KBr) spectrum of NaTA·HTA·0.5NaAc·2H₂O.
h) IR (KBr) spectrum of IMH-TA·HTA.

i) IR (KBr) spectrum of Imidazole (IM).
Figures S3: Calorimetric and Thermogravimetric curves of all compounds

a) DSC and TGA curves of HTA Form I (batch)

b) DSC curve of HTA Form II (the Form I $\rightarrow$ Form II conversion reported in literature was not observed)
c) DSC and TGA curves of NaTA·0.5H₂O. The TGA curve of NaTA·0.5H₂O shows two steps attributed to adsorbed and stoichiometric H₂O loss, respectively. The DSC is quite complex since presents solid-solid transitions at 67.3 and 92.3°C leading to polymorphic mixtures as observed by ¹³C CPMAS measurements (Figure S9) acquired on heated samples. On the other hand, the peak at 191.4 is assigned to the formation of NaTA HT Form.

d) DSC and TGA curves of NaTA·HTA·H₂O/NaHCO₃. The two steps observed in the TGA curve are assigned to the release of CO₂ and H₂O, respectively. The high temperature regions (above 200°C) of TGA and DSC
of NaTA·HTA·H₂O/NaHCO₃ is different from those of NaTA·0.5H₂O even if they both lead to HTA HT Form (as confirmed by $^{13}$C CPMAS spectra). This is probably due to the different heating methods used or to the presence of small amount of impurities.

e) DSC and TGA curves of NaTA·HTA·0.5NaAc·2H₂O.

f) DSC and TGA curves of IMH-TA·HTA.
Figures S4: XRPD patterns of co-formers of HTA.

(a) Experimental pattern of NaHCO$_3$.

(b) Experimental pattern of Sodium Acetate (NaAc).
c) Experimental pattern of imidazole (IM).

**Scheme 1**: Temperature ramp applied to NaTA·0.5 H₂O
k) VT XRPD patterns of NaTA·0.5 H₂O from 25°C (r.t.) to 210°C.

Scheme 2: Temperature ramp applied to NaTA·HTA·H₂O/NaHCO₃
1) VT XRPD patterns of NaTA·HTA·H₂O/NaHCO₃ from r.t. (25°C) to 225 °C.

2) XRPD comparison between NaTA·HTA·H₂O/NaHCO₃ (after heating at 225°C), NaTA·0.5 H₂O (after heating at 210°C) and NaTA HT Form.
A Variable Temperature (VT) XRPD study was performed and reported in Figures S3-c and S3-d for NaTA·0.5 H₂O and NaTA·HTA·H₂O/NaHCO₃, respectively. The ramp programs (Schemes 1 and 2) were set according to the most significant thermal transitions observed in the DSC and TGA data. The temperature was alternatively increased and decreased in order to check the irreversibility of the conversion processes. The VT XRPD analysis confirms the conversion of both NaTA·0.5 H₂O and NaTA·HTA·H₂O/NaHCO₃ into the same NaTA·HT Form, in agreement with the solid-state NMR and Raman characterization.

**Figures S5:** Dissolution kinetic tests (DKT)

**Table 1:** Standard solutions of pure HTA for the calibration curve

<table>
<thead>
<tr>
<th>Solution</th>
<th>Conc (mg/l)</th>
<th>ABS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.00E-01</td>
<td>1.68E+00</td>
</tr>
<tr>
<td>2</td>
<td>1.00E-01</td>
<td>4.63E-01</td>
</tr>
<tr>
<td>3</td>
<td>1.00E-00</td>
<td>6.49E-02</td>
</tr>
<tr>
<td>4</td>
<td>1.00E-01</td>
<td>2.01E-02</td>
</tr>
<tr>
<td>5</td>
<td>1.00E-02</td>
<td>1.25E-02</td>
</tr>
<tr>
<td>6</td>
<td>1.00E-03</td>
<td>2.08E-02</td>
</tr>
</tbody>
</table>

UV absorption spectrum of Solution 2.

Calibration Curve of HTA at 286.9 nm
$y = 41.492x + 0.0228$

$R^2 = 0.9996$
Figure S6: $^{13}$C CP MAS of NaTA polymorphs mixture. $^{13}$C CPMAS spectrum of NaTA polymorphic mixture obtained from HTA salification with NaOH; multiplicity and bandwidth of the signals highlight the co-presence of different polymorphic forms of NaTA.

Figure S7: 2D $^1$H-$^{13}$C FSLG on-resonance HETCOR spectrum of NaTA·HTA·0.5NaAc·2H$_2$O. 2D experiment acquired with a short contact times (100 µs) for highlighting only the short- (single bond) spatial proximities.
Figure S8: $^{13}$C CPMAS of NaTA·HTA·0.5NaAc·2H$_2$O after thermal treatment. $^{13}$C (100 MHz) CPMAS spectra of a) sodium acetate (batch of Sigma Aldrich), b) NaTA·HTA·0.5NaAc·2H$_2$O, c) NaTA·HTA·0.5NaAc·2H$_2$O heated at 150°C and d) NaTA·HTA·0.5NaAc·2H$_2$O heated at 250°C recorded at 12 kHz.
Figure S9: Dissolution rate profiles of the samples. HTA (red line with red circle), NaTA·0.5H₂O (blue line with blue square), NaTA HT Form (black line with yellow circle), IMH-TA·HTA (green line with green triangle), NaTA·HTA·H₂O/Na₂CO₃· (black line with black triangle) and NaTA·HTA·0.5NaAc·2H₂O (black line with white circle respectively)