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| Original Citation: | |
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| | |
| | |
| Availability: | |
| This version is available http://hdl.handle.net/2318/149571 | since |
| | |
| | |
| Published version: | |
| DOI:10.1039/C4CE00549J | |
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This is an author version of the contribution published on: Questa è la versione dell'autore dell'opera:

CRYSTENGCOMM, v. 16 (2014), 8252-8262.

DOI: 10.1039/c4ce00549j

The definitive version is available at: La versione definitiva è disponibile alla URL: http://pubs.rsc.org/en/content/articlelanding/2014/ce/c4ce00549j#!divAbstract

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

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Received (in XXX, XXX) XthXXXXXXX 20XX, Accepted Xth XXXXXXXX 20XX 5 DOI: 10.1039/b000000x

Tolfenamic Acid (HTA) is a drug which is characterized by very poor water solubility (13.6 nM in acidic conditions) and moderate solubility in ethanol (0.17 M). A series of new multicomponent crystals have been obtained, by applying mechanochemical methods (i.e. kneading), to mixtures of HTA with sodium acetate, sodium carbonate, sodium hydroxide and imidazole. These reactions resulted in two salts

- ¹⁰ (NaTA·0.5H₂O and NaTA HT Form), a co-crystal of salts (NaTA·HTA·0.5NaAc·2H₂O) and two salt co-crystals (NaTA·HTA·H₂O/NaHCO₃ and IMH-TA·HTA). Due to the lack of suitable crystals for single crystal X-ray diffraction analysis, the structural features of the samples have been characterized by solid-state NMR (¹H MAS, ¹³C CPMAS, ¹H-¹³C FSLG LG-CP HETCOR and ¹⁵N CPMAS), IR(ATR) and Raman spectroscopies, VT-XRPD and elemental analysis. The evaluation of thermal stability and
- ¹⁵ dissolution behavior was performed using thermogravimetry, differential scanning calorimetry and dissolution kinetic tests. The new solid-state forms show better thermal stability than pure HTA and an improved dissolution rate, which is most pronounced in NaTA·HTA·H₂O/NaHCO₃, the NaTA HT Form and NaTA·0.5H₂O.

20 Introduction

Multicomponent crystal formation (salts and co-crystals) is an effective means with which to tune the properties of a molecule or, in the pharmaceutical field, of an active pharmaceutical ingredient (API) by changing its crystal packing.¹ A co-crystal is ²⁵ a multicomponent molecular crystal; that is, a crystalline

- substance formed of two or more chemically different molecules.² Thus solvates, hydrates and both stoichiometric and non-stoichiometric lattice inclusion compounds are included in this definition.³ With respect to the pure polymorphism ³⁰ phenomenon, co-crystal formation provides much more in terms
- of possibilities for modulating crystal packing and this is due to the choice of two parameters: the co-former and the type of weak interaction.⁴ The use of inorganic salts as co-formers has already been explored, by our group, as an effective method for
- ³⁵ producing ionic co-crystals and salt co-crystals of barbituric acid.⁵ The difference between ionic co-crystals and salt cocrystals is found in the type of co-former. Ionic co-crystals are formed of an organic molecule and an ionic salt (i.e. alkali halide) in the same asymmetric unit, while salt co-crystals are formed of ⁴⁰ an organic molecule and one of its salts in the same asymmetric
- unit.⁶

Tolfenamic acid (HTA, 2-[(2-methyl-3-chlorophenyl) amino] benzoic acid – Scheme 1) is a drug which belongs to the fenamate family. It is a potent, well-tolerated non-steroidal anti-⁴⁵ inflammatory drug (NSAID) which displays low gastroulcerogenicity,⁷ low overall toxicity and high therapeutic indices as well as analgesic and antipyretic properties.⁸ Recent studies have revealed that it is a Cox-2 inhibitor.⁹ It is also extensively used in both human and veterinary medicine for its ⁵⁰ analgesic and antipyretic properties.¹⁰

A common property of fenamates is their general lack of solubility in water and in other common organic solvents (obviously their solubility is influenced by their polymorphic form)¹¹ thus HTA belongs to class II of the Biopharmaceutics ⁵⁵ Classification System (high permeability in cells and low solubility in water).¹²

HTA is known to exist in at least five different polymorphic forms.¹³ The most prominent are anhydrous Form I and Form II which show very poor water solubility.¹⁴ In order to improve the ⁶⁰ water solubility and, thus the biopharmaceutical properties of HTA, we herein report a synthetic strategy for new HTA cocrystal forms which is based on mechanochemical and solution reactions between HTA, inorganic reagents [NaOH, Na₂CO₃ and sodium acetate (NaAc)] and an organic compound such as ⁶⁵ imidazole (IM). IM is used as a precursor for many pharmaceutical compounds, but is toxic (LD₅₀ in pig= 760 mg/kg), and thus not therapeutically used.¹⁵ Nevertheless, we decided to use IM as model co-former in order to study the possibility of an interaction with the COOH group of HTA.

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Table 1 Summary of the performed experiments involving HTA and additional components (k = kneading, h= heating).

| Comp | onents | Preparation | Class | Formula/Name | Ratio |
|--|---------------------------------|--|--|--|-------|
| HTA | NaOH | Salification | salt | NaTA polymorphic mixture | 1:1 |
| NaTA 1 | mixture | k (1-BuOH, THF, DMF, H ₂ O) | salt | NaTA•0.5 H₂O | |
| HTA | Na ₂ CO ₃ | k (EtOH/H ₂ O 2:1) | heterogeneous mixture with a salt co-crystal | NaTA·HTA·H ₂ O/NaHCO ₃ | 2:1 |
| HTA | NaAc | k (EtOH 99%) | co-crystal of salts | NaTA·HTA·0.5NaAc·2H ₂ O | 2:1.5 |
| NaTA·0.5H ₂ O 2H₂O/N | or NaTA·HTA IaHCO3 | h (170-180°C) | salt | NaTA HT form | |
| HTA | IM | k (EtOH 99%) | salt | ІМН-ТА•НТА | 2:1 |
| | | | | | |

Experimental and methods

HTA (Tokyo Chemical Industry Company and Sigma ⁵ Aldrich), Na₂CO₃, NaOH, IM and NaAc (all Sigma Aldrich) were used without further purification.

The HTA commercial batch was characterized by solid-state NMR analysis as pure Form I. HTA Form II was reproduced following the method reported in literature¹⁶ only for comparison.

- ¹⁰ All samples were obtained via mechanochemical [kneading with mortar and pestle *i.e.* grinding with catalytic amount (from 50 to 150 μ l, corresponding to two-six drops) of solvent] and solvent techniques.¹⁷·2 Experiments performed and products obtained are summarized in Table 1.
- ¹⁵ The **NaTA polymorphic mixture** was prepared by refluxing 128 mg of HTA and 1 ml of NaOH 0.5 M (stoichiometric ratio 1:1) in 5 ml of absolute EtOH for 3h.

 $NaTA{\cdot}0.5H_2O$ (salt): A white powder of this hemihydrated salt was quantitatively obtained by kneading (H_2O; 50 $\mu l)$ a

- ²⁰ NaTA polymorphic mixture at room temperature for 5 minutes. **NaTA-0.5H₂O** was also obtained by directly kneading (H₂O; 100 μ l) HTA with NaOH. However, this procedure did not allow for precise stoichiometric control because the hygroscopic nature of NaOH makes correct weighing difficult. [Elem. Anal. Calc. for
- $_{25}$ C_{14}H_{12}N_1O_{2.5}Cl_1Na_1: C, 57.45; H, 4.13; N, 4.79; O, 13.67; Cl, 12.11; Na, 7.85 %. Found: C, 57.26; H, 4.29; N, 4.88; O, 13.72; Cl, 12.08; Na, 7.77 %.]

NaTA·HTA·H₂O/NaHCO₃: This is a heterogeneous mixture between NaTA·HTA and NaHCO₃. It was not possible to ³⁰ determine whether H₂O co-crystallizes with NaTA·HTA or NaHCO₃. It occurs as a white powder and was obtained quantitatively by kneading (ethanol/water 2:1; 150 µl) HTA (200 mg) and Na₂CO₃ (40.5 mg), stoichiometric ratio 2:1, at room temperature for 20 minutes. It was not possible to obtain pure ³⁵ NaTA·HTA without NaHCO₃ using different starting material ratios either. The stoichiometric formula:

NaTA·HTA·H₂O/NaHCO₃ was confirmed by solid-state NMR, thermal analysis and elemental analysis. [Elem. Anal. Calc. for $C_{29}H_{28}N_2O_9Cl_2Na_2$: C, 52.34; H, 4.24; N, 4.21; Na, 6.91 %. 40 Found: C, 52.47; H, 4.29; N, 4.08; Na, 6.88 %.]

NaTA·HTA·0.5NaAc \cdot **2H**₂**O**: This co-crystal of salts was obtained as a white powder and in maximal yield by kneading (EtOH 99%, 150 µl) stoichiometric ratios (2:1.5) of HTA (200 mg) and NaAc (90 mg) at room temperature for 20 minutes.

⁴⁵ Solid-state NMR, thermal analysis and elemental analysis indicated that the formula is NaTA·HTA·0.5NaAc·2H₂O. [Elem. Anal. Calc. for $C_{29}H_{28.5}N_2O_7Cl_2Na_2$: C, 55.96; H, 4.62; N, 4.50; Na, 7.39 %. Found: C, 55.78; H, 4.56; N, 4.69; Na, 7.19 %.]

NaTA HT Form (salt): A white powder was obtained after ⁵⁰ heating **NaTA·0.5H₂O** or **NaTA·HTA·H₂O/NaHCO₃** at 170-180°C in a muffle oven (ramp 5°C/min). [Elem. Anal. Calc. for $C_{14}H_{11}N_1O_2Cl_1Na_1$: C, 59.27; H, 3.91; N, 4.94; O, 11.28; Cl, 12.50; Na, 8.10 %. Found: C, 59.07; H, 4.13; N, 4.70; O, 11.46; Cl, 12.46; Na, 8.18 %.]

IMH-TA·HTA (Salt co-crystal): This product (white powder) was obtained by kneading HTA (200 mg) and IM (26 mg) in a 2:1 ratio for 15 minutes in the presence of absolute EtOH (50 μ l). [Elem. Anal. Calc. for C₃₁H₂₈N₄O₄Cl₂: C, 62.95; H, 4.77; N, 9.47 %. Found: C, 62.87; H, 4.66; N, 9.32 %.]



60 Scheme 1 HTA structure with atom labelling.

All solid-state NMR spectra were recorded with a Bruker Avance II 400 instrument operating at 400.23, 100.65 and 40.55 MHz for ¹H, ¹³C and ¹⁵N nuclei, respectively. For ¹³C and ¹⁵N CPMAS (Cross Polarization Magic Angle Spinning) spectra, 65 cylindrical 4 mm o.d. zirconia rotors with a sample volume of 80 μ L were employed. Samples were spun at 12 and 9 kHz for ¹³C and ¹⁵N, respectively. A ramp cross-polarization pulse sequence was used with contact times of 3-5 (13 C) or 4 ms (15 N), a 1 H 90° pulse of 3.8 µs, recycle delays of 1-60 s and 48-4096 transients 70 for ¹³C and 1598-5956 transients for ¹⁵N. Proton spin-lattice relaxation times, ¹H T₁, were obtained using the ¹³C-detected Inversion Recovery Cross Polarization technique [¹H(180°-τ-90°)-CP-¹³C(FID)], where one measures the ¹³C magnetization that appears through the CP process after the relaxation of ¹H 75 magnetization over time τ . 160-1024 transients were acquired and a variable delay list file (from 22ms to 42s) was used. 2D ¹³C-¹H FSLG (Frequency Switched Lee Goldburg) on- and off-resonance HETCOR (Heteronuclear Correlation) spectra were measured according to the method developed by van Rossum et al.¹⁸ The



MAS rate was set at 12 kHz. The proton rf field strength used during the t_1 delay for FSLG decoupling and during the 5 acquisition for TPPM (Two-Pulse Phase-Modulated) decoupling was 83 kHz. Two off-resonance pulses with opposite phases (i.e., +x, -x or +y, -y) used during the FSLG decoupling were set to 9.8 μ s. The contact time used was 100 μ s. The magic angle (54.7°) pulse length for protons was set at 2.0 µs, while the recycle delay 10 used was 15 s. Quadrature detection was achieved using the States-TPPI method. All data for 64 t_1 increments with 140 scans were collected. A B₁(¹H) field intensity for the CP of 75 kHz and a mixing period of 2.0 ms were used for FSLG off-resonance CP (LG-CP) HETCOR NMR. The ¹H NMR chemical shift scale in ¹⁵ the HETCOR spectra was corrected by a scaling factor of $1/\sqrt{3}$ because the ¹H NMR chemical-shift dispersion is scaled by a factor of $1/\sqrt{3}$ during FSLG decoupling. ¹H MAS experiments were performed on a 2.5 mm Bruker probe at a spinning speed of 32 kHz. The ¹H MAS spectra were acquired using the DEPTH ²⁰ sequence $(\pi/2 - \pi - \pi)$ which suppresses the probe background signal.¹⁹ The ¹H 90° pulse length was set to 2.50 μ s, the recycle delays to 1-40 s and 32-64 transients were averaged for all samples. ¹H, ¹³C and ¹⁵N chemical shifts were referenced via the resonance of solid adamantane (¹H signal at 1.87 ppm), HMB 25 (¹³C methyl signal at 17.4 ppm) and (NH₄)₂SO₄ (¹⁵N signal at -

355.8 ppm with respect to CH_3NO_2), respectively.

IR and Raman spectra were only used to screen the products and to monitor reaction conversion. In order to discriminate between the different forms, particular attention was given to the 30 regions from 3500 to 3300 cm⁻¹ (NH and OH stretching), 3100 and 3000 cm⁻¹ (CH and CH₂ stretching) and 1700-1600 cm⁻¹ (C=O stretching). All IR and Raman spectra are reported in Figures S1 and S2 in the Supporting Information. Fourier transform infrared (FTIR) spectra were collected directly on the 35 sample using а Bruker IFS 25 spectrometer (BrukerAnalytischeMesstechnik GmbH, Ettlingen, Germany) connected to a Bruker IR microscope I (15x-Cassegrain-

- objective). The samples were prepared on ZnSe-disks and measured in transmission mode (spectral range 4000-600 cm⁻¹, ⁴⁰ resolution 4 cm⁻¹, 32 interferograms per spectrum).²⁰ Raman spectra were measured on a Bruker Vertex 70 spectrometer equipped with a RAM II using a 1064 nm Nd:YAG source and a Ge diode detector (laser power 10-50 mW, spectral resolution 4
- ⁴⁵ Differential Scanning Calorimetry (DSC) was performed on a TA instrument Q200. Samples (5-10 mg) were placed in sealed alumina pans and heated at a rate of 10°C min⁻¹ (temperature range: 30 to 400 °C).

 cm^{-1}).

Thermogravimetric (TGA) measurements were performed ⁵⁰ under N₂ flow (heating rate: 10° Cmin⁻¹) on a TA instrument Q600 SDT Simultaneous DSC-TGA heat flow analyzer. The samples (5-10 mg) were placed in alumina pans. All DSC and TGA thermograms are reported in Figures S3 in the Supporting Information.

- ⁵⁵ X-ray powder diffraction (XRPD) patterns of the samples under investigation were collected on a PW3050/60 X'Pert PRO MPD diffractometer, from PANalytical, working in the Debye-Scherrer geometry and using, as the source, a high-powered ceramic tube PW3373/10 LFF with a Cu anode equipped with a
- $_{\rm 60}$ Ni filter to attenuate Kb which was focused by a PW3152/63 -



Scheme 2 Supramolecular Synthons and Hydrogen Bond motif of anhydrous HTA Form I and II.

X ray mirror. Powdered samples were hosted inside a 0.8-mm ⁵ boron silicate capillary and mounted on a rotating goniometer head.

Variable Temperature (VT) XRPD studies were carried out on an X-Pert Diffractometer (PANalytical, Cu K α radiation) equipped with a hot-stage and an environmental chamber (Anton

¹⁰ Paar XRK 900), to analyze the conversion of both NaTA·0.5H₂O and NaTA·HTA·H₂O/NaHCO₃ to the NaTA HT Form. XRPD patterns of HTA Form I, Form II, and all multiple component crystals are reported in Figure 1, while XRPD patterns of used co-formers, VT-XRPD patterns, used ramps and technical details ¹⁵ are reported in the Supporting Information (Figures S4 and in

Schemes 1 and 2). Dissolution kinetic tests (DKT) were performed in a pH 7.4 buffer (0.2 M KH₂PO₄/0.2 M NaOH). 5 mg of HTA (as a pure

- compound or co-crystal and salt) were added to 150 cm³ of ²⁰ dissolution medium at 37°C in each experiment. The release test lasted 180 min. In these experiments, the solution was kept homogeneous using an impeller (rotational speed 200 rpm) and the determination of HTA concentration was performed using fibreoptic apparatus (HELLMA, Milano, Italy) connected to a
- ²⁵ spectrophotometer (ZEISS, Germany,).²¹ Measurement was performed at 286.9 nm (HTA maximum absorption, supporting information). Each sample was tested in triplicate. The mother solution was obtained by dissolving 100 mg HTA in 100 ml methanol. The concentration of the standard solutions obtained
- ³⁰ from the mother solution and the calibration curve are reported in Figures S5 in the Supporting Information. In this dissolution medium, the equilibrium solubility of pure HTA was 28.5 mg/l. Elemental analysis was performed on a CHN analyzer (CE Instruments, NA2100 Protein), and a Perkin Elmer 3030 flame
- as atomic absorption spectrometer (FAAS) for sodium determination, to clarify the stoichiometry of compounds. The data confirm the stoichiometries deducted by solid-state NMR. Data are reported in the Experimental and methods section.

Results and discussion

- ⁴⁰ The two anhydrous forms of HTA are characterized by the presence of a dimer which is connected through the very robust $R_2^2(8)$ carboxylic acid homo-dimeric synthon (Scheme 2), as observed in the X-ray structures.²² Such a feature gives rise to a single COOH resonance around 175 ppm in the ¹³C CPMAS
- ⁴⁵ spectra (Figure 2a and 2b). This is an intermediate value between typical COOH and COO⁻ chemical shifts (~173 and ~178 ppm, respectively).²³ The strength of this interaction most likely explains the poor water solubility of HTA. Although one example of a HTA co-crystal,²⁴ five metal-complexes²⁵ and a calcium salt
- ⁵⁰ are reported in literature,²⁶ the $R_2^2(8)$ carboxylic acid homodimeric synthon is strong enough to prevent the formation of other co-crystals in which the COOH group must be accessible. Indeed, the NH group is not particularly suitable for hydrogen

bond interaction as both the steric hindrance of the methyl and ⁵⁵ COOH groups and the formation of an intramolecular hydrogen bond with the COOH moiety hamper it. This is probably the main reason why it does not form classic organic co-crystals with malonic acid, succinic acid, sodium malonate, glycine, L-alanine, aspartic acid, sodium glycinate, sodium acetate (NaAc), adenine, ⁶⁰ thymine, guanine and resorcinol. The ionic co-crystal approach,²⁷

⁶⁰ thymne, guanne and resortion. The fonc co-crystal approach, using inorganic salts (KI, KF, KBr, NaCl, KBr, KHCO₃, K₂CO₃, NaHCO₃, AlCl₃ e FeCl₃.) was also unsuccessful. For this reason we decided to use co-formers which are either able to react quantitatively with HTA, to form the corresponding salt, or to ⁶⁵ partially salify HTA and form a salt co-crystal such as salts and bases: NaOH, Na₂CO₃, NaAc and IM.

All samples were obtained via simple kneading. Crystallization with different solvents resulted in either a NaTA polymorphic mixture or pure HTA Form I or II. Different forms are present in 70 the NaTA polymorphic mixture, as shown by the ¹³C CPMAS spectrum (Figure S6 in the Supporting Information). Several attempts to promote the selective crystallization of single forms using various solvents (EtOH, 1- BuOH, THF, DMSO, DMF, H₂O or CH₃CN) failed. Thus, in this case, mechanochemistry 75 allowed us to obtain pure compounds. The chemical shifts of the solid-state NMR spectra of all crystal forms are listed, with assignments, in Table 2.







Fig. 3 ¹H (400 MHz) MAS spectra of HTA Form I and II, NaTA·0.5H₂O, NaTA·HTA·H₂O/NaHCO₃, NaTA·HTA·0.5NaAc·2H₂O, NaTA HT Form and IMH-TA·HTA recorded at 32 kHz.

- NaTA-0.5H₂O, prepared in a pure form by kneading stoichiometric amounts of HTA and NaOH, shows the splitting of almost all resonances in the ¹³C CPMAS spectrum (Figure 2c), indicating the presence of two independent molecules in the unit cell. The splitting is especially marked for atoms C3, C8 and C14.
 Salification was confirmed by the shift of the carboxylic resonance from 175.3 ppm (typical of the cyclic dimerization of the COOH moieties in pure HTA) to 178.3 ppm, which is characteristic of the COO group. The possible formation of a
- 50:50 mixture between two polymorphs was ruled out by ¹H T₁ measurements which provided the same value for all ¹H atoms. Indeed, according to a simplified but reliable approach,²⁸ the spin diffusion process averages ¹H T₁ when protons belong to the same phase or in the case of homogeneous samples on a nanometer scale.²⁹ On the other hand, protons with different
- $_{20}$ relaxation times belong to different domains with an average linear dimension of greater than about 100 Å and *vice versa*. 30 In this case all resonances possess the same T₁ values, thus, two molecules are present in the asymmetric unit. The presence of half a water molecule in the structure has been predicted by
- ²⁵ combining data from TGA (see Figures S3 in the Supporting Information) and integral values of the ¹H MAS spectrum (Figure 3c). This value agrees with the elemental analysis. The NH proton chemical shift suggests the presence of the NH…COO⁻ intramolecular interaction that characterizes both HTA Form I ³⁰ and II and all the crystal forms presented in this paper.

NaTA·HTA·H₂O/NaHCO₃ was obtained by kneading HTA

and Na₂CO₃ (2:1) with an EtOH/H₂O (2:1) mixture used as the mediating solvent. This heterogeneous mixture consists of a salt co-crystal (concomitant presence of both neutral HTA molecule and NaTA salt; NaTA·HTA) and an inorganic salt (NaHCO₃) in a different domain. Any other attempt to change either the stoichiometric ratio or grinding conditions yielded a heterogeneous mixture of components. The ¹³C CPMAS spectrum (Figure 2d) shows two sets of signals which indicate the 40 presence of a HTA and a NaTA molecule in the unit cell. The carboxylic region of the spectrum is characterized by three peaks at 179.3, 170.1 and 164.5 ppm. The two former signals are attributed to the COO⁻ (179.3 ppm, NaTA) and COOH (170.1 ppm, HTA) groups. The latter peak (at 164.5 ppm) is assigned to ⁴⁵ the bicarbonate formed during the reaction. Interestingly, ¹H T₁ measurements indicate that HTA and TA⁻ signals belong to the same phase, which is in agreement with the formation of a salt co-crystal, while the NaHCO₃ resonance belongs to a different domain.³⁰ The ¹H MAS spectrum (Figure 3d) is characterized by 50 two signals in the hydrogen bond region (14.0 and 12.8 ppm, integral ratio 1:2) which are attributed to the COOH of HTA and NH of HTA and TA⁻. TGA and ¹H integral values suggest the presence of one molecule of H₂O which is in agreement with the elemental analysis. However, it was not possible to establish 55 whether the water is associated with the salt co-crystal or NaHCO₃.

NaTA·HTA·0.5NaAc·2H2O was obtained as a pure compound via kneading (EtOH 99%) HTA with NaAc. The carboxylic/carboxylate region of the 13C solid-state NMR 60 spectrum (Figure 2e) reveals the number of independent molecules in the unit cell and revealed the presence of one HTA $(\delta_{COOH} = 175.9 \text{ ppm})$, one NaTA $(\delta_{COO} = 179.0 \text{ ppm})$ and one NaAc (δ_{COO-} = 184.7 ppm) in a 1:1:0.5 ratio. The signals due to the NaAc are only slightly shifted from the pure compound 65 values, indicating a weak interaction with NaTA·HTA (184.7 and 22.8 ppm in NaTA·HTA·0.5NaAc·2H₂O with respect to 183.5 and 26.7 ppm in pure NaAc). The ¹H MAS spectrum (Figure 3e) shows two resonances in the weak hydrogen bond region at 10.8 and 8.6 ppm (ratio 2:1), which are assigned to COOH and NH 70 proton and to the other NH proton (overlapped with aromatic resonances), respectively. By evaluating the ¹H integration, we can assume the presence of two molecules of water in the structure, as confirmed by TGA and elemental analysis. The final composition is: NaTA·HTA·0.5NaAc·2H₂O. The same 1 H-T₁ 75 value for all the protons confirms that the best definition for describing such structure is a co-crystal of salts (NaTA·HTA·0.5NaAc·2H₂O), because the solid is composed of a salt co-crystal (NaTA·HTA) and a salt (NaAc). ¹H-¹³C FSLG on- and off-resonance CP HETCOR experiments were performed 80 in order to obtain a deeper understanding of the spatial proximities and to complete the assignment of the strongly overlapped ¹H resonances. The spectra are reported in Figures S7 (Supporting Information) and Figure 4, respectively. These experiments allow intra- and intermolecular heteronuclear 85 correlations to be obtained.^{31,18} By acquiring 2D experiments with short or long contact times (100 and 2000 µs, respectively), it is possible to discriminate between short- (single bond) and long-range spatial proximities, respectively. In particular, the use of off-resonance CP (LG-CP) allows for a more detailed analysis

| Note | HTA Form I | HTA Form II | NaTA •0.5 | NaTA·HTA ·H2O/NaHCO3 | NaTA·HTA·0.5 NaAc·2H ₂ O | NaTA HT Form | IMH- TA·HTA | IM |
|--|---------------|----------------|------------------|-------------------------|--|-----------------|--------------------|--------------------|
| | | | H ₂ O | ¹³ C CPM | AS | | | |
| C1 | 175.4 | 175.5 | 178.3 | 179.3 | 179.0 | 178.9 | 175.7 | |
| | | | | 170.1 | 175.9 | | 174.3 | |
| C2 | 109.4 | 108.2 | 118.4 | 114.2 | 114.0 | 111.7 | 113.4 | |
| | | | | 111.4 | | | 112.2 | |
| CH _{Ar} /CH _{IM} | 136.2 | 132.8sh | 134.6 | 136.3 | 133.3 | 133.4 | 133.9 | 137.0 |
| | 135.0 | 125.0 | 127.0 | 132.5 | 128.0 | 132.5 | 133.1 | 127.3 |
| | 130.1 | 123.6 | 125.4 | 130.5 | 117.1 | 128.4 | 131.3 | 115.7 |
| | 129.4 | 122.9 | 122.8 | 120.2 | 116.7 | 127.9 | 127.4 | |
| | 127.8 | 117.8 | 120.2 | 117.9 | | 127.1 | 126.1 | |
| | 116.6 | 116.6 | | 115.7 | | 125.4 | 117.6 | |
| | 112.1 | 111.9 | | | | 121.9 | 115.8 | |
| | | | | | | 120.2 | | |
| | | | | | | 118.7 | | |
| C9 | 133.6 | 125.9 | 131.3 | 134.0 | 130.4 | 128.4 | 124.0 | |
| | | | | 127.7 | | or 127.1 | 120.6 | |
| C10 | 137.0 | 136.3 | 137.8 | 139.4; | 136.2; | 134.7 | 139.9 | |
| | 136.1 | | | 138.2 | 135.5 | | 136.2 | |
| C3 | 150.4 | 146.9 | 147.3 | 150.5 | 151.7sh | 147.0 | 148.8 | |
| | | | 145.6 | | 151.1 | | 146.9 | |
| C8 | 138.9 | 138.7 | 141.9 | 147.5 | 142.4sh | 140.5 | 141.4 | |
| | | | 140.5 | | 141.9 | | | |
| C14 | 15.6 | 14.6 | 15.4 | 16.4 | 19.3 | 14.7 | 14.7 | |
| | | | 13.4 | 15.6 | 16.0 | | 13.9 | |
| | | | | | | | 13.2 | |
| \mathbf{C}^{a} | | | | 164.5 ^b | 184.7 ^c | | | |
| | | | | | 22.8 | | | |
| | | | | ¹⁵ N CPM | AS | | | |
| NH | 66.5 | | 72.2 | 66.1 | | 64.6 | 71.7 | |
| | | | 70.8 | 60.4 | | | 67.6 | |
| | | | | | | | 62.5 | |
| | | | | | | | 59.1sh | |
| $\mathrm{NH}^{+}\mathrm{IM}/\mathrm{N}\mathrm{IM}$ | | | | | | | 153.2 ^d | 220.5 ^e |
| NHIM | | | | | | | 145.5 | 149.2 |
| | | | | ¹ H MA | S | | | |
| COOH | 12.8 | 12.9 | | 14.0 | 10.8 | | 15.4 | |
| | | | | 12.8 | | | | |
| NH | 8.8sh | 8.9sh | 9.3 | 14.0 | 10.8 | 9.8 | 10.4 | |
| | | | | 12.8 | 8.6sh | | | |
| CH _{Ar} /CH _{IM} | 7.1 | 7.0 | 7.5 | 6.6 | 7.5 | 6.4 | 8.5 | 7.2 |
| | 6.0 | 6.7 | 6.4 | | 6.7 | | 6.5 | |
| CH_3 | 1.4 | 1.6 | 1.7 | 1.5 | 1.3 | 1.7 | 1.4 | |
| | | | | | 1.2 | | | |
| H ₂ O | | | 42 | 67 | 0.9 | | | 28 |
| $\rm NH^+_{IM}$ | | | | | | | 20.2 | |
| | | | | | | | 19.5 | |
| NHIM | | | | | | | 15.4 | 14.7 |

| Table 2 ¹ H, ¹³ C and ¹⁵ N chemical shifts with assignments for all obtained compounds and pure IM and HTA Form I a | nd II. |
|--|--------|
|--|--------|

^aCarbon atoms of either molecules in other phases or of solvents or of co-former molecules. ^b NaHCO₃. ^c NaAc. ^d NH⁺_{IM}. ^e N_{IM}.



Fig. 4 ¹H-¹³C FSLG LG-CP HETCOR spectrum of **NaTA·HTA·0.5NaAc·2H₂O** acquired with a contact time of 2000 μs with relevant assignments. Intramolecular and intermolecular correlations are indicated in red and light blue, ⁵ respectively.

of long range spatial ¹H-¹³C contacts. This is achieved using a Lee-Goldburg (LG) spin-lock (LG-CP) which efficiently suppresses unwanted ¹H-¹H spin exchange which leads to fake ¹⁰ correlation peaks that reflect ¹H-¹H homonuclear rather than ¹H-¹³C heteronuclear dipolar couplings.^{32,18} All ¹H-¹³C proximities are depicted in Scheme 3. The ¹H-¹³C FSLG LG-CP HETCOR experiment (Figure 4), allowed us to establish the presence of an intramolecular NH···O-C hydrogen bond in the NaTA molecule



Scheme 3 'H-¹³C correlations between HTA, NaTA and NaAc in NaTA·HTA·0.5NaAc·2H₂O as deduced from ¹H-¹³C FSLG LG-CP HETCOR.

- ²⁰ (correlation between the ¹H NH signal at 8.6 ppm and the ¹³C COO⁻ at 179 ppm). The lack of a similar correlation between signals assigned to the HTA molecule points to a non-planar conformation of the two rings for this molecule. On the other hand, the HTA OH proton (10.8 ppm) correlates with the COO⁻
- 25 carbon of NaTA (179.0 ppm), indicating that the two groups are involved in a O-H…O hydrogen bond. Other correlations were

found for the NH hydrogen of NaTA (8.6 ppm) with the NaAc methyl and carboxylate carbons (22.8 and 184.7 ppm, respectively). Finally, polarization transfer is observed from the ¹H HTA OH (10.8 ppm) to the NaAc methyl (22.8 ppm).

30

NaTA HT Form - It is possible to obtain an anhydrous high temperature form, called the NaTA HT Form which is also stable at room temperature, via heating both NaTA-0.5H₂O and NaTA·HTA·H₂O/NaHCO₃ in a oven at around 180°C. However, 35 heating NaTA·HTA·0.5NaAc·2H₂O results in a mixture of phases, as observed by ¹³C CPMAS NMR (see Figure S8 in the Supporting Information). The formation of the new form (NaTA HT Form) involves the dehydration of NaTA-0.5H₂O (release of water and formation of NaTA) and the complete salification of 40 the HTA molecule in NaTA·HTA·H₂O/NaHCO₃ after the bicarbonate decomposes to CO₂ and H₂O. A combination of ¹³C and ¹⁵N CPMAS data made it possible to reveal the presence of only one NaTA molecule in the unit cell. The shift to 178.9 ppm in the ¹³C spectrum (Figure 2f) confirms the presence of COO⁻ 45 groups, while the small NH shift (from 66.5, HTA, to 64.6 ppm, NaTA) indicates a slight rearrangement of the weak intramolecular hydrogen bond which involves the NH. This is in agreement with the ¹H MAS spectrum (Figure 3f) where the NH group falls at 9.8 ppm.

⁵⁰ The solid-state conversions of **NaTA**·**0.5H**₂**O** and **NaTA**·**HTA**·**H**₂**O**/**NaHCO**₃ to **NaTA HT Form** were also followed by VT-XRPD (Figure S4, Schemes 1 and 2). The 5-40° 2θ range was used to evaluate the most significant changes in the patterns. In particular, **NaTA**·**0.5H**₂**O** is characterized by five

⁵⁵ principal reflections at 9.58, 12.57, 29.76°, which all disappear at 60°C, and at 15.77 and 19.45°, which vanish at 190°C. The appearance of three principal new reflections at 14.70, 17.63 and 20.51°, at the same temperature, points to the formation of the NaTA HT Form. On the other hand, NaTA·HTA·H₂O/NaHCO₃
⁶⁰ is characterized by reflections at 12.42, 17.38 and 18.34°, plus the signals attributed to NaHCO₃ (at 30.43 and 34.39°). Upon increasing the temperature to 190°C, the reflection at 17.38° decreases in intensity while all the others disappear, giving the characteristic signals of the NaTA HT Form. The disappearance
⁶⁵ of the NaHCO₃ signals agrees with the salification of HTA by the bicarbonate.

IMH-TA·HTA was obtained by kneading (EtOH 99%) HTA and IM in a 2:1 ratio. Two TA⁻ and two HTA independent molecules are present in the unit cell as shown by the ¹³C 70 CPMAS spectrum (Figure 2g), which is characterized by the splitting of the C1 (175.7 and 174.3 ppm in 3:1 ratio) and C14 (14.7, 13.9 and 13.2 ppm in 1:2:1 ratio) signals. This is also confirmed by ¹⁵N CPMAS (Figure 5) where four peaks, caused by the NH group (71.7, 67.6, 62.6 and 59.1sh ppm), are clearly ⁷⁵ observable. The number of IM molecules is determined, in this case, by ¹⁵N CPMAS because the IM ¹³C resonances fall under the aromatic CH of the TA⁻/HTA molecules. The estimated number of independent IM molecules is two (¹⁵N δ_{NH}=153.2 and 145.5 ppm). The observed shifts for the IM NH resonances (from ⁸⁰ 220.5 and 149.2 ppm to 153.2 and 145.5 for N and NH,



Fig. 5 ¹⁵N (40.56 Hz) CPMAS of HTA Form I, **IMH-TA·HTA** and pure IM recorded at 9kHz.

respectively) suggest that the IM is present in the protonated form

- ⁵ (imidazolium, IMH⁺) as has already been reported in literature.³³ This implies that the proton transfer occurs from one HTA (becoming TA⁻) to the IM (becoming IMH⁺). The similarity between COOH and COO⁻¹³C chemical shifts may suggest that an interaction between two groups is able to delocalize the
- ¹⁰ negative charge. It is possible to note, from ¹H MAS (Figure 3g), that the IMH⁺ NH⁺ groups form very strong hydrogen bonds (20.2 and 19.5 ppm), while the IMH⁺ NH and the HTA COOH hydrogen atoms, both involved in hydrogen bonds, fall at the same chemical shift (15.4 ppm). For HTA, as in the ¹H MAS ¹⁵ spectra of the other samples, the NH hydrogen is located at 10.4 ppm.

Infrared and Raman Spectroscopy

The Raman and FT-IR spectra of all prepared samples are

shown in Figures S1 and S2 in the Supporting Information.

²⁰ The Raman spectra show clear differences in almost all spectral regions. The most important differences can be found in the COOH/COO⁻ frequency range (1750-1550 cm⁻¹), reflecting the differences in hydrogen bonding interactions and salt formation. In particular, COOH groups are characterized by v and ²⁵ δ around 1680 and 890 cm⁻¹, respectively. On the other hand, v_aCOO⁻ and v_sCOO⁻ are at about 1610 and 1385 cm⁻¹, respectively. Other differences are found in the NH and aromatic CH stretching regions (3500-3050 and 3000-2800 cm⁻¹, respectively). The frequencies of some characteristic bands of the ³⁰ solid-state MIR spectra of the polymorphs and multiple component crystals are listed in Table 3.

Differential Scanning Calorimetry (DSC) and Thermogravimetric (TGA) Analysis

All compounds were investigated using TGA and DSC in ³⁵ order to characterize thermal behavior and to determine the water molecule ratios in the samples. Results are listed in Table 4, while all DSC and TGA figures are displayed in Figure S3 in the Supporting Information.

Heating both NaTA-0.5H₂O and NaTA-HTA-H₂O/NaHCO₃ ⁴⁰ in an oven at 180°C yielded the same polymorphic form (NaTA HT Form). In the case of NaTA-HTA-0.5NaAc·2H₂O, water release (around 160 °C) is followed by the loss (sublimation) of one HTA molecule (at 182.6°C) that leads to mixtures of anhydrous phases of NaTA and NaAc, as confirmed by ¹³C ⁴⁵ CPMAS spectra (see Figure S7 in the Supporting Information).

It is worth noting that the melting and/or decomposition point of all samples, except **IMH-TA·HTA**, are found between 320-339 °C (pure HTA sublimates around 212 °C followed by decomposition) indicating that multicomponent HTA crystals 50 exhibit significantly improved thermal stability over single component forms of HTA.

Table 3 Wavenumbers (cm⁻¹) of characteristic MIR vibrations with assignments for all multiple component crystals and two HTA polymorphs.

| | HTA FormI | HTA FormII | NaTA·0.5 H ₂ O | NaTA·HTA ·H2O/NaHCO3 | NaTA·HTA·0.5N aAc·2H ₂ O | NaTA HT Form | IMH- TA·HTA |
|------------------------------------|----------------------|----------------|---------------------------|-------------------------|--|------------------------------|--------------------|
| NH | 3340,s | 3326,s | 3343,3255 broad | 3279,m | 3312,s | 3367.5,s3243 .7, broad | 3290,s |
| Ar-CH | 3083-2870 w | 3078-2914 w | 3078-2859 w broad | 2676-2388 w broad | 3075-2934 w | - | 3110-2586 broad |
| v(CO)OH | 2736-2493 w broad | 2733-2487 w | - | - | 2740-2591 w | - | - |
| δ(CO)OH | 900,s | 886,m | - | - | 884,m | - | - |
| vCO(OH) | 1660,s | 1668,s | - | 1689,s | 1775w,1727vs | - | - |
| $v_a CO(O^-)$ | - | - | 1610,s | 1611,s | - | 1608.4,s | 1579.7,s |
| v _s CO(O ⁻) | - | - | 1388,s | 1391,1378 broad | - | 1379.2,s | 1385.4,w |
| CC1 | 778,751,m | 743,m | 756,m | 758,m | 750,m | 752.8,m | 752.1,m |

Table 4 TGA and DSC data for all achieved samples. $T_{\rm H2O}$: dehydration temperature, T_{trans} : transition temperature, T_{fus} : melting temperature, T_{dec} : decomposition temperature.

| Sample | $T_{ m H2O}$ | $T_{ m trans}$ | T _{fus} | T _{dec} | |
|--|--------------|-------------------------------|------------------|------------------|--|
| НТА | | | 210 | -214 | |
| NaTA·0.5H ₂ O | 158.5 | 67.3, 92.3,191.4 ^a | 32 | 0.9 | |
| NaTA·HTA ·H2O/NaHCO3 | | 136.6,160.6 ^b | 247. 5 | 339. 1 | |
| NaTA·HTA ·0.5NaAc·2H ₂ O | 158.0 | 182.6 ^c | 33 | 4.1 | |
| ІМН-ТА•НТА | | 109.7 | 181 | -213 | |
| ^a solid-solid transitions (see Supporting Information). ^b CO ₂ and H ₂ O | | | | | |

5 release due to the HTA salification. ^c release of HTA.

Dissolution kinetic tests (DKT)

In order to confirm that the co-crystallization process is a successful strategy for the improvement of the dissolution 10 properties of HTA, the in vitro dissolution performance of pure HTA and various salts and co-crystals were evaluated. Due to its acidic character, the solubility of HTA depends on the pH of the aqueous medium. In fact, it is reported that the solubility of this drug in a pH 1.2 buffer is about 13.6 nM.³⁴ It is very difficult to 15 detect such extremely low concentrations of HTA using the UV method. Therefore, in the present study a pH 7.4 buffer (where HTA is more soluble) is used as a dissolution medium. The solubility profiles of pure HTA and selected composites are reported in Figure 6 (see Figure S9 in the Supporting information





Fig. 6 Dissolution rate profiles of the samples measured in the first 15 minutes: HTA (red line with red circles), NaTA-0.5H2O (blue line with 25 blue squares), NaTA HT Form (black line with yellow circles), IMH-TA·HTA (green line with green triangles), NaTA·HTA·H₂O/NaHCO₃· (black line with black triangles) and NaTA·HTA·0.5NaAc·2H₂O (black line with white circles).

Table 5 Dissolution data: amount (mg/l) of dissolved or released HTA 30 calculated after 1, 15 and 180 minutes with the respective percentage of solubilized sample.

| Sample | after 1' | % | after 15' | % | after 180' | % |
|--|-------------|------|--------------|------|---------------|------|
| HTA | 0.0 | 0.0 | 7.3 | 21.8 | 28.5 | 85.4 |
| NaTA-0.5 H ₂ O | 33.0 | 98.9 | 33.3 | 99.8 | 33.4 | 100 |
| NaTA•HTA• H ₂ O/NaHCO ₃ | 26.1 | 78.4 | 32.3 | 96.8 | 33.3 | 100 |
| NaTA∙HTA∙ 0.5NaAc∙2H₂O | 3.7 | 11.4 | 19.7 | 59.1 | 25.7 | 77.2 |
| NaTA HT Form | 32.1 | 96.2 | 33.5 | 99.8 | 33.2 | 99.4 |
| IMH-TA·HTA | 0.3 | 1 | 5.3 | 15.8 | 24.1 | 72.4 |
| | | | | | | |

Pure HTA shows the typical dissolution profile of a poorly soluble drug: the amount of the drug solubilized remains very low 35 in the first 30 minutes of analysis and increases linearly (due to the protonation phenomenon) in the following part of the dissolution test. Figure 6 shows that the dissolution profile of IMH-TA·HTA is very similar to the dissolution profile of pure

40 Table 6 Concentration C (mg/l), AUC values (mg/l·h) and Frel of all the samples reported for 180, 70 and 15 minutes.

| Sample | AUC ₀₋₁₈₀ | S.D. | Frel | dFrel |
|--|----------------------|------|------|-------|
| HTA | 48.6 | 3.7 | | |
| NaTA·0.5H ₂ O | 99.8 | 2.0 | 2.1 | 0.2 |
| NaTA·HTA·H ₂ O/ NaHCO ₃ | 98.6 | 3.0 | 2.0 | 0.5 |
| NaTA·HTA·0.5NaAc·2H ₂ O | 54.6 | 13.8 | 1.1 | 0.3 |
| NaTA HT Form | 99.7 | 4.0 | 2.1 | 0.2 |
| IMH-TA·HTA | 42.9 | 5.2 | 0.9 | 0.1 |

HTA. Better results are obtained by NaTA·HTA·0.5NaAc·2H₂O, especially in the first part of the analysis (up to 90 minutes), 45 where HTA solubilizes in higher amounts. In the case of NaTA-0.5H₂O and the NaTA HT Form, instantaneous HTA solubilization is observed. In fact, HTA solubilizes completely in the first minute of the dissolution test and high concentrations are maintained throughout. Moreover, no precipitation phenomenon is observed in the dissolution profiles of these forms. It is also worth noting that NaTA·HTA·H2O/NaHCO3 is completely dissolved in only 15 minutes of analysis, like the NaTA salts (Figure 6). Table 5 lists the data extrapolated after a dissolution time of 1 and 15 minutes. These data highlight how the active component is liberated from the multicomponent samples, and that this process is strongly accelerated not only in the salts but also in NaTA·HTA·H₂O/NaHCO₃.

Subsequently, FDA bioequivalence limits were adopted and used for the in vitro solubilization experiments in order to make a 60 comparison between the performed samples. In more detail, FDA guidance suggests that two compounds/formulations can be considered bioequivalent if the ratio of their Area Under the Curve (AUC) is in the 0.80-1.25 interval.³⁵ This evaluation parameter is proposed for in vivo studies, but it has been

successfully applied to compare AUC values obtained from *in vitro* data.²¹.

For each sample (pure HTA Form I, HTA salts and HTA cocrystals), AUC was calculated from time 0 to the last measured ⁵ point (AUC₀₋₁₈₀), using the classical trapezoidal method. The AUC of HTA was then used as the reference and indicated as AUC_{ref}. Furthermore, the ratio (indicated as *Frel*) between the AUC of each formulation (AUC_{sample}) and AUC_{ref} was calculated, as follows:

$$Frel = \frac{AUC_{sample}}{AUC_{ref}}$$

The associated uncertainty (indicated as dFrel) for all *Frel* ratios was calculated using the classic formula for the relative error of a ratio:³⁶

(I)

$$dFrel = |Frel| \sqrt{\left(\frac{dAUC_{sample}}{AUC_{sample}}\right)^{2} + \left(\frac{dAUC_{ref}}{AUCref}\right)^{2}}$$
(II)

15

10

where $dAUC_{sample}$ and $dAUC_{ref}$ indicate the S.D. of the AUC_{sample} and AUC_{ref} values, respectively. The calculated *Frel* ± *dFrel* values are listed in Table 6.

It can be seen from Table 6 that **IMH-TA·HTA** and ²⁰ **NaTA·HTA·0.5NaAc·2H**₂**O** are bioequivalent with pure HTA *in vitro*. The other products are probably more bioavailable than pure HTA (Table 6). These results confirm that co-crystallization is an efficient and innovative technique with which to improve the biopharmaceutical performance of poorly soluble drugs.

25 Conclusions

Three new multicomponent crystals of tolfenamic acid (NaTA·HTA·H₂O/NaHCO₃, NaTA·HTA·0.5NaAc·2H₂O and IMH-TA·HTA) and two sodium salts (NaTA·0.5H₂O and NaTA HT Form) have been prepared using mechanochemical

- ³⁰ techniques (see Scheme 4). The stoichiometries of the samples were successfully elucidated using a combination of solid-state NMR and TGA data, due to a lack of single crystal XRD analysis. The results are consistent with elemental analysis data. This study thus highlights the great potential that solid-state
- ³⁵ NMR techniques possess when analyzing the composition and structural characteristics of complex multi-component crystals,³⁷ for which it may difficult or impossible to acquire single crystal structure data. Indeed, important structural information (asymmetric unit, salt or co-crystal formation, weak interactions, ⁴⁰ molecule proximities, hydration degree...) for the samples was
- provided by 1D and 2D solid-state NMR experiments.



Scheme 4 Representation of the preparation paths. k = kneading, $\Delta = heating$.

Mechanochemistry is a successful method for producing new solid-state forms. One big advantage that this technique provides is the fact that it gives pure products that do not require further purification.

The peculiarities of these HTA derivatives are the following:

50 - Heating NaTA·0.5H₂O and NaTA·HTA·H₂O/NaHCO₃ results in the same NaTA HT Form, as confirmed by solid-state NMR and RAMAN spectroscopy as well as by VT-XRPD measurements. The transformation of the salt hydrate only involves a dehydration process while the transformation of the

⁵⁵ NaTA·HTA·H₂O/NaHCO₃· to the NaTA HT Form includes a salification reaction between the HTA of NaTA·HTA and NaHCO₃, which releases CO₂ and H₂O.

 NaTA·HTA·0.5NaAc·2H₂O behaves differently upon heating and loses HTA to yield a NaTA + NaAc mixture, as characterized
 by solid-state NMR data.

All samples show increased thermal stability and improved solubility behavior (especially the NaTA HT Form, NaTA·HTA·H₂O/NaHCO₃· and NaTA·0.5H₂O). All the samples showed this trend for the first ten minutes, while
 ⁶⁵ NaTA·HTA·0.5NaAc·2H₂O and IMH-TA·HTA were found to be less soluble than pure HTA, but only after 180 minutes.

This investigation has also demonstrated that the Crystal Engineering approach makes it possible to change, and in these cases improve, the macroscopic properties (dissolution profile 70 and thermal behavior) of an active pharmaceutical ingredient. Dissolution studies confirm that co-crystallization is an efficient and innovative technique with which to improve the biopharmaceutical performance of poorly soluble drugs.

Acknowledgements

⁷⁵ We are indebted to Prof. L. Celi for the elemental analyses and Dr. A. Castellero and G. Fiore for the VT XRPD experiments.

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

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Figures S1: Raman spectra of all prepared compounds.







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









Figures S3: Calorimetric and Thermogravimetric curves of all compounds

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.



observed in the 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 ¹³C CPMAS spectra). This is probably due to the different heating methods used or to the presence of small amount of impurities.



f) DSC and TGA curves of IMH-TA-HTA.

Figures S4: XRPD patterns of co-formers of HTA.





Scheme 1: Temperature ramp applied to NaTA-0.5 H₂O









I) VT XRPD patterns of NaTA·HTA·H₂O/NaHCO₃ from r.t. (25°C) to 225 °C.



m) 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 H_2O and NaTA-HTA- H_2O /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 H_2O and NaTA HTA H_2O /NaHCO₃ into the same NaTA HT Form, in agreement with the solid-state NMR and RAMAN characterization.

| : Standard soluti | ons of pure HTA | for the calibrati |
|-------------------|-----------------|-------------------|
| Solution | Conc (mg/l) | ABS |
| 1 | 4.00E-01 | 1.68E+00 |
| 2 | 1.00E-01 | 4.63E-01 |
| 3 | 1.00E-00 | 6.49E-02 |
| 4 | 1.00E-01 | 2.01E-02 |
| 5 | 1.00E-02 | 1.25E-02 |
| 6 | 1.00E-03 | 2.08E-02 |

Figures S5: Dissolution kinetic tests (DKT) **Table 1**: Standard solutions of pure HTA for the calibration curve



UV absorption spectrum of Solution 2.



Figure S6: ¹³C CP MAS of **NaTA polymorphs mixture**. ¹³C CPMAS spectrum of **NaTA polymorphic mixture** obtained from HTA salification with NaOH; multiplicity and bandwidth of the signals highlight the copresence of different polymorphic forms of NaTA.



Figure S7: 2D ¹H-¹³C FSLG on-resonance HETCOR spectrum of **NaTA-HTA-0.5NaAc-2H₂O**. 2D experiment acquired with a short contact times (100 μs) for highlighting only the short- (single bond) spatial proximities.



Figure S8: ¹³C CPMAS of **NaTA-HTA-0.5NaAc-2H**₂**O** after thermal treatment. ¹³C (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)

