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Unlocking the reversibility of the mechanochemical synthesis of a pharmaceutical cocrystal

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Synopsis: Opposite transformations (synthesis or decomposition of the cocrystal) in the system “piroxicam – succinic acid – their 2:1 cocrystal” are documented depending on the type of mechanical action, and the presence of a fluid as an additive. Possible reasons for the observed effects are rationalized.

Abstract: Opposite transformations (synthesis or decomposition of the cocrystal) in the system “piroxicam **(P)** – succinic acid **(S)** – their 2:1 cocrystal (**P_2S**)” are documented depending on the protocol of mechanical action (milling in a vibrational mill varying the impact to rolling ratio and the impact frequency; rolling in a rotational mill), and the presence of a fluid (ethanol, acetone, tetrahydrofuran) as an additive. A striking difference in the impact-to-rolling ratio appearing upon seemingly benign change to the milling jar shape was observed and studied with the help of acoustic analysis. The synthesis of **P_2S** cocrystals occurred only in the presence of a solvent. The degree of

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transformation achieved after a fixed treatment time correlated with the solubility of **P** in the solvent. LAG of a mixture of **P** and **S** with an additive of acetonitrile gave a solvate cocrystal **P_4S x $2CH_3CN$** instead of **P_2S**. The decomposition of **P_2S** cocrystals, on the contrary, was observed only when dry sample was ground. The frequency of impacts was shown to be directly related with the degree of the synthesis of **P_2S** cocrystals in LAG experiments. Possible reasons for the observed effects are rationalized in terms of mechanochemical crystallization in the presence of liquids and solid-state decomposition resulting from shear stress.

Key words: mechanochemistry, ball milling, LAG, pharmaceutical cocrystals, effect of fluids in mechanochemistry, effect of the treatment protocol, impact, grinding, piroxicam, succinic acid

Introduction

Mechanochemistry is widely used in organic synthesis involving non-covalent interactions, making it possible to obtain cocrystals, salts, polymorphs with high (up to 99%—100% yields and sometimes scaled up to kg production [1–3]. At the same time, appropriate experimental optimizations and tool selection are known to be very important for the success of organic mechanochemistry [4,5]. The protocol of the mechanical treatment of a sample is known to have a pronounced effect on possible transformations. Many examples were reported when the kinetics of the transformation and its very possibility, its completeness, or the composition of the products changed if a device for mechanical treatment, the protocol of using the same device, the jar material, or the presence of some solid, polymer, or fluid additives (e.g. – water) changed [6–8]. In the “piroxicam (**P**) – succinic acid (**S**)” system a 2:1 piroxicam – succinic acid cocrystal (**P_2S**) formed when a mixture of the two components was treated in a model device with restricted impact by falling metal cylinder, whereas, on the contrary, the cocrystal decomposed into piroxicam and succinic acid, when ground in another model device between two disks rotating with respect to each other [9]. The reason for this phenomenon remained unclear. In the present work we revisited the system and studied the effect of changing the protocol of mechanical treatment in a commercial

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vibrational ball mill Fritsch Pulverisette 23 mini, and of the presence of a solvent (ethanol, acetonitrile, acetone, tetrahydrofuran) as an additive.

Experimental

Materials

Pure piroxicam (**P**) (Figure 1, a) used in all procedures (form I, also known as β-polymorph [10,11], monoclinic, CCDC: BIYSEH01; Sigma Aldrich, >= 98%) was stored refrigerated. The particles in the powder of (**P**) were found to be less than 100 μm, for that reason no further size separation was made. Succinic acid (**S**) (Figure 1, b) (Reahim) stored at room temperature was found to contain more than 99% of monoclinic β-polymorph [12] (CCDC: SUCACB02), with triclinic α-polymorph [13] (CCDC: SUCACB01) as the second minor component. Succinic acid powder was fractioned with Retsch lab sieves to have particle size 100—200 μm.

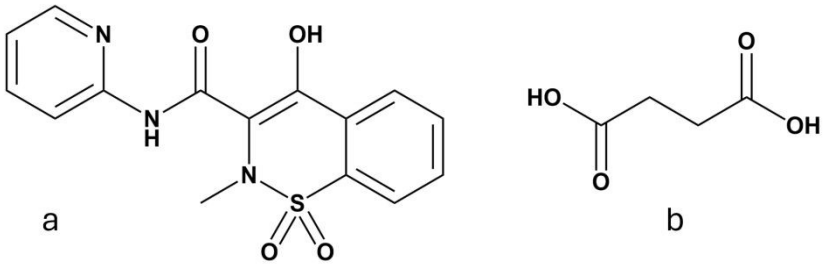

Figure 1. Molecular structures of piroxicam (a) and succinic acid (b)

Ethanol (95%, Kemerovo Pharmaceutical Factory, Russia), acetone (> 99%, Vecton, Russia), acetonitrile (HPLC grade, 99,9%, CDH, India), tetrahydrofuran (99,5% Komponent-Reaktiv, Russia) were used as solvents in slow evaporation crystallization and liquids for LAG experiments.

Mechanical treatment

In this work, liquid-assisted mechanical co-grinding was carried out in a vibrational ball mill (Fritsch Pulverisette 23 mini; supplied with a 27 mm spherical stainless steel milling jar consisting of two halves and a rubber O-ring between them; steel ball with mass 10.6

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g and diameter 13.7 mm, Figure 2, a). Both jar oscillations frequency and the total time of non-stop (continuous) milling[i] were controlled as parameters.

In special experiments, the same milling jar was put in a custom-designed 3D-printed rotational ball mill (Figure 2, b) that rotated the milling jar around its symmetry axis at controlled revolutions per minute (RPM).

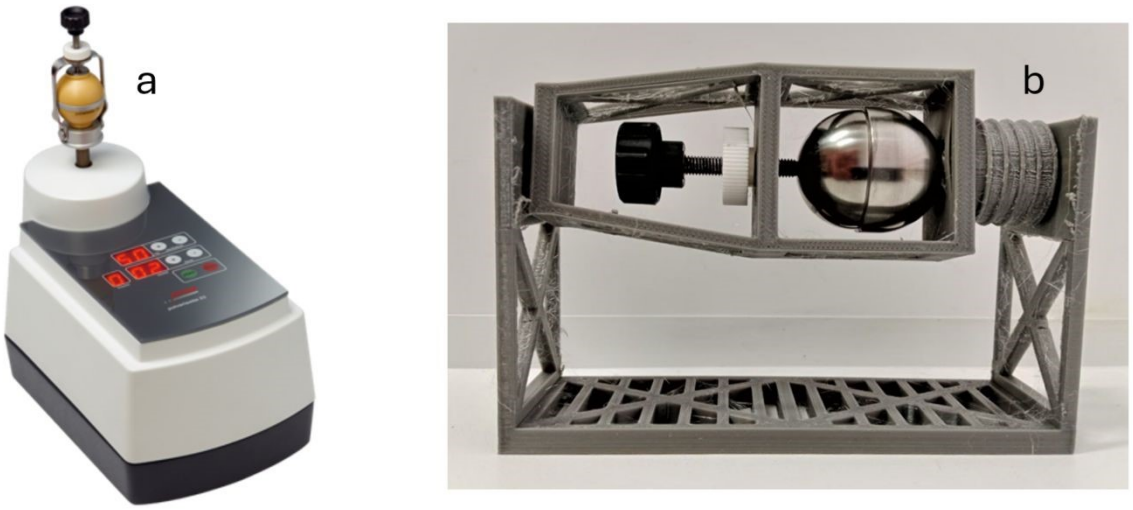

Figure 2. Mechanical devices used in this work: a) Fritsch Pulverisette 23 mini – official picture from fritsch.de; b) 3D-printed home-made rotational ball mill.

For every sample that was used for **P_2S** synthesis evaluation, a stoichiometric 2:1 molar ratio piroxicam (85 mg) and succinic acid (15 mg) mixture was prepared.

The reactants were preliminarily mixed dry after weighing the samples and transferring them to a vial by manual rotation of the vial around a tilted axis for ~1 min. In all experiments, the total mass of samples was 100±1 mg and the calculated amounts of reactants were weighted on analytical scales with no more than 0.5% mass tolerance. Before the treatment, the surfaces of milling jar and milling body were cleaned with ethanol and dried, to eliminate contaminants. The milling jar was tightly closed right after adding solvents (when necessary), to prevent significant solvent evaporation. The air humidity in the room was in the range of 35-50%. When using the Fritsch mill we did not observe the temperature of the milling jar rising above “slightly warm to hand”, thus

[i] The time during which the mill motor was working. No interruptions were made in any of the experiments.

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no specific temperature control was used; in rotational mill the jar never felt warmer than the room temperature. The treatment was done at controlled mill frequency between 15 and 50 Hz and for controlled period of time between 0 and 90 min. Composition of all the samples was analyzed *ex situ* at the end of treatment based on X-ray powder diffraction; all the material in LAG experiments (with negligible amount remaining in the jar evenly on ball and the jar's sides) was extracted onto a paper filter and dried for 3 min on ambient air (~20 °C, ~30-50% RH) without any special air circulation. For every time point at the kinetic curve the jar was loaded new. Mechanical treatment was not interrupted before having reached this point. To improve the statistics, the measurements at each time point were repeated 2—3 times.

Solution-based **P_2S** crystallization

2:1 cocrystals of piroxicam and succinic acid were synthesized from solutions containing 2:1 stoichiometric amounts of **P** and **S** by slow cooling and evaporation of solvent as described in [14]. Ethanol, acetonitrile, acetone, and THF were tested separately under the same conditions. 255 mg of piroxicam and 45 mg of succinic acid were placed in a 40 mm diameter beaker with 20—25 ml of solvent. Mixture was stirred and heated in the beaker with a metal heat accumulating beaker holder, with small amount of solvent added until full dissolution of solid components was observed, while the temperature was kept below the solvent boiling point, and an hourglass was put atop of the beaker. After that, the heater and the hourglass were removed, the crystals were obtained after full evaporation of solvent (several hours). Both single-crystal and powder X-ray diffraction patterns were compared to the ones for previously reported crystal structure of the **P_2S** cocrystal (CCDC: DIKCIK [15]), and the structures were found to match. The crystals belong to space group P-1.

X-ray powder diffraction (XRPD)

For X-ray powder diffraction, XRPD, a STOE STADI MP diffractometer was used ($CuK\alpha_1$ radiation, Ge (111) monochromator, 40 kV operating potential and a current of 40 mA, linear detector Dectris MYTHEN 1K; data were collected in transmission mode using flat sample holders with 2θ in range from 5° to 50°, detector step 1°). The total scanning time per sample was ~35 min. Resulting experimental patterns were analyzed

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qualitatively by comparing them with theoretical patterns calculated from single-crystal diffraction data and with the experimental patterns of the reactants. Quantitative Rietveld analysis was performed with help of GSAS-II program [16], with refinement to minimum possible Rw (6—8% in all cases) and no residual peaks above the noise level in the “calculated – experimental” difference plots. Parameters of structure refinement and the difference plots are given in Supplementary Information.

Results and discussion

Treatment of mixtures of **P** and **S** (testing the possibility of synthesis)

Dry samples

After 30 minutes of ball milling of the 2:1 stoichiometric mixture of **P** and **S** at 25 Hz without adding any solvents, no **P_2S** cocrystals could be detected (Figure 3, d). The only result of treatment of originally white sample was its comminution to a very fine powder colored light yellow. The positions of the peaks of **P** and **S** in the powder diffraction pattern did not change, but a significant broadening of the peaks and a high-intensity uneven background could be observed that could be interpreted both as particle size reduction and/or partial amorphization of the sample. The outcome was the same if steel milling balls of different weight and diameter were used, all other conditions being the same.

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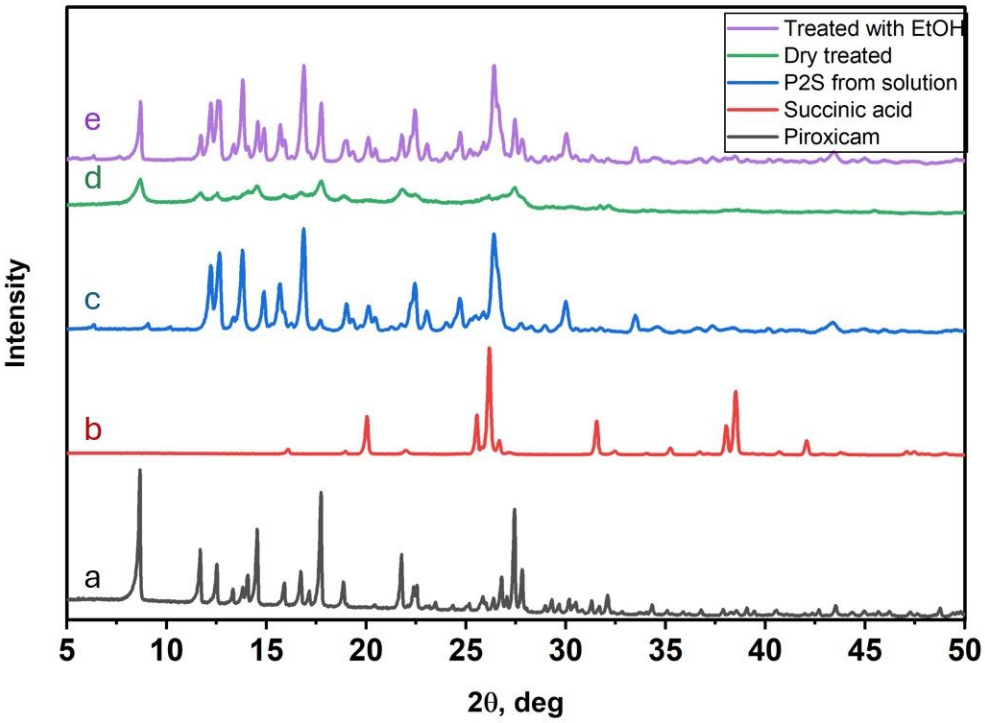

*Figure 3. The powder diffraction patterns of pure **P** (a), **S** (b), **P₂S** cocrystal obtained from solution (c), their mixture after dry treatment (d), and their mixture after treatment with EtOH (e). For dry sample the Rietveld phase composition analysis showed 2/3 and 1/3 molar fractions of **P** and **S**, respectively; zero content of **P₂S**. Note also significant peaks broadening and a high-intensity uneven background. EtOH sample exhibits ~50 mol% **P₂S** alongside the reactants, as well as much less background and sharper peaks.*

For a comparison, the samples of pure succinic acid (100 mg) and of pure piroxicam (100 mg) were treated separately under same conditions. In both cases we could observe approximately the same levels of background in the diffraction patterns. The **S** sample remained colorless, while **P** sample became yellowish.

So, no synthesis of a **P₂S** cocrystal was possible under dry conditions on ball milling at this level of total milling energy, whereas at the same level of total milling energy in LAG conditions the synthesis proceeded to high conversion depths. The yellow coloring can be attributed to mechanochromism of **P** on ball-milling, reproducing previously reported observations, which were interpreted earlier as originating from zwitter-ionic transitions in **P**[17,18].

Samples with solvent drops (LAG)

For LAG treatment, ethanol, tetrahydrofuran, acetonitrile, and acetone were used in the amount of 75 μl, which corresponded to the value of η = 0.75 μl per a mg of dry sample

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mass[ii]. Right after treatment, the mixture had dough-like, smooth consistency and was either distributed evenly on the surfaces of the milling body and the milling jar or formed a wide ring inside the milling jar. In most experiments, the mixture after treatment was colored light brown to light yellow while wet then became very pale after drying.

Diffraction patterns (Figure 3, e) showed clearly that the mechanochemical synthesis of **P_2S** occurred in the presence of solvent. Some unreacted crystalline piroxicam was remaining in the sample after milling. However, the reflections of the remaining crystalline succinic acid were almost undetectable in the diffraction patterns of the same sample, when ethanol, acetonitrile, or acetone were added as solvents. With THF added as solvent, the reflections of the succinic acid crystals were noticeable, but its amount was almost ¾ less than expected based on piroxicam amount determined with Rietveld method. We can suppose that the remaining small amount of succinic acid was either truly amorphous, or X-ray amorphous (finely dispersed) after LAG with piroxicam, and therefore not detectable properly by the X-ray diffraction. Another option that seems less likely is that the remaining particles of succinic acid could be covered with piroxicam and piroxicam **P_2S** cocrystal, which absorb X-rays stronger than succinic acid, and could in this way shield succinic acid from the radiation. Such examples are known from inorganic mechanochemistry, when particles of lithium carbonate were covered by the particles of stronger absorbing compounds containing transition metals, and thus were shielded from X-ray radiation, seemingly disappearing from the sample [21].

The same 2:1 **P_2S** cocrystal was formed as a result of LAG of **P** and **S** under the same conditions (30 min, 25 Hz) with ethanol, acetone, or THF added, but the molar fraction of **P_2S** in the sample varied significantly (Table 1, row 1). When acetonitrile was added, a different product – acetonitrile-solvated cocrystal with stoichiometric ratio of 4 **P** to 1 **S** to 2 **CH_3CN** – was formed (**P_4S x 2CH_3CN**). Its crystallization from acetonitrile solution was documented earlier [22], even though also solvent-free **P_2S** cocrystals can grow from solutions of acetonitrile (this method was used, e.g., in this work, to crystallize **P_2S** as a

[ii] The η criterion is used to demonstrate how wet the reaction mixture is and to what degree should mechanochemical processes be accounted: η between 0 and 1 µl/mg is associated with LAG, 1—6 µl/mg is a typical slurry condition, the larger values are considered as reactions in solution [19,20]. The value has been chosen to match the descriptions of solvent volumes in previous works (refs. 9,14,15).

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starting reactant, in order to study its mechanochemical decomposition). The structure of **P_4S** x **$2CH_3CN$** is remarkable in that it contains piroxicam in two different forms, one of which is zwitterionic. The details of the mechanochemical synthesis of **P_4S** x **$2CH_3CN$** are not analyzed further in this work, since a direct comparison with the synthesis of **P_2S** in the presence of three other solvents is not straightforward. It deserves a special study.

Table 1. Effect of different solvents on the synthesis of piroxicam cocrystals, and solubility of piroxicam and succinic acid in these solvents for a possible correlation. Solubility data from [23–25] for room temperature.

Solvent added on LAG	THF	EtOH	Acetone	CH_3CN
Product	2:1 P:S **(P_2S)**			4:1:2 P:S:CH_3CN **(P_4S** x **$2CH_3CN$)**
Molar fraction of **P_2S** after 30 min of treatment at 25 Hz	0.04	0.50	1 (0.75 if treated for 10 min)	
Solubility of **P**, max mol fraction	<< $6 \cdot 10^{-4}$	$1.77 \cdot 10^{-4}$	$49 \cdot 10^{-4}$	
Solubility of **S**, max mol fraction	0.023	0.026	0.017	
Solvent boiling point, °C	66	78	56	

*Kinetics of **P_2S** synthesis*

With the same stoichiometric load, a standard amount of ethanol and fixed 25 Hz milling jar oscillations frequency, we varied the processing time in order to study the kinetics of the synthesis of **P_2S** (Figure 4**)**. The transformation had no induction period. In order to further confirm this, we performed another experiment, in which the sample wet with ethanol was not subject to mechanical treatment, but instead was stirred lightly with a

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spatula for 1—2 mins, and after this treatment the trace amounts of P_2S were already clearly visible on the diffraction pattern. The degree of conversion increased continuously with time.

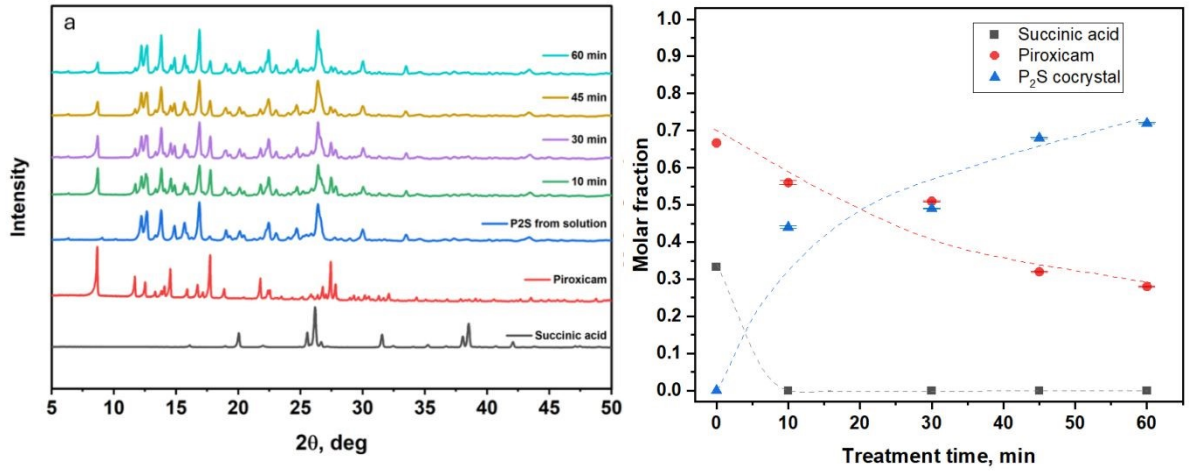

*Figure 4. (a) The powder diffraction patterns of the samples extracted from the jar after different durations of milling in the presence of ethanol at 25 Hz milling jar vibrations frequency, (b) the corresponding changes in the molar contents of the reactants (**P** and **S**) and of the product (**P_2S**). The dotted curves reflect the general trend and are not a mathematical approximation.*

The frequency of milling jar oscillations had a pronounced effect on the rate of the mechanochemical synthesis. The available range for frequency variations (15—50 Hz) was scanned with a variable step with 2—3 repetitions per point. For all the experiments with the variable oscillations frequency we used the same treatment time of 30 minutes. During this time approximately 50% of **P_2S** were formed at 25 Hz frequency. The higher the frequency of milling jar oscillations, the more **P_2S** was synthesized during the same time (Figure 5). For some of the points, the milling jar geometry was modified slightly (~1% of total height deviation from ideal spherical shape of the jar) by changing the rubber O-ring between the two halves. This change was originally purely “technical” and not expected to cause a dramatic change in the transformations. However, serendipitously, we observed that the slight distortion of the jar shape resulted in a significant increase in the amount of the **P_2S** product formed as compared with the originally ideally spherical jar during the same treatment time under the same conditions. Also, the results scattered more when treating the sample in slightly aspherical jar (Figure 5).

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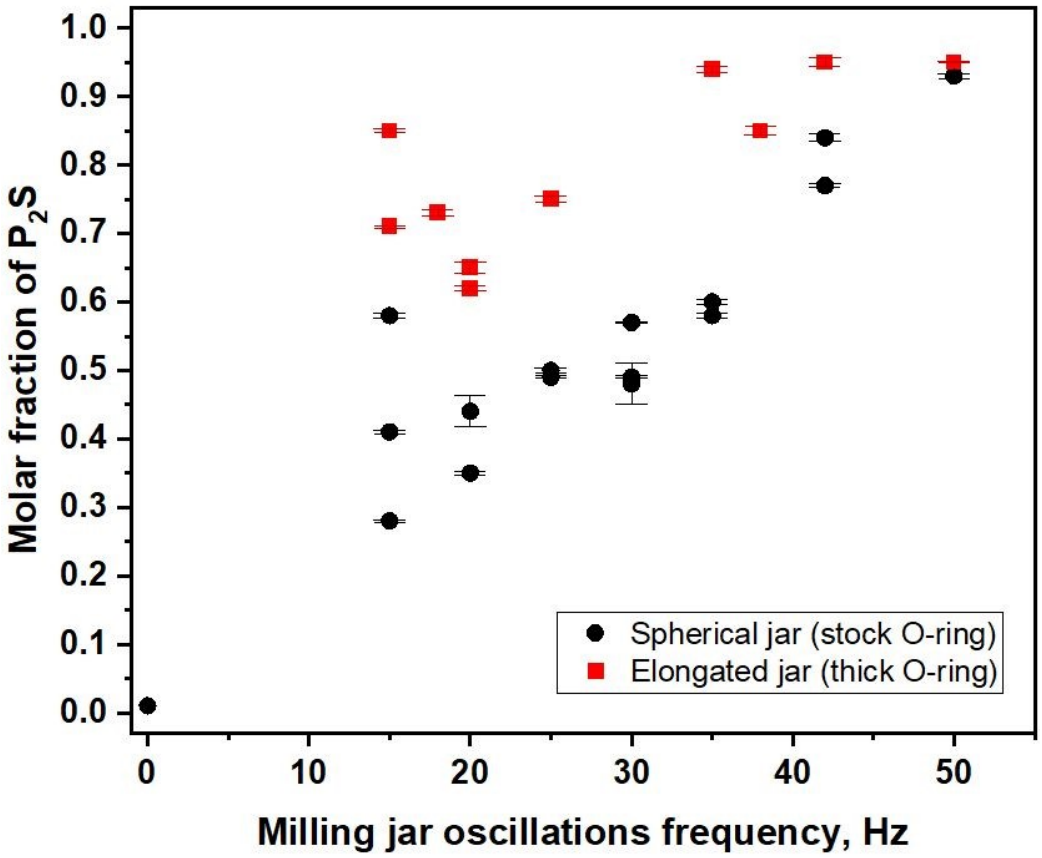

*Figure 5. Molar fraction of **P_2S** in the sample treated for 30 minutes at various milling jar oscillations frequency. Black circles – spherical jar, red squares – a slightly (1%) elongated jar.*

The change of the standard O-ring for a thicker one and the corresponding deviation of the jar from the spherical shape resulted also in the change in the sound of the ball hitting the jar walls during ball milling (Figure S3 in Supplementary Information).

The analysis of the sound made by the ball impacting the jar shows that slight changes in the milling jar geometry led to significant changes in the milling body movements, changing, in particular, the ratio between the impacts and the rolling of the ball. Three characteristics were used to describe the sound differences:

1. The appearance of waveform peaks that have a sharp left-side profile and are close in shape to a single manually initiated impact sound waveform. To consider the waveform, we introduce criterion *A*, which we define as the mean number of milling body impacts during one vibration cycle: $A = \frac{Number\ of\ impacts}{Number\ of\ vibration\ cycles}$. By counting the peaks corresponding to the impacts for each frequency *f* (Table 2,

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Figure 6) over no less than 2 seconds of recorded sound, we establish the linear interpolating functions *A(f)*, whose coefficients depend on milling jar geometry. Using these functions for each series, we convert the 'milling jar frequency' x-axis dimension to the number of impacts that happened during each experiment (Figure 7). This conversion is applied to correlate the molar fraction of **P_2S** with this number, and clearly the three different series are now much closer to each other, supporting the discussed role of impacts.

2. The general loudness, because clearly the impacts make louder noise than sliding or rolling. Quantified as root-mean-square (RMS) amplitude in dBFS[iii] of the recorded sound, 10 seconds of recorded sound were used. Clearly, the louder sounds do correlate with larger values of *A* (Table 2).
3. The spectral composition of the sound. It was qualitatively analyzed by presence or absence of the low-frequency-band noise, which is present on the impact sound sample but absent on sliding and rolling.

Table 2. The results of the sound recording analyses used to evaluate the A criterion – the mean number of impacts occurring in one milling jar oscillation cycle.

Frequency, Hz	No. of cycles	No. of impacts	*A*	Amplitude RMS, dBFS[iii]
Regular O-ring				
15	114	93	0,8	-25,6
25	93	102	1,1	
25 (another experiment)	127	171	1,4	-23,3
30	146	191	1,3	
50	132	277	2,1	-20,7
Thick O-ring				
15	116	188	1,6	-22,4
25	105	250	2,4	-22,5
30	99	205	2,1	
50	101	230	2,3	-20,0
Rotational mill				
15	138	13	0,1	-37,2

[iii] The amplitude of the recorded sound is measured here (and in Audacity software by default) in decibels full-scale (dBFS), which express the amplitude of the recorded digital signal relative to the analog-digital converter's maximum possible digital output and therefore is always negative; the larger (closer to zero) the value, the louder is the sound.

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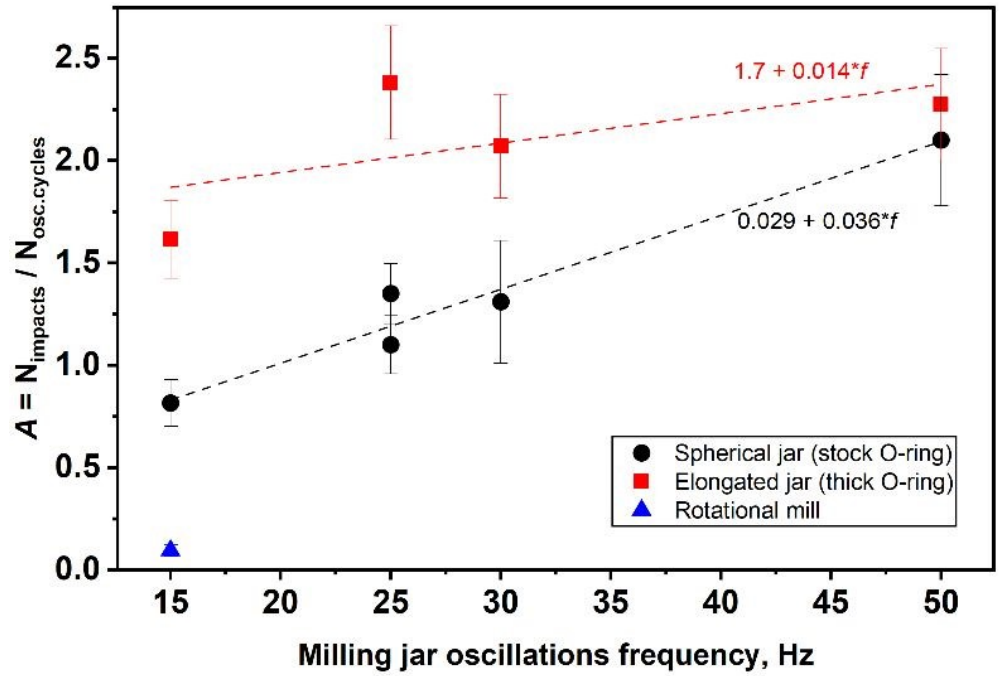

Figure 6. The experimental values of A – the mean number of impacts per one vibration cycle – plotted against frequency of mill oscillations. See Table 2. Black circles – spherical jar, red squares – a slightly (1%) elongated jar; blue triangle – rotational mill (very few impacts occur during treatment).

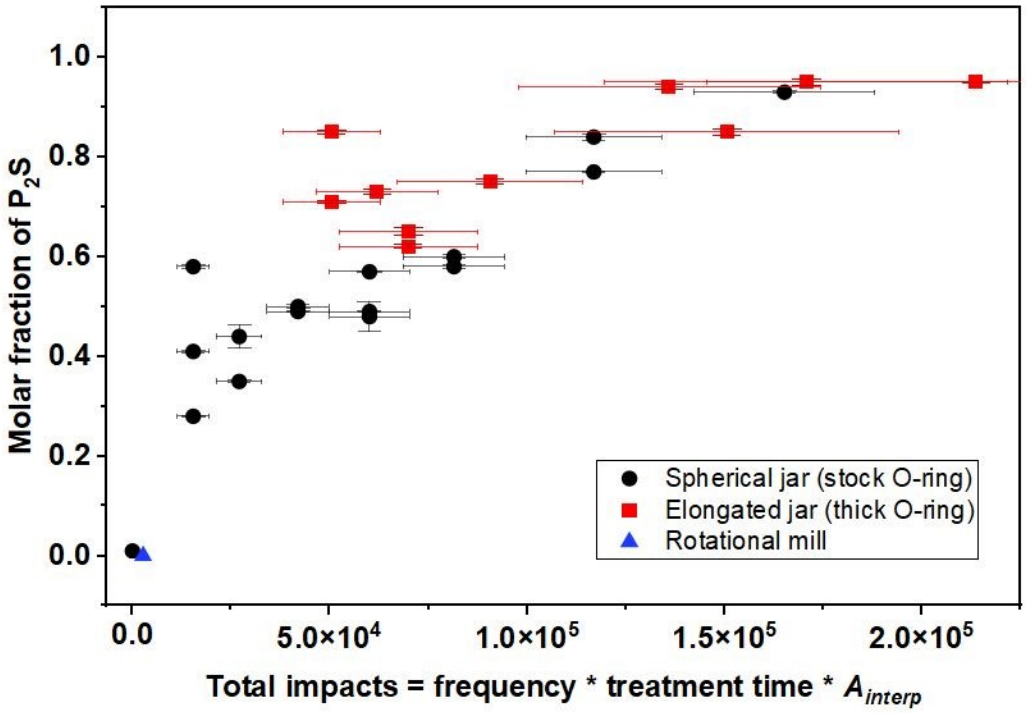

*Figure 7. Molar fraction of **P_2S** in the sample treated for 30 minutes at various milling jar oscillations frequency, plotted against the estimate of total number of impacts. Black circles – spherical jar, red squares – a slightly (1%) elongated jar; blue triangles – rotational mill (very little impacts occur during treatment).*

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In agreement with (4), impacts favored the synthesis of **P_2S** from the components, in contrast to rolling the ball against the walls. For a comparison, we have designed, manufactured and used a model device with pure rolling of a ball against the walls – a rotational mill (Figure 2, b). With the rotation frequency of this mill equal to 15 Hz (900 rpm) the conversion depth of a mixture of **P** and **S** to **P_2S** was zero as evidenced by X-ray diffraction; the mixture of **P** and **S** remained white after treatment, even before drying, in contrast to light brown color after a typical treatment in vibrational mill. So, as already documented in (4), synthesis of **P_2S** from a mixture of **P** and **S** required ball impacts and was not initiated by ball rolling.

Treatment of **P_2S** cocrystals (testing the possibility of decomposition)

Dry cocrystal

In contrast to the synthesis of **P_2S**, its mechanochemical decomposition was partly successful for dry samples, though not complete. After 100 mg of dry **P_2S** powder (crystallized from acetonitrile solution as described in Experimental) were ball milled for 30 minutes at 25 Hz, the sample contained approximately equal molar amounts of **P_2S** and α-polymorph of the orthorhombic piroxicam (CCDC: BIYSEH02). The mixture had deep and bright yellow color. Noteworthy, the α-polymorph formed on mechanochemical decomposition of **P_2S** is another polymorph of **P** but not the monoclinic β-polymorph used in the experiments on mechanochemical synthesis. No reflections of significant intensity corresponding to succinic acid could be detected in the powder diffraction patterns. We cannot find any better interpretation for this fact than assuming the succinic acid formed on decomposition to be either truly, or X-ray amorphous.

At the same time, after 30 minutes treatment in the rotational mill at 15 rev/s no decomposition of **P_2S** could be detected by X-ray powder diffraction, although the sample became pale yellow. The absence of the decomposition of dry **P_2S** in the rotational ball mill, although it could be expected for shear treatment based on (4) and on the results obtained using Fritsch Pulverisette 23 mini in this work, may be explained by the comparison of the ‘static’ or ‘quasi-static’ pressure: the 9 g milling metal ball used

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in our rotational mill, versus the added weight of 1.2 kg[iv] on the top of the shearing device in (4).

Cocrystal with solvent

Also in contrast with the synthesis of **P_2S**, adding fluids did not favor the decomposition of the **P_2S** on ball milling. On the contrary, no decomposition at all could be observed, when **P_2S** was treated either in a vibrational ball mill, or in the rotational mill under the same conditions as the dry sample (30 minutes treatment; 25 Hz for vibrational mill, 15 and 22.75 Hz in rotational mill), but with 75 µl ($\eta = 0.75$) of ethanol added. The powder diffraction patterns before and after mechanical treatment looked almost identical, with the FWHM slightly increased after the treatment. The sample turned light yellow while wet and colorless after drying.

Discussion

In this work we have revisited the mechanochemical transformations in the "piroxicam – succinic acid – their cocrystal(s)" system that was studied earlier [9,15]. We used not model devices with a dominating type of mechanical action (restricted impact or shear), as in [9], but a commercial vibrational ball mill, in which both impacts and rolling are possible, their ratio depending on the jar oscillation frequency. If dry reactants were used, we could not observe the synthesis of **P_2S** from **P** and **S**, whereas the decomposition of dry **P_2S** into the components occurred. The decomposition was not complete during the standard treatment time used in this work (30 minutes); we did not attempt to increase the treatment time further. If ethanol was added to the reactants (like in [9]), the synthesis of **P_2S** could be observed on ball milling; on the contrary, no decomposition of the **P_2S** was possible in the presence of solvent.

In general, the fact that a solvent facilitates the synthesis of a cocrystal, and, in particular, of a piroxicam cocrystal, agrees with published data [9,14,15,20,26]. On the contrary, dry grinding has much lower "success rate", as screening experiments showed [15,26,27]. On mechanochemical synthesis of piroxicam-saccharin [26], and caffeine-oxalic acid [28] cocrystals, the presence of the products of chemical interaction between the

[iv] The details of both devices were obtained in personal discussion with the authors of [9].

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reactants after dry ball milling was confirmed, but they failed to crystallize without solvent and the samples remained amorphous. In our case, we also observed the background of the X-ray powder diffraction pattern from the dry mixture of **P** and **S** after ball milling, which could belong to an amorphous sample (Figure 3, d). We could not determine reliably whether this background was due to the presence of amorphous succinic acid, piroxicam, or an amorphous product of their mechanochemical reaction, but we could conclude reliably that neither crystalline **P_2S**, nor any other crystalline products formed.

One of the most common mechanisms of the effect of a fluid on the mechanochemical transformation is related to partial dissolution in one or more reactants in the fluid with subsequent (re)crystallization [6,7,20,29–31]. The liquids used in this work - ethanol, THF, acetone, acetonitrile – can in fact dissolve the components **P** and **S** of the powder mixture, and their cocrystals are known to crystallize from these solutions without any mechanical action (on slow cooling and evaporation) [14,15,22–25,27]. Therefore, indeed, the mechanochemical synthesis can be supposed to proceed *via* the dissolution of one or both components in solution with subsequent crystallization of the cocrystal as the product. For ethanol, THF, and acetone, two orders of magnitude difference in conversion degree when adding different solvents (after same 30 min treatment under otherwise identical conditions) was observed, suggesting that the interaction between reactants and solvent may limit the rate of the overall process. The solubility of reactants, especially that of piroxicam, in a selected solvent[v], looks related to the rate of mechanochemical synthesis (Table 1). At the same time, the dissolution in a small amount of solvent at the contacts between the particles and subsequent crystallization are different from these processes in a bulky vessel under equilibrium crystallization conditions. It is worth noting that this experiment was done at the fixed η = 0.75 µl/mg, which yields close but different molar amounts of the solvents: 12.8 mmol/g for ethanol, 10.2 mmol/g for acetone and 9.25 mmol/g for THF. By fixing η, we initially aimed to guarantee same physical properties of the reaction mixtures, not being sure that the

[v] The solubility data for piroxicam and succinic acid in Table 1 correspond to ambient conditions. Solubility may increase under mechanical activation of molecular solids [32], and also for piroxicam [18], however exact values for the solvents used in this work are not available for piroxicam and succinic acid.

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chemical role of the solvent would be that significant. The comparison still remains appropriate because the molar content of solvent does not explain the different reaction rate in the supposed correlation, but instead further increases the significance of solubility of piroxicam. The mechanochemical synthesis of the acetonitrile solvate of piroxicam with succinic acid under mechanical treatment with acetonitrile[vi] in this work instead of the **P_2S** (which was expected based on previous work [14]) illustrates that the results of a mechanochemical crystallization on LAG are not always easy to predict *a priori*. A further study of the mechanochemical transformations in the presence of acetonitrile under different conditions may help to rationalize the factors that control the outcome of the mechanocrystallization in the presence of this solvent.

Reactions of the mechanochemical synthesis that are liquid-mediated may have an induction period, if time is needed to release the liquid from a reactant (a crystal solvate, *e.g.* a crystal hydrate) and/or to dissolve the reactants. Such an example is provided by the synthesis of the glycinium oxalates from glycine and oxalic acid dihydrate, in which release of water from a crystal hydrate and its accumulation as a liquid phase seemed to be a rate-limiting stage, the induction period shortening as humidity increased, or as water was added to the sample as a liquid deliberately [33]. The induction period of the mechanosynthesis of glycinium oxalates also depended on which polymorph of glycine was used as a starting reactant, being shorter for the form that dissolved faster (γ-glycine), thus revealing the role of the dissolution of the reactants in the kinetics of the synthesis [33]. The synthesis of **P_2S** during LAG with solvent added as a drop of liquid "ready-to-use" from the very beginning had no induction period (Figure 4). Apparently, also the dissolution of the reactants and their crystallization were not delayed.

One more difference in the mechanocrystallization of **P_2S** as compared to the mechanocrystallization of the glycinium oxalates [33] is the opposite effect of the frequency of impacts on the two transformations. The increase in this frequency is favorable for the synthesis of **P_2S** (Figure 7), whereas in the case of the synthesis of glycinium oxalates an increase in the impacts frequency resulted in an increase in the induction period of the transformation, suggesting that rate-limiting stages occurred

[vi] Apparently, this is the first evidence of the mechanochemical synthesis of this solvated cocrystal.

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between the impacts [33]. Apparently, the LAG synthesis of **P_2S** proceeds at the same moments as impacts occur. The role of mechanical treatment is to comminute and possibly disorder the crystal structure(s) of the reactant(s) facilitating their dissolution in the added liquid, and crystallization of the cocrystal occurs as soon as the dissolved components meet each other.

An interesting point is the somewhat unusual effect of added solvent on the reverse reaction, namely on the mechanochemical decomposition of **P_2S**: it occurs only if the reactant is dry, but not if some liquid is added. In previous work [9] decomposition of **P_2S** was connected with shearing (grinding) action of the milling bodies (as opposed to impacting), being observed only in a model apparatus specifically designed for this type of mechanical action. Dry decomposition in a vibrational mill supports the hypothesis that this is a solid-state transformation and its mechanism is related to the crystal structure of **P_2S**. Considering the layered crystal structure of **P_2S** (Figure 8, a), where the flat layers are formed by strongly bonded …-P-P-S-P-P-S-… chains [15], its mechanically initiated decomposition could hypothetically be explained by the possible disruption of weaker interlayer contacts upon relative displacement of the layers when the lattice is deformed. The layers are held together by H-bonds that are formed by a single oxygen atom of piroxicam molecule (that is displaced from its molecule's layer towards the nearest other layer) and two nearest H atoms belonging to different molecules; the lengths of these H-bonds are approx. 2.6 Å and 2.9 Å, with O-to-donor distances 3.5 Å and 3.6 Å, respectively. The orthorhombic α-piroxicam (Figure 8, b) is produced in the decomposition process, and the possible reason why this polymorph, but not the β-polymorph, is formed, is that the piroxicam molecules in the α-polymorph interact side-by-side with the same part of molecule as in **P_2S** structure.

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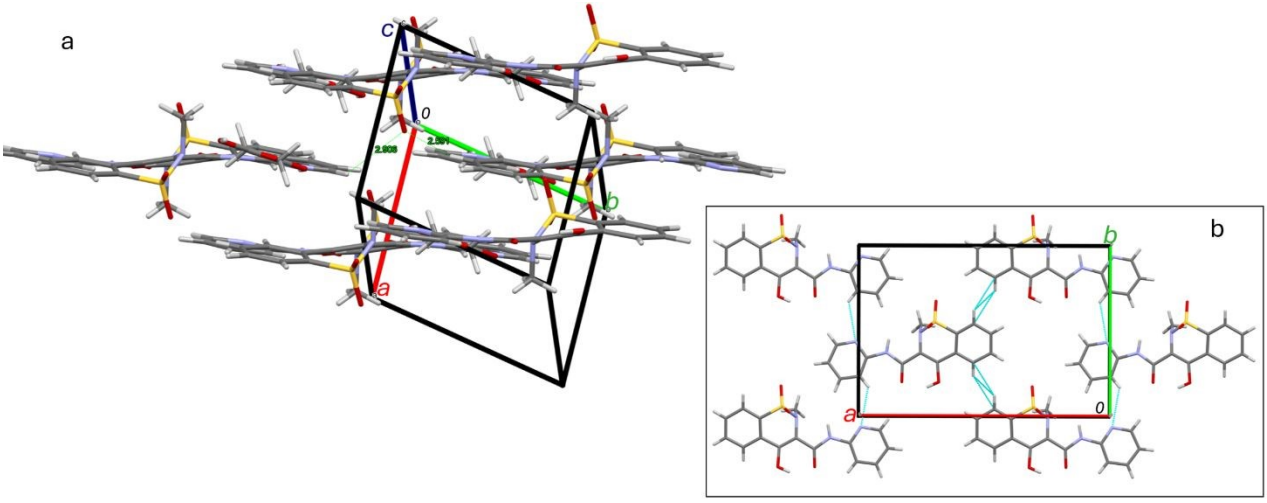

*Figure 8. a) The layered structure of **P_2S** crystals, showcasing single oxygen atom that provides interlayer bonding, b) crystal structure of α-piroxicam, where the piroxicam molecules have similar side contacts to the piroxicam molecules of the neighboring chains of the **P_2S** structure*

A question, why the decomposition of **P_2S** does not occur on LAG, when some solvent is present in contact with the solid, is not a trivial one. We may suppose that the reason is in the existence of an equilibrium between decomposition and reverse crystallization in the presence of a solvent. When ball milling initiates the decomposition of **P_2S** cocrystals to **P** and **S**, the two components can re-assemble again in solution to form the cocrystal again, and no transformation is observed. If the amount of solvent permits, the synthesis rate will exceed the decomposition rate. This hypothesis could also explain why the decomposition of **P_2S** was observed in [9] for wet (with ethanol additive) grinding in a model shear device. The amount of liquid added to the sample in [9] was smaller than in this work. Besides, ethanol could evaporate from the sample in the model device with shear action, which was not airtight, so that treatment became dry.

The hypothesis of the existence of an equilibrium between the synthesis of **P_2S** and its decomposition to the **P** and **S** components adds one more argument, why the synthesis of **P_2S** could not be observed, when dry components were ball milled. Under these conditions a dry **P_2S** cocrystal, even should it be formed, would decompose under mechanical treatment back to **P** and **S**, and this would manifest itself as no synthesis. The same hypothesis may explain also, why the synthesis in the restricted impact device in [9] was documented, when ethanol was added to the sample. Even though this device was not hermetically sealed, so that the added liquid could eventually evaporate,

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the synthesis was possible as long as η was still high enough. The latter hypothesis is supported by the fact that even though the product of the synthesis in [9] was dry, it was caked, and this indicated that a fluid was involved in its formation.

Conclusions

This work illustrates once again that mechanochemical transformations can be affected by many factors simultaneously, and even the systems that have been studied earlier and may seem well understood can bring surprises. The opposite direction of the transformation (synthesis or decomposition of the **P_2S** cocrystal from **P** and **S**) was observed earlier depending on the type of mechanical action. In this work we have shown that also the presence of a solvent can have opposite effect on these transformations. Under the conditions of treatment used in this work, the synthesis could be observed only in the presence of a solvent, whereas decomposition – only if the sample was dry. The choice of solvent, its amount, the frequency of impacts on ball milling also had effect on the mechanochemical transformations.

The seemingly 'solid + solid = solid' mechanosynthesis can only proceed with or after local dissolution of coformers, followed by crystallization of cocrystal phase. The dissolution stage is likely to affect the reaction rate, since the latter is directly related to the solubility of **P** in the solvent. In turn, the decomposition of **P_2S** cocrystals was proved to be a solid-state transformation, a mechanically induced and likely governed by the structural anisotropy and relative mechanical weakness of specific intermolecular interactions within the **P_2S** crystal structure phenomenon, which becomes the only direction of the reaction under dry conditions. While we may conclude that it is the mechanical load which leads to the decomposition, our data were not sufficient to state that the difference between impacting and shear-loading (grinding) is solely responsible for the direction of the transformations in case of treating the samples in a vibrational mill. The results show with certainty only that a competition between synthesis and decomposition of **P_2S** will always occur in the milling devices, in which mechanical treatment is a combination of impact and shear.

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The milling jar oscillations frequency (which is set as a treatment parameter and is therefore known) was shown to affect the transformation *via* changing the frequency of impacts in the mechanochemical device (an important parameter which is often hard, or even impossible to calculate directly). The 30-min conversion depth of the synthesis of **P_2S** was found to be directly related to the total number of impacts of the milling body, but not to the total number of vibration cycles. We could not find any direct evidence of the induction period of the reaction. In the transformation studied in this work each impact seems to contribute to the synthesis.

Summing up, the mechanochemical synthesis of **P_2S** is best described as a solvent-mediated transformation where mechanical energy input primarily overcomes kinetic barriers to dissolution and recrystallization, whereas the reverse mechanochemical decomposition is a solid-state process that occurs only in dry samples, when reverse synthesis is not possible. Shear stress accounts for the cleavage of the **P_2S** structure separating the layers from each other and facilitates the decomposition of **P_2S** into the metastable α-polymorph of piroxicam (**P)** and succinic acid **(S)**.

The complex interplay of factors – solvent nature, exact liquid amount, milling jar geometry, impact regime – makes it challenging, but still possible to establish a control over this reversible cocrystal formation, avoiding its decomposition. This case study can be extended to other drugs and coformers, considering the importance of mechanochemical technologies for the synthesis of pharmaceutical cocrystals, in particular – of cocrystals of various oxicams[14,15,25,26,34–42]. The issues that remained not considered in this work – the possibility and the nature of partial amorphization on different types of mechanical treatment in the presence of different solvents in relation to the effect of a solvent on the zwitter-ionic transitions – deserve a special study using spectroscopy, DSC and molecular modelling.

Authors contributions

Golomolzin: Investigation, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. Losev: Investigation, Formal analysis, Writing – review & editing.

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Boldyreva: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Funding acquisition.

Conflicts of interest

There are no conflicts to declare.

Data availability

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

The data supporting the findings of this study are openly available. This study utilized publicly available crystallographic data obtained from the Cambridge Crystallographic Data Centre (CCDC). The specific reference codes for the structures referenced in this work are: DIKCIK, BIYSEH01, BIYSEH02, SUCACB01, SUCACB02. These data can be accessed free of charge from https://www.ccdc.cam.ac.uk/.

The raw experimental sound recordings have been deposited in a Figshare repository under accession DOI: 10.6084/m9.figshare.32065077.

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Generative AI was not used at all in the process of writing this article.

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The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

The data supporting the findings of this study are openly available. This study utilized publicly available crystallographic data obtained from the Cambridge Crystallographic Data Centre (CCDC). The specific reference codes for the structures referenced in this work are: DIKCIK, BIYSEH01, BIYSEH02, SUCACB01, SUCACB02. These data can be accessed free of charge from https://www.ccdc.cam.ac.uk/.

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