Supplementary Information (SI) for Physical Chemistry Chemical Physics.

Supporting information

Kinetics of the mechanically induced ibuprofen-nicotinamide co-crystal formation by *in-situ* X-ray diffraction

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PXRD data

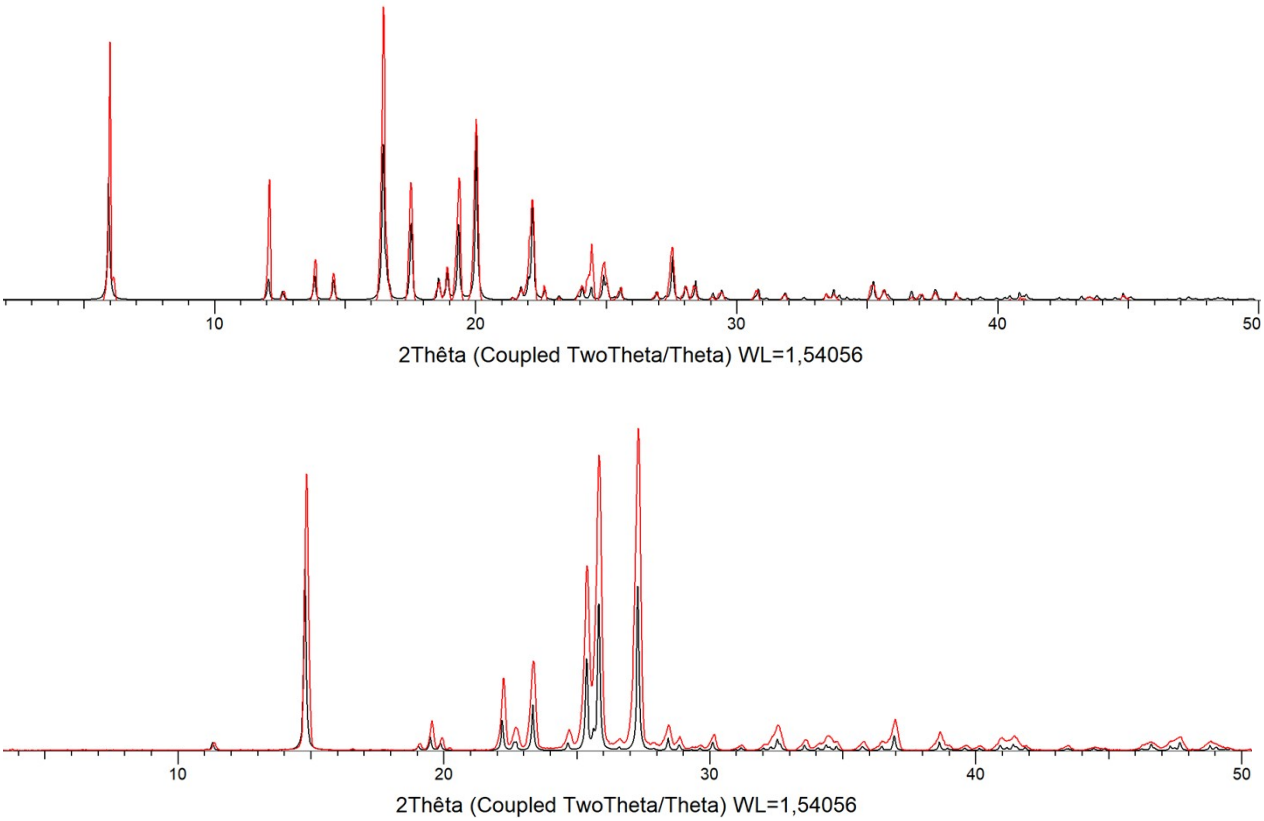


Fig.SI1a. Comparison between the tabulated (black line) and the experimental (red line) pattern for the reagents ibuprofen (up) and nicotinamide (bottom).

For the reaction performed for 1 hour at 50 Hz with a 10 mm ball size, the mechanical stimulation didn't lead to an amorphous state of the starting materials. By comparing the experimental and the tabulated PXRDs, it is notable that the crystallinity is surely worsened upon the mechanical stimulation, but undoubtedly still detectable. Therefore, the disappearance of the reagents monitored over time is surely ascribable to their conversion in the final product, and not to the impossibility of detecting the amorphous state.

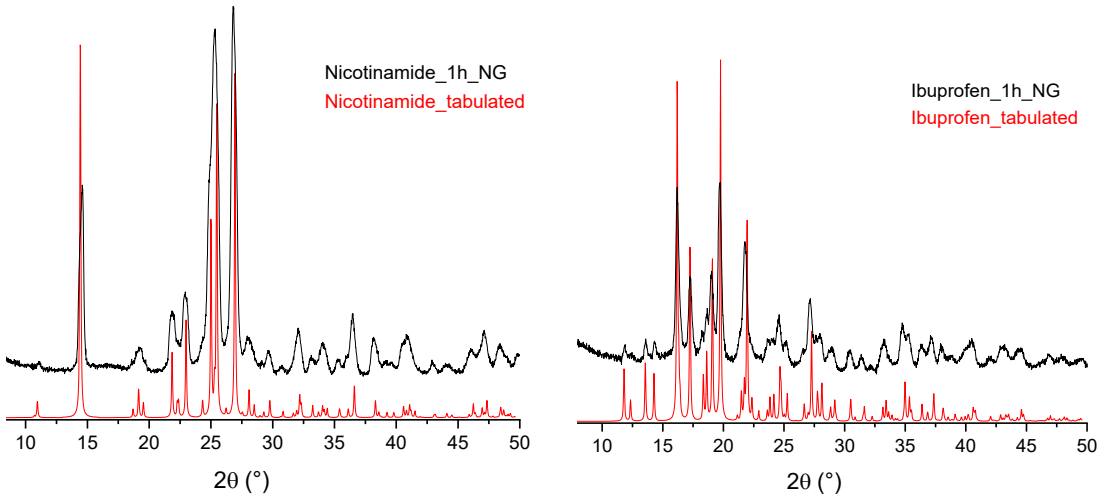
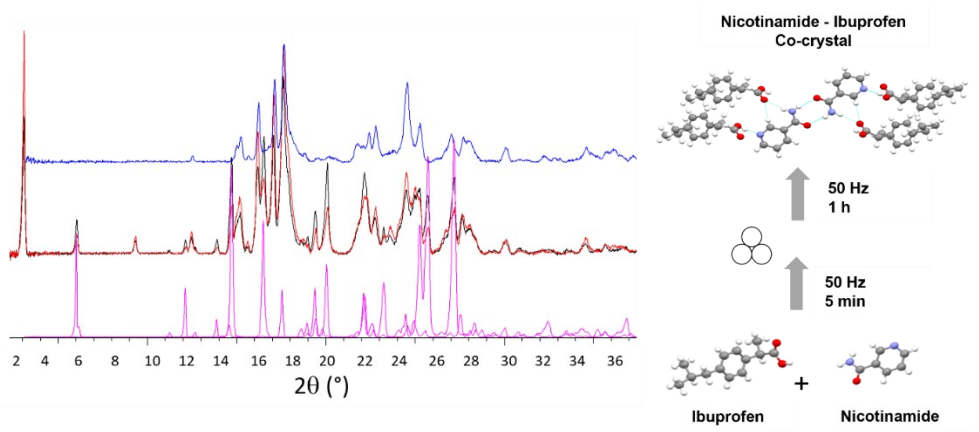


Fig.SI1b. Comparison between the tabulated (black line) and the experimental (red line) pattern for the reagents ibuprofen (up) and nicotinamide (bottom).

a)



b)

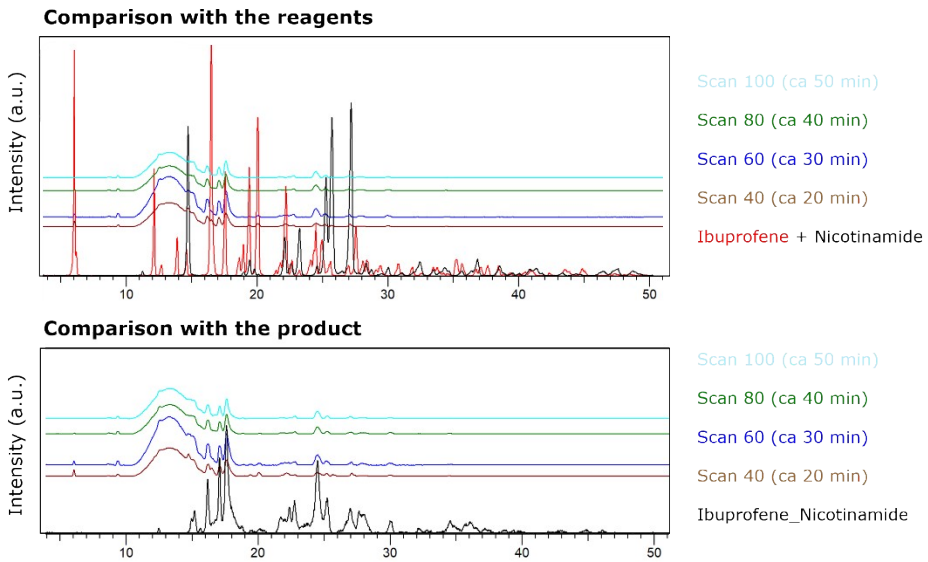


Fig.SI2. a) Comparison between reagents (pink line), product (blue line), the powder after 5 minutes of reaction collected immediately (black line) and two days later (red line). On the right, it is showna a scheme of the mechanochemical reaction. b) Comparison of selected diffractograms at different milling times.

Consumption of reactant phases

By comparing a few diffractograms at different milling times both with the reagents and with the expected product (see Fig.SI2b)), we could appreciate better the variations of the relative intensities, and check if the qualitative methods were suitable in detecting the consumption of the reactant phases. By looking in the details of the single diffractograms, the reaction is surely completed between 30 and 40 minutes, accordingly to what found with the MCS-ALS method.

Kinetic Modelling

In the absence of more detailed information, it is reasonable to consider the simplest possible assumptions that allow obtaining an exponential transformation kinetics in line with experimental evidence. We note that Eq. 2 (in the main text) results in an exponential rate law if we hypothesize that the degree of chemical conversion in individual volumes v^*, α_i, changes abruptly from 0 to 1 as the volumes undergo a single CLC. In other words, this hypothesis implies that all the volume v is involved in the formation of the co-crystal between ibuprofen and nicotinamide already at the very first CLC it undergoes. In such volume, the transformation is complete.

Therefore, the fraction of final co-crystal can be expressed as

$$\alpha(m) = 1 - exp(-\kappa\, m). \qquad (2a)$$

It follows that

$$ln[1 - \alpha(m)] = -\kappa\, m. \qquad (2b)$$

that leads to (3) and (4) in the main text.

Numerical simulations

The numerical reconstruction of the ball motion inside the moving jar makes use of two different frames of Cartesian axes. The inertial Cartesian frame is used to describe the harmonic motion undergone by the jar along the vertical direction. The non-inertial Cartesian frame undergoes integral motion with the jar and is used to suitably identify the geometric constraints on the ball motion.

The ball can freely sample the volume inside the moving jar as far as it is not in contact with it. As the ball comes into contact with the jar, the component of the non-inertial velocity perpendicular to the impacted surface is reversed and its modulus scaled by a coefficient of restitution ranging between 0 (perfectly inelastic impact) and 1 (perfectly elastic impact).

A threshold value in the impact velocity of 0.1 m s^{-1} was used to discriminate between simple contacts and real impacts. The time step used to integrate the equations of motion was set equal to 0.01 ms, which is, approximately, the time duration of a perfectly elastic impact.

A typical example of the ball trajectories inside the moving jar is shown in Fig. SI3.

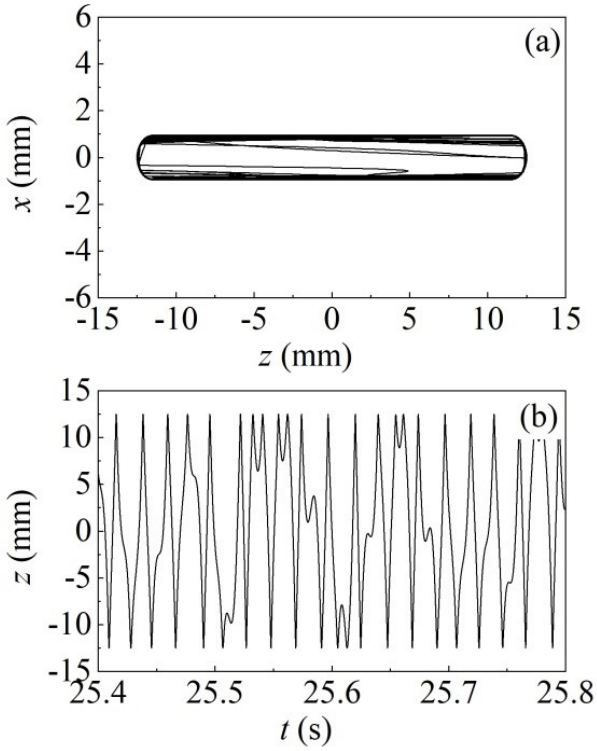
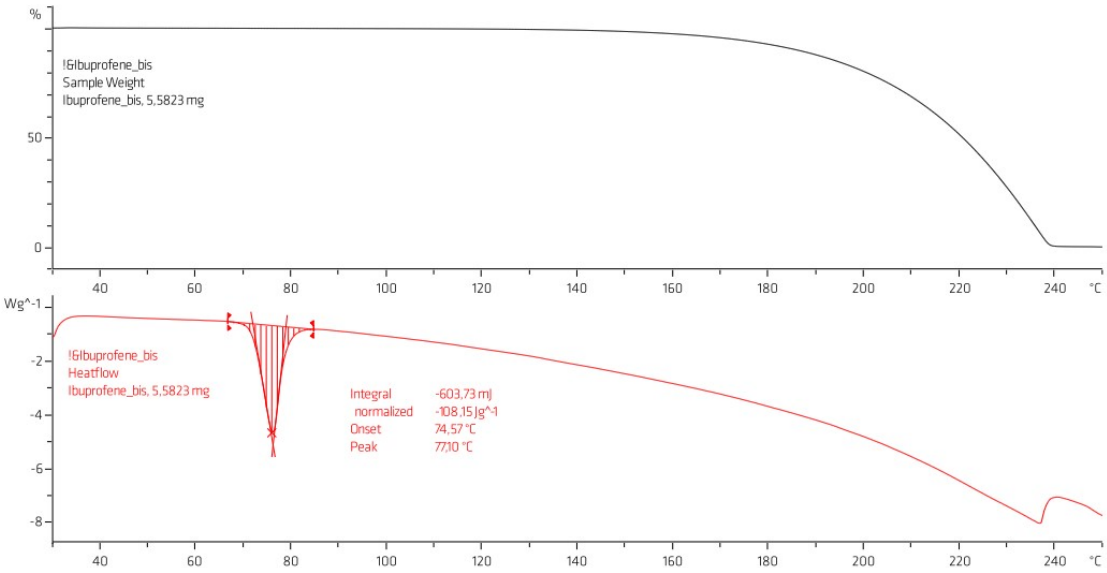
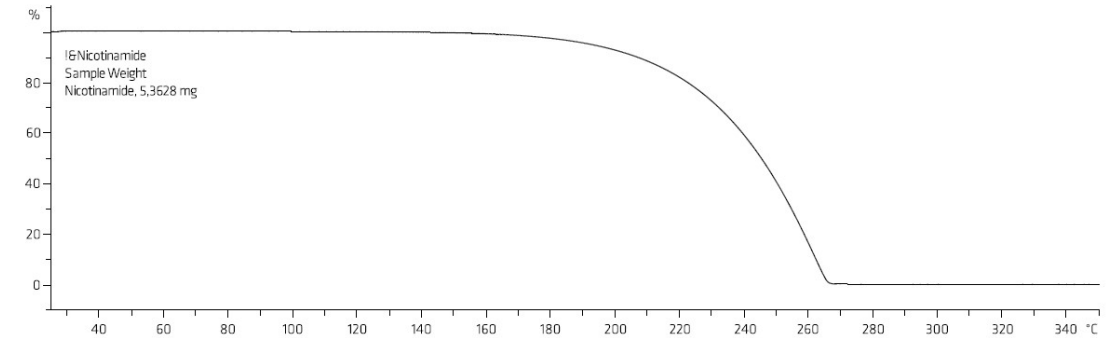


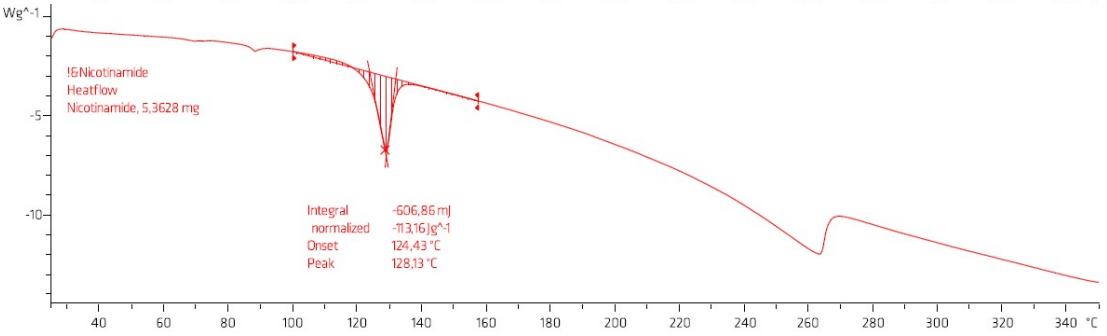
Fig. SI3. (a) Two-dimensional projection of the ball trajectories. Data refer to a ball of 10 mm in diameter and a coefficient of restitution of 0.4. (b) The ball coordinate along the jar main axis, z, as a function of time, t. Absolute maxima and minima mark the occurrence of impacts on the hemispherical caps.

DSC


%
!&Ibuprofene_bis
Sample Weight
Ibuprofene_bis, 5,5823 mg
50
0
40
60
80
100
120
140
160
180
200
220
240
°C

Wg^-1
!&Ibuprofene_bis
Heatflow
Ibuprofene_bis, 5,5823 mg
Integral -603,73 mJ
normalized -108,15 Jg^-1
Onset 74,57 °C
Peak 77,10 °C
-2
-4
-6
-8
40
60
80
100
120
140
160
180
200
220
240
°C


%
!&Nicotinamide
Sample Weight
Nicotinamide, 5,3628 mg
80
60
40
20
0
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
°C


Wg^-1
!&Nicotinamide
Heatflow
Nicotinamide, 5,3628 mg
Integral -606,86 mJ
normalized -113,16 Jg^-1
Onset 124,43 °C
Peak 128,13 °C
-5
-10
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
°C

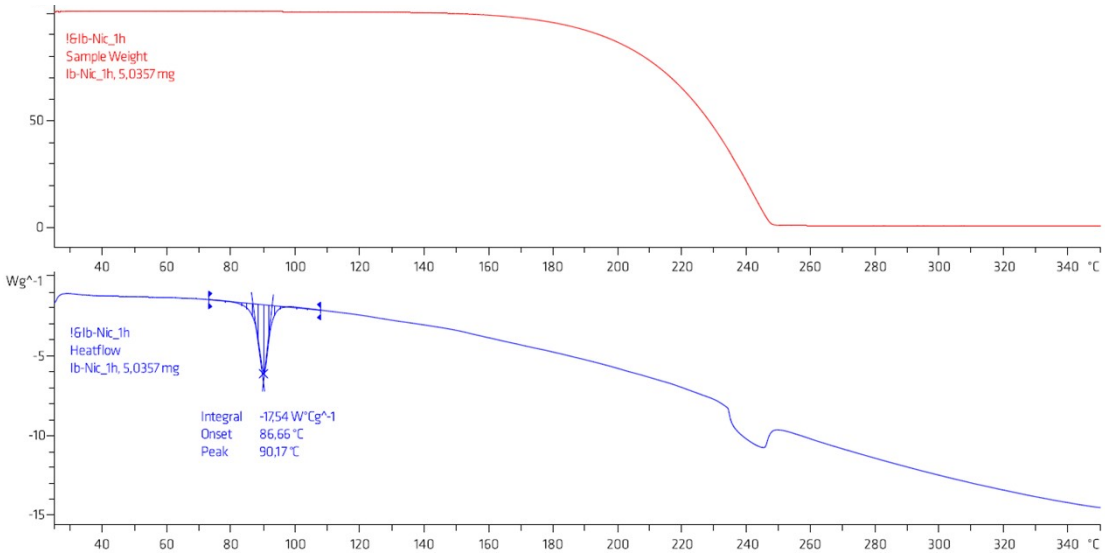


Fig.SI4: TGA and DSC profiles for ibuprofen (up), nicotinamide (middle) and the co-crystal ibuprofen-nicotinamide (bottom).

Ball motion in the jar

Although most intense signals due to main impacts partially overlap with those due to rebounds, the sequence of impacts generated by the piezoelectric sensor matches well with the sequence generated by numerical simulations. The intensity of most intense signals follows an alternating pattern, thus suggesting that main consecutive impacts occur on opposite jar bases, in agreement with the outcomes of calculations. Furthermore, the experimentally determined impact frequency is equal, on the average, to about 93 Hz, which compares remarkably well with the value of about 96 Hz estimated numerically. Accordingly, experimental data seem to provide support to the numerical simulations. It follows that the coefficient of restitution used in calculations can be also thought to represent realistically the elasticity of impacts, at least to a first, rough approximation.

Encouraging indications in this respect come from the analysis of videos recorded using a high-speed video camera (Fig.SI 5). Indeed, the videos reveal that the ball impacts on the jar bases with a velocity, v_{imp}, ranging in the interval between 2.0 m s^{-1} and 4.0 m s^{-1} and a frequency of about 98 Hz. Considering the uncertainties affecting these estimates, they are very close to the ones obtained by the experimental and numerical methods mentioned above, so that the coefficient of restitution of 0.4 gains further credibility.

In light of this, the energy transferred to compressed powders of ibuprofen ranges approximately between 3.0 mJ and 20.0 mJ, but the energy required to induce the melting of 0.44 mg of ibuprofen (ibuprofen value estimated to be trapped in the milling ball) ranges between 0.076 J and 0.118 J. It follows that even the most severe impacts transfer to the powders an amount of energy that is much lower than the one required to melt all the

ibuprofen affected by a single impact. In particular, the energy transferred at impacts would be able to induce the melting of about 0.11 mg of ibuprofen at best and 0.01 mg, i.e. 10 μg, at worst. Ultimately, the impact energy is not enough to melt all the ibuprofen compressed during an impact, but the amount affected by CLCs in individual impacts is much less, therefore the impact energy is largely enough to melt it.

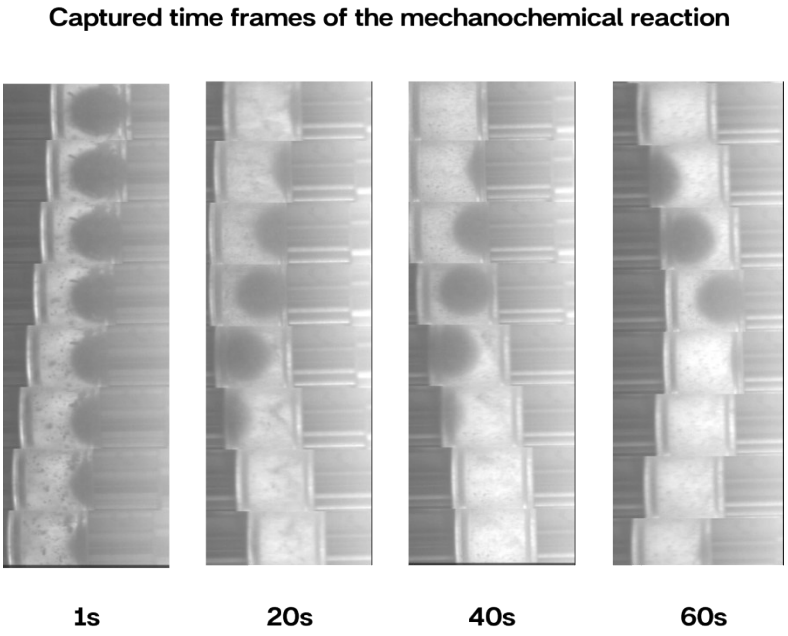


Fig. SI5. Time frames of the mechanochemical reactions. The powder flow decreases over time (from left to right).