RSC Mechanochemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Mechanochem.*, 2025, **2**, 224

Mechanochemical kilogram-scale synthesis of *rac*-ibuprofen:nicotinamide co-crystals using a drum mill†

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Within pharmaceutical research and development, co-crystallization has emerged as a common strategy to modify the physicochemical properties of active pharmaceutical ingredients, tackling a wide array of challenges in drug formulation. Contrasting with conventional solution-based methods that typically consume substantial amounts of solvents and energy, we herein present a more eco-friendly and efficient mechanochemical process for producing co-crystals at kilogram scale. Our study pioneers the use of a drum mill for pharmaceutical co-crystal synthesis, using *rac*-ibuprofen:nicotinamide as a representative example. Our findings demonstrate the viability of repurposing common industrial milling equipment for potential large-scale production of pharmaceutical co-crystals. With the optimized system and utilizing liquid-assisted grinding techniques, the reaction was completed within 90 min and yielded 99% of pure *rac*-ibuprofen:nicotinamide co-crystals by simply sieving off the grinding media. Examination of the resulting co-crystals showed minimal metal contamination from abrasion, with levels well within acceptable regulatory standards for daily intake. Our findings underscore the promise of drum mill technology in creating greener processes for large-scale pharmaceutical co-crystal synthesis, paving the way for more sustainable industrial drug manufacturing practices.

Received 21st August 2024
Accepted 2nd December 2024

DOI: 10.1039/d4mr00096j

rsc.li/RSCMechanochem

Introduction

Pharmaceutical co-crystals have been established in the industry for many years and have gained recognition for their ability to enhance drug performance, offering solutions to common challenges in drug formulation.[1–4] These multicomponent crystalline materials are composed of an active pharmaceutical ingredient (API) and at least one coformer, held together by supramolecular interactions.[5] By incorporating APIs into co-crystals, their mechanical and physicochemical solid-state properties can significantly be improved, addressing issues such as fragility, polymorphism, and hygroscopicity, thereby enhancing the overall stability of pharmaceutical products.[6,7] Moreover, the design of co-crystals with carefully selected coformers can significantly improve the solubility and dissolution rate of poorly water-soluble drugs, often translating to improved bioavailability.[8–10]

The *rac*-ibuprofen:nicotinamide (*rac*-IBU:NIC) co-crystal exemplifies these advantages. Ibuprofen (IBU), a pain-relieving medication listed by the World Health Organization (WHO) as an essential medicine,[11] faces challenges due to its limited water solubility, low bioavailability, and sensitivity to heat.[12–15] The co-crystal formation with nicotinamide (NIC)[16–22] exhibited significantly improved solubility and physicochemical properties without altering, or even improving, IBUs therapeutic action.[17,21,23,24]

Traditionally, co-crystals have been synthesized using solution-based methods, which often require large volumes of solvents and energy-intensive processes such as heating and cooling.[25,26] The extensive use of organic solvents in these processes raises significant safety and environmental concerns.[27–29] Moreover, these solution-based methods present challenges, particularly when dealing with insoluble materials or when co-crystal components show orthogonal solubility.[30,31]

Mechanochemistry, which induces chemical transformations through mechanical forces,[32–37] has emerged as a promising alternative to address these limitations. One of the key benefits of mechanochemistry is that reactions can be performed without solvents (neat grinding) or with only minimal amounts of solvents (liquid-assisted grinding, LAG).[38–41] This makes mechanochemistry particularly advantageous for large-scale production,[22,42–45] offering reduced energy consumption and a smaller environmental footprint.[37,46–49] As the pharmaceutical industry increasingly prioritizes sustainability, these solvent-free or solvent-reduced approaches represent a significant step forward in the development of more eco-friendly manufacturing processes.[50]

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† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d4mr00096j

However, mechanochemical transformations on an industrial scale remain largely unexplored. For the mechanochemical co-crystal synthesis of *rac*-IBU:NIC, smaller-scale batch approaches using a mortar with pestle or ball milling machines have been reported,[18,21,51] as well as continuous processes employing extrusion techniques.[52–55] We recently reported on the first kilogram-scale batch synthesis of *rac*-IBU:NIC using an industrial eccentric vibratory mill.[22,56,57] Building upon this study, we sought to explore whether *rac*-IBU:NIC synthesis could also be performed in a drum mill, further expanding the potential for large-scale mechanochemical processes in pharmaceutical manufacturing.

Industrial drum or tumbling mills, widely used in various sectors for the energy-efficient grinding and mixing materials, operate on a simple yet effective principle. These rotating cylindrical vessels contain grinding media that tumble as the drum rotates, applying mechanical forces to the materials within. Commonly employed in mining, cement production, and other large-scale industrial processes, drum mills are capable of efficiently handling high volumes of material, processing thousands of tons per day.[58–61]

Despite their widespread use in mining and cement production, drum mills have not been explored, to the best of our knowledge, for the synthesis of pharmaceutical co-crystals. This prompt us to explore the potential of these readily available industrial tools for large-scale co-crystal production. In this context, we report herein a proof-of-concept study on the mechanochemical kilogram-synthesis of *rac*-IBU:NIC co-crystals as a model system using a drum mill.

Results and discussion

Identification and preliminary assessment of process parameters

To find the optimal process parameters, a 1 : 1 mixture of *rac*-IBU (2.03 kg, 9.83 mol) and NIC (1.20 kg, 9.83 mol) were placed in a 14.1 L stainless steel vessel in a Retsch Drum Mill TM 300 (see ESI, Fig. S1†). Initially, 10 kg of stainless steel balls ($d = 10$ mm) were added, resulting in a ball filling degree of $\varphi = 0.09$. The critical speed for this setup was calculated to be 77 rpm (detailed calculations and additional data are provided in ESI†). It is essential to operate a drum mill below the critical speed to ensure that the milling balls are lifted as the drum rotates, but fall back down due to gravitational forces before completing a full revolution. This falling motion generates impact and shear forces, which are crucial for efficient milling and to transfer mechanical energy for the co-crystal formation to the substrates. Therefore, we set the operating speed to 60 rpm, which is approximately 78% of the critical speed. This setting is within the typical range of 65–80% of critical speed used in industrial applications.[58–60,62–64]

The progress of the reaction was measured by the consumption of *rac*-IBU and monitored using DSC measurements. As reported earlier, the DSC thermograms show distinct thermal behaviors for the individual components and the co-crystal system (Fig. 1 and S2, ESI†).[52,54,65] Pure IBU exhibits a sharp endothermic peak at 73 °C, corresponding to its melting point, while pure NIC shows a melting endotherm at 127 °C. After 30 min of milling, the DSC thermograms display two endothermic signals at 67 °C and 87–88 °C, likely corresponding to *rac*-IBU with a slight temperature depression due to the formation of an eutectic and *rac*-IBU:NIC co-crystal, respectively. The expected melting signal for NIC (127 °C) was not detected, presumably because nicotinamide dissolves in the molten ibuprofen, forming a peritectic mixture.[54,65,66]

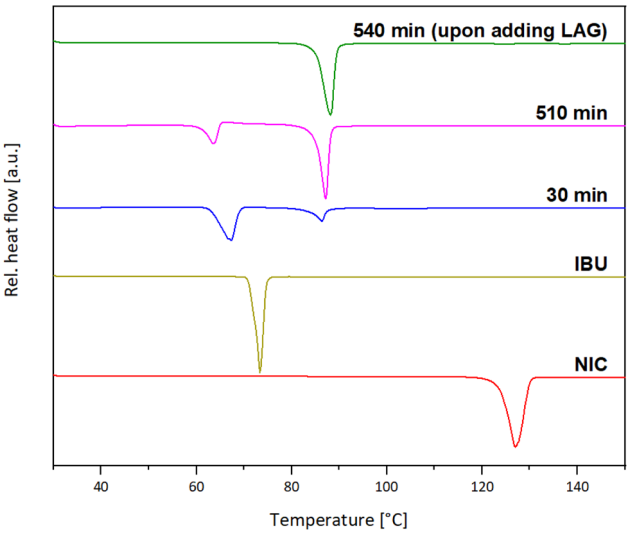

Fig. 1 DSC measurements for NIC (red, m.p.: 127 °C), IBU (yellow, m.p.: 73 °C), and *rac*-IBU:NIC co-crystal (m.p.: 87–88 °C) formation after 30 min (blue), 510 min (magenta), and 540 min (green). LAG additive was added after 510 min. Note: additional data are provided in ESI.†

To evaluate the impact of various process parameters on the co-crystallization process, further samples were collected at 30 min intervals for DSC analysis (Fig. 2). An exponential conversion was observed in the first 30–90 min, when *rac*-IBU and NIC were milled at 60 rpm at room temperature. Interestingly, the reaction mixture morphology changed over time. A fine powdery mixture was observed at 30 min and 60 min, but a hard solid had formed and adhered to the reactor wall after 90 min. This formation was accompanied by a slowdown in the conversion of *rac*-IBU, possibly due to the enclosure of *rac*-IBU and NIC substrates under the hard solid, preventing the transfer of sufficient mechanical impact from the milling balls. To address this issue, the hard solid was manually removed from the walls before continuing the mechanochemical process. Despite this intervention, the conversion rate remained slow. Consequently, another 10 kg of stainless steel balls ($d = 10$ mm) were added after 270 min, increasing ball filling degree φ to 0.17. Unfortunately, this increase in grinding energy resulted in only minor improvements in conversion. In a further attempt to enhance conversion, an additional 10 kg of larger stainless steel balls ($d = 30$ mm, $\varphi = 0.27$) were introduced. We expected the combination of smaller and larger balls and a greater overall mass to more effectively crush the hard solid from the reactor wall.[67,68] However, only marginal improvements were observed. The hard solid continued to form and adhere to the reactor wall and the conversion reached a plateau at approximately 85%

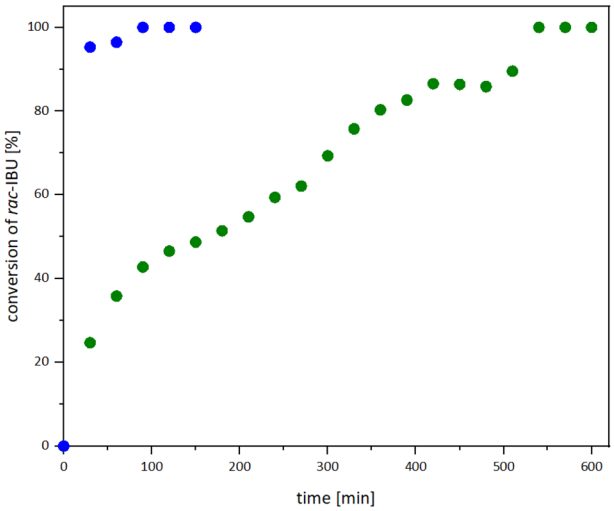

Fig. 2 Conversion of *rac*-IBU. Green plot: neat grinding approach with addition of 10 kg of balls ($d = 10$ mm) after 270 min and 10 kg of balls ($d = 30$ mm) after 360 min; addition of LAG additive EtOH after 510 min. Blue plot: LAG-assisted approach with EtOH added prior to the reaction. The conversion of *rac*-IBU into the *rac*-IBU:NIC co-crystal was determined by the ratio of integrals of NIC and *rac*-IBU in the DSC thermograms (additional DSC data are provided in ESI, Fig. S2†).

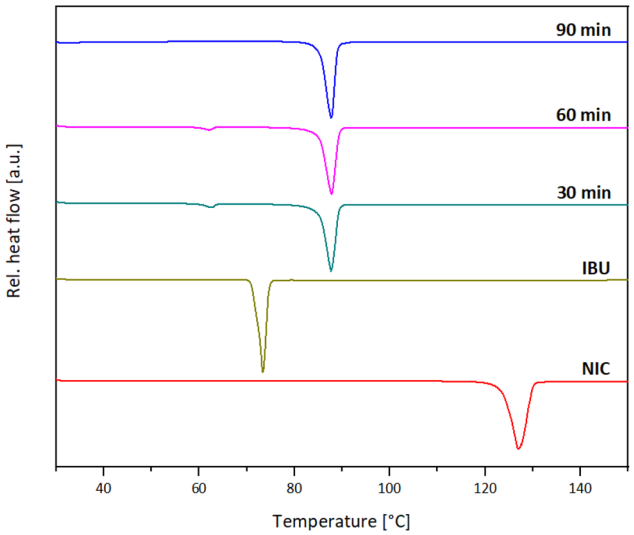

Fig. 3 DSC measurements for NIC (red, m.p.: 127 °C), IBU (yellow, m.p.: 73 °C), and *rac*-IBU:NIC co-crystal (m.p.: 87–88 °C) formation after 30 min (cyan), 60 min (magenta), and 90 min (blue). LAG additive was added prior to the reaction.

after 400 min. At this point, LAG technique was employed by adding EtOH as an additive ($\eta = 0.1$ mL g^{-1}). This addition dramatically accelerated the reaction, achieving full conversion of the remaining substrates within 30 min. The final product yield for this process was 3.19 kg (99%) of *rac*-IBU:NIC co-crystals, which were easily recovered by sieving the reaction mixture to separate the grinding media.

Following the initial experiment, which required 540 min to achieve complete conversion, efforts were made to enhance efficiency and minimize energy consumption, aligning with principles of green chemistry and sustainable manufacturing.[22,42–45] In an additional experiment, EtOH ($\eta = 0.1$ mL g^{-1}) was added at the beginning of the milling process, along with *rac*-IBU and NIC and 20 kg of stainless steel balls ($d = 10$ mm). Within just 30 min of milling at 60 rpm at room temperature, the conversion had already reached 95% (Fig. 2 and 3). Full conversion was achieved after 90 min, representing a six-fold reduction in reaction time compared to the initial experiment. The recovery of *rac*-IBU:NIC was 3.20 kg (99%), matching the excellent yield obtained in the previous reaction.

Characterization of *rac*-IBU:NIC co-crystals

Powder X-ray diffraction (PXRD) analysis was performed to complement the results from DSC experiments and provide additional information about the quality and stability of *rac*-IBU:NIC. Fig. 4 presents the X-ray diffraction patterns. First, to verify that the co-crystal was formed solely by mechanical energy rather than through thermal activation during the DSC measurements, PXRD analysis of a representative sample from the neat grinding process after 300 min of milling in the drum mill was conducted. As shown in the cyan graph (Fig. 4), the co-crystal was present in the reaction mixture, as indicated by the intense and characteristic diffraction peak at 3.1° (2θ), along with remaining *rac*-IBU and NIC. For the final *rac*-IBU:NIC co-crystal product after milling of 90 min under LAG conditions, the PXRD data showed complete conversion of the substrates, as proven by the absence of characteristic peaks associated with *rac*-IBU ($2\theta = 6.1°$) and NIC ($2\theta = 14.8°$, 25.4°, 25.8°, and 27.3°).[16,20,21,52,55,66] Of note, only the *rac*-IBU:NIC co-crystal was detected, with no evidence of additional crystalline or non-crystalline forms, such as *rac*-IBU or NIC dimers.[52,69,70] Moreover, no amorphization was observed, demonstrating the high

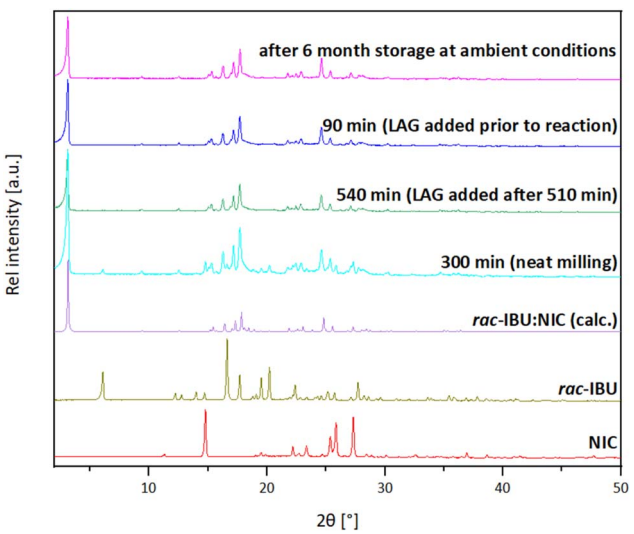

Fig. 4 PXRD pattern: NIC (red), *rac*-IBU (yellow), calculated *rac*-IBU:NIC co-crystal (purple), reaction after 300 min of neat milling (cyan), final *rac*-IBU:NIC co-crystal product for both approaches (green and blue), and *rac*-IBU:NIC co-crystal after storage for 6 months at ambient conditions (magenta).

quality of the *rac*-IBU:NIC co-crystals obtained from this mechanochemical process.

In addition, stability testing of *rac*-IBU:NIC under ambient conditions was performed. The co-crystal was stored in air at room temperature for a period of 6 months. Subsequently, PXRD analysis was conducted. Despite the co-crystal being exposed to moisture, the results show no degradation of the product or changes in crystallinity. This stability is crucial for the potential formulation of the co-crystal into tablets or other dosage forms, as it ensures the safety of the drug compound over time.

Assessment of trace metal impurities from abrasion

Due to stringent quality regulations on residual trace metal impurities in pharmaceutical products,[71–73] we analyzed samples from the mechanochemical process using Inductively Coupled Plasma Optical Emission Spectrometry (ICP-OES).[74,75] This analysis aimed to evaluate the potential abrasion of milling media during the co-crystal synthesis. Samples were collected at different time points throughout the process, and the starting materials were also analyzed as a reference (Table 1).

Trace amounts of the investigated elements (Al, Cr, Co, Fe, Ni) were already present in the starting materials *rac*-IBU and NIC.

After 30 min of milling, it appeared that no additional abrasion could be detected beyond the trace metals already present in the starting materials. As anticipated, longer reaction times correlated with higher metal concentrations in the samples when the reaction time was extended from 30 min to 90 min. To our delight, the processed samples showed only a slight increase in metal concentrations, suggesting minimal abrasion of the grinding media during mechanochemical synthesis. Importantly, under the optimized protocol with a 90 min milling duration, the levels of trace metals were found to be in the lower parts per million (ppm) range. These concentrations are significantly below the regulatory limits for daily permitted exposure, ensuring the safety and quality of the co-crystal product.[76] Compared to our recent study about the abrasion of metals during mechanochemical processes in different ball, planetary, and eccentric vibratory mills,[22] the drum mill used in this study exhibited significantly lower abrasion levels of aluminium and iron. Specifically, aluminum abrasion could be reduced from 96–119 ppm (depending on the grinding material used) to 17 ppm, and iron abrasion from 95–772 ppm to 66 ppm.[22] This notable difference in abrasion levels could be attributed to the lower energy input of drum mills,[57,77] resulting in less intense mechanical stress on the grinding media and reactor walls. These findings underscore the importance of monitoring and controlling metal contamination in pharmaceutical co-crystal synthesis using mechanochemistry. While the observed metal levels are well within acceptable limits,[76] this analysis highlights the need for careful consideration of milling devices, materials, and parameters to minimize potential impurities in scaled-up mechanochemical processes.

Table 1 Trace metal content analysis determined by ICP-OES

Sample	Al (ppm)	Cr (ppm)	Co (ppm)	Fe (ppm)	Ni (ppm)
IBU	11, 3	39, 0	25, 7	71, 9	34, 9
NIC	8, 9	33, 3	26, 7	40, 0	33, 3
30 min	10, 8	35, 9	30, 8	51, 3	38, 5
60 min	11, 0	37, 0	31, 7	63, 4	39, 6
90 min	17, 2	43, 8	35, 9	65, 6	45, 3

Conclusions

In summary, we demonstrated that drum mills are promising devices for the kilogram-scale mechanochemical synthesis of high-purity *rac*-IBU:NIC co-crystals. By employing LAG technique with EtOH as an additive the reaction rate was significantly accelerated, achieving full conversion within 90 min. The process proved operationally simple, involving only the loading of starting materials, LAG additive, and grinding media into the reactor, followed by a simple filtration after the reaction to recover 99% of *rac*-IBU:NIC co-crystals. PXRD and DSC measurements confirmed the high purity of the obtained co-crystals, revealing the absence of other crystalline or amorphous phases and no dimerization of the starting materials. Our study provides a proof of concept for using drum mills in mechanochemical processes for the production of pharmaceutical co-crystals, demonstrating success at the kilogram scale and suggesting potential applicability to larger industrial-scale operations. Leveraging technology already established in other industries, this approach offers a pathway to manufacturing with reduced solvent use and lower energy consumption.

Data availability

All experimental and characterization data, along with detailed experimental procedures, are available in the published article and the ESI.†

Author contributions

J.-H. S. drafted the original manuscript, performed experiments, and conducted data analysis. F. W. conducted initial test experiments. J. B. supported experimental work and data collection. M. F. provided project supervision and guidance. All authors contributed to the review and editing of the final manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors gratefully acknowledge BASF Pharma Solutions for providing sufficient quantities of *rac*-IBU for this study. We extend our thanks to Florian Baum (Max-Planck-Institut für Kohlenforschung) for measuring ICP-OES samples. We are grateful to Retsch for providing the drum mill used in this study. The authors acknowledge IMPACTIVE (Innovative

Mechanochemical Processes to synthesize green ACTIVE pharmaceutical ingredients),[78] the research project funded from the European Union's Horizon Europe research and innovation programme under grant agreement: No. 101057286. Open Access funding enabled and organized by Projekt DEAL.

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