Please cite this article in press as: Broker et al., *In situ* energy dispersive X-ray diffraction achieved in twin screw extrusion, Chem (2024), https://doi.org/10.1016/j.chempr.2024.10.011

Chem

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Preview

In situ energy dispersive X-ray diffraction achieved in twin screw extrusion

Edward J. Broker, Jr.,[1] Kathleen Floyd,[1] and James D. Batteas[1,2,*]

In the current issue of *Chem*, Gugin et al. are showcasing the power of energy-dispersive X-ray diffraction to track kinetics and chemical phenomena *in situ* during twin screw extrusion. This technique holds great promise for industrial scale-up of green chemical syntheses.

Mechanochemistry, which uses force to drive chemical transformations, is quickly becoming a key technology for greener and more sustainable approaches for chemical synthesis.[1] While reactions are often carried out in batch syntheses in ball mills or via reagent grinding in traditional mortar and pestles, twin screw extrusion (TSE) offers the possibility of continuous mechanochemical manufacturing by utilizing a hopper for the feeding of precursors, followed by a series of temperature-controlled co-rotating screws, to drive chemical reactions within an extruder barrel until product is obtained at the outlet.[2] Reaction optimization of this process is challenging, however, requiring large amounts of precursors and rationalization of the many complex and interrelated variables of the mechanics at work on the reactions.[2,3]

The recent work of Gugin et al.[4] is aimed at revealing the chemical details inside the "black box" of the extruder barrel, thus bringing the field significantly closer to realizing the goal of green chemical manufacturing at industrial scales.[3] In this work, the authors utilize *in situ* temporal and spatial resolution energy-dispersive X-ray diffraction (EDXRD) measurements of the reaction extrusion matrix in TSE for a variety of chemical systems, ranging from metal organic frameworks (MOFs) to ionic cocrystals. The approach they describe can enable mechanochemists to optimize the TSE manufacturing processes by probing the inherent chemical transformations occurring in real time.

Ex situ studies of mechanochemical phenomena can be plagued by atmospheric effects, sampling challenges associated with altering the grinding process, and the inherent chemistry of reactants and products.[1] Such complexities are compounded in the TSE system where removal of feedstocks for analysis throughout the barrel requires continuous dismantling and rebuilding of portions of the system.[2] As a result, research to develop the capacity for *in situ* measurements of solid state reactions in mechanochemical mills began to proliferate, with a variety of new ball milling configurations being reported to accommodate the addition of spectroscopic and structural techniques such as Raman, fluorescence, X-ray absorption spectroscopy (XAS), and X-ray diffraction (XRD).[1,5–9] Tandem real-time spectroscopic characterization has also been realized in the ball mill for model pharmaceutical systems involving drug compounds as in the case of indometacin[5] and its mechanically driven polymorphism or cocrystal systems like that of nicotinamide and salicylic acid,[6] organometallic systems such as for metallic organic frameworks (MOFs),[10] and inorganic materials, including the synthesis of nanoparticles.[9]

While useful in garnering information on changes in chemical composition, *in situ* ball mill spectroscopic methods have experimental challenges, as delineated by Lukin et al.,[6] such as the necessity for translucent milling jars, in addition to considerations regarding the spectral activities and physical properties of the reacting compounds. Thus, additional work has been devoted to crystallographic characterization rather than chemical composition, utilizing X-ray diffraction as the *in situ* technique of choice.[1,7,8] XRD provides critical insights to the evolution of crystal structure, and real-time diffraction data yield information pertaining to crystalline intermediates that might otherwise be neglected.[8]

Other researchers have combined spectroscopic techniques along with XRD.[9,10] While the combination augments the information garnered about a particular reaction mechanism by providing evidence for either direct conversion or two-step crystallization,[10] milling analyses were still limited by batch size. Although downsized systems can be beneficial in studying toxic or scarce compounds as noted by Lampronti et al.,[7] the impact on translating those efforts to processes for industrial scale has remained limited. As such, the findings presented in this new work are squarely in the interests of those seeking not only spatial and temporal *in situ* reaction data, but to those pursuing routes for industrial scale-up of mechanochemical processes.[3]

[1]Department of Chemistry, Texas A&M University, College Station, TX 77843-3255, USA

[2]Department of Materials Science and Engineering, Texas A&M University, College Station, TX 77843-3127, USA

*Correspondence: batteas@chem.tamu.edu

https://doi.org/10.1016/j.chempr.2024.10.011

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The application of *in situ* Raman spectroscopy to TSE was previously reported by the Emmerling group in the synthesis of the zeolitic imidazolate framework ZIF-8.[2] While useful, Raman reaction monitoring can be limited based on the spectral activity of the molecules involved; further, neither mechanistic nor phase transition insights can be readily gleaned. In contrast, EDXRD can be utilized to monitor reactions in the solid state while deducing phase, potential transition states, crystallinity, and kinetic information.

In their recent report, Gugin et al. apply EDXRD to assess the effect of critical variables on four model reactions: (I) a salt metathesis and (II) a MOF synthesis, as well as the formation of (III) ionic and (IV) organic cocrystals that are of interest to the pharmaceutical industry. Many of these systems serve as benchmarks used to validate previous *in situ* milling studies.[7,10] The experimental set-up involves an extrusion chamber with a moveable stage such that X-ray patterns can be analyzed at specific positions along the chamber at any given time. However, a single position can also be monitored over extended periods of time with patterns acquired ca. every 10 seconds. The design used addresses challenges associated with *in situ* EDXRD, e.g., ensuring that the detector is angled so the aluminum peak associated with the screw itself is outside the energy range of interest (15–100 keV).

The salt metathesis reaction (I) of cesium chloride and potassium iodide served as the first validation of the technique, employing the most strongly scattering system. They found that unique to EDXRD of TSE, spectra have a characteristic dotted shape caused by the intermittent and partial nature of powder filling in the reactor barrel. Despite this challenge, XRD patterns were readily able to observe changes at single sites within the reactor over time and the general behavior along the length of the grinding barrel. They proceeded to demonstrate the necessity of experimental optimization even with compounds wherein strong diffraction patterns are expected, an important validation of the utility of EDXRD to simplify optimization. For example, water flowing at 0.4 mL/min showed a complete reaction in the final TSE position, while substituting ethanol (EtOH) in water's place showed reaction comparable to dry conditions. Further, the screw speed was found to impact the efficacy and overall possibility of reaction, with optimal yield at 40 rpm with high intensity diffraction peaks compared to the near absence of peaks at 80 rpm.

The second model reaction (II) involves synthesis of the ZIF-8 MOF, a system of medium scattering strength. As with system (I), the reaction matrix could be examined readily throughout the extruder barrel. Here, Gugin et al. utilized EDXRD to measure particle size information. Surprisingly, it was observed that Hmelm crystals, upon reaching suitable sizes, would fall out of focus, likely due to their sinking below the X-ray beam level toward the bottom of the barrel. This study further showed that a steady-state must first be achieved to form the ~40-nm MOF particles; temperature was shown to strengthen signal intensity if one—but not both—of the barrels in the extruder are heated, due in part to the symbiotic relationship associated with the presence of EtOH in the reactor. Two heated barrels evaporate the solvent too quickly to allow it to enable effective extrusion. With water as the liquid at higher temperatures, an otherwise undetected side phase was seen, further demonstrating that small changes in reaction conditions, down to the identity of the auxiliary solvent, can cause significant changes in the synthetic route.

In reaction (III), sodium iodide:glucose ionic cocrystals were synthesized, while in reaction (IV), a completely organic cocrystal of theophylline:benzamide was formed. In the case of the former, methanol (MeOH) was probed as the added liquid, optimizing at 0.2 mL/min as higher loadings led to undesirable dissolution. The entirely organic cocrystal (IV) proved interesting in that one kinetic product was favored in TSE over another observed through ball milling. Further, the *in situ* methodology evidenced a previously unknown phase and provided snapshots into the intermediary cocrystals that preceded the final products. These systems demonstrate the utility of the technique for pharmaceutical investigations of APIs and pharmaceutically acceptable excipients, even with their comparatively poor scattering.

Gugin et al. demonstrate an excellent method for revealing the inner workings of the "black box" of twin-screw extrusion, by enabling mechanochemists to simplify the optimization process in real time, while simultaneously probing the underlying chemistry. To further correlate currently established TSE conditions, and to expand this approach to a broader range of reaction systems, future work will likely aim to vary the grinding screw materials, increasing screw speed, and altering the chemical composition of the windows to prevent unfavorable interactions with reagents. While a limitation of this approach resides in the cost and added logistical complexities associated with beamline utilization, this is an exciting advance, and the field can clearly look forward to learning more about the capacity of this methodology and its expanding application for bridging the knowledge gap between fundamental and applied mechanochemistry.

ACKNOWLEDGMENTS

J.D.B. acknowledges support from the NSF Center for the Mechanical Control of Chemistry under grant CHE-2303044.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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