TITLE: Use of mechanochemistry to improve agrochemical formulations

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Proposal submitted to: International Fine Particle Research Institute (IFPRI)

A. Background

In the field of agrochemicals, the use of herbicides has been an effective strategy for managing the growth of undesired plants, also referred to as weeds.[1] Development of herbicides has and continues to require significant investment of both time and financial resources. Although highly effective, the use of herbicides has limitations and challenges.[1] For example, some herbicides are significantly affected by the weather and are prone to being volatilized in the sun or washed away in rain.[2] Moreover, issues including drift and runoff have resulted in losses of non-resistant crops, herbicide resistance, and water/soil contamination.[3–7] While non-herbicidal approaches are being investigated and show promise, scalability issues persist.[8] Ultimately, strategies that improve the delivery and/or efficacy of herbicides are needed to address the growing global agriculture demand.

Herbicides can be applied to crops in either a powder/granular form or as a solution/spray. When solid materials are used, either as the final product or dissolved in solution for the final product, the properties of the solid, such as solubility, thermal stability, and mechanical properties are impactful. For example, the intrinsic solubility is dictated by the component(s) in the solid; however, particle-size reduction is a common strategy used to increase solubility based on increased surface area for solvation.[9,10] Particle-size reduction can be accomplished by applying mechanical force or pressure to the system and is frequently achieved through milling/grinding. During the grinding process, some materials do undergo size reduction; however, some can become amorphous or undergo a phase change (i.e., polymorph conversion).[11,12] Strategies that not only improve the solid-state properties of agrochemicals, but understand how mechanical force influences the resulting properties, size, and overall behavior[13] of the agrochemical during milling would be advantageous for the development of superior materials.

The Hutchins group aims to understand how the structure of organic solid-state materials gives rise to function. We use a suite of synthetic and characterization methods to design, prepare, and elucidate solid-state structures, investigate properties, and determine structure-based features that afford desired behaviors. *As organic solid-state chemists, our group will use a multifaceted strategy to prepare agrochemical materials, investigate the impact of milling on particle size and crystal phase, and determine the impact that milling parameters (time, speed, aging, etc.) have on material outcome.* From our recent progress (in section B), our group has developed the following hypotheses, which are driving this research direction (Fig. 1, top):

1. Mechanochemical milling of herbicides reduces particle size, affords amorphization under long milling times, and enables polymorph conversion with addition of liquid additives.
2. Mechanochemical cocrystallization of herbicides with non-toxic coformers affords increased or decreased aqueous solubility that depends on coformer structure.

Mechanochemistry. Mechanochemistry is a chemical transformation that is initiated or sustained by mechanical force.[14] Although the technique is not new, mechanochemistry has recently re-emerged as a result of the need to develop more efficient and safer synthetic methods. Mechanochemical transformations are achieved by grinding or milling reagents, typically require minimal or no solvent, and reactions can be conducted from bench to industrial scale. Mechanochemistry has been used to conduct organic transformations[14] and synthesize materials including cocrystals[15] and metal-organic frameworks,[16] all with minimal to no solvent. Mechanochemistry has also been used to synthesize molecules not obtainable via traditional solution-phase techniques[17–19] and control polymorphism (crystal form).[20–22] Finally, and perhaps the most common, milling and ball mill grinding have been used to achieve changes in crystal form, reduction in particle size, and in some cases, amorphization.[11–13]

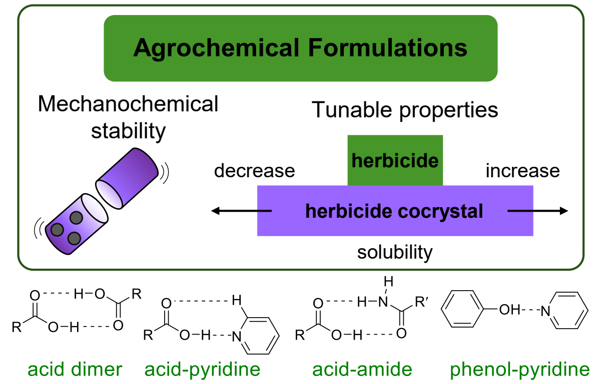


Fig. 1 Overview: top: two key research areas and bottom: common intermolecular interactions.

Polymorphism. One challenge that arises in development of small-molecule solids is polymorphism, the ability of a compound to exist in more than one form or crystal structure.[23–25] In drug development, for example, polymorph screening is a critical component because polymorphs can exhibit different properties. Arguably, one of the most impactful cases in recent history was for the pharmaceutical Ritonavir,[26] an antiretroviral drug used to treat HIV/AIDS in the late 1990s. Two years after market release, a polymorph of Ritonavir was obtained (Form II) that exhibited significantly lower solubility than the first form (Form I) due to differences in the solid-state hydrogen-bonding network, causing substantial problems in both production and drug efficacy.[27] Ritonavir was removed from the market, as preparation attempts for Form I continually failed by affording less soluble Form II. The Ritonavir situation caused significant impact to Abbott Laboratories, who marketed it, and to patients needing the life-saving medication. Excitingly, Ritonavir Form I was reproduced for the first time in 2024 through milling, demonstrating the strong potential of mechanochemistry for controlling polymorphism[28] and prompting the headline, "*Could mechanochemistry have saved Abbott Laboratories $250 million?*"[29] This study showed crystal breakage, Oswald ripening, and crystal shape all play a role in polymorph stability, and polymorph switching can happen at the nanoscale using milling.

Cocrystallization and solid-state properties. Many compounds including pharmaceuticals, agrochemicals, and fine chemicals are frequently prepared in the solid phase (specifically, crystalline) due to its high stability and ease of quality control. Cocrystallization is a process that combines two or more species into a single crystal lattice, and components are designed to interact through specific noncovalent bonds[30–33] (Fig. 1, bottom). Multi-component solids obtained from cocrystallization are classified by their intermolecular bonds – solids held together by neutral interactions are termed cocrystals and solids where proton transfer occurs are termed salts. Cocrystallization has gained considerable attention in the past two decades because solids often exhibit improved physical or chemical properties compared to individual components.[34–36] Specifically, as related to agrochemicals, cocrystallization strategies have been applied to prepare improved fertilizers,[37,38] control release in the herbicide metamitron,[39] and improve properties, including thermal stability, solubility and efficacy, of insecticides and pesticides.[40–44] For example, the solubility of 2,4-D has been either increased or decreased by cocrystallizing the herbicide with different types of coformers.[45,46] During development of herbicides and cocrystalline herbicides in both industry and academia, aggregation, particle enlargement, and low melting point compounds have caused challenges in the application of herbicides to fields (e.g., clogging spray equipment, inhomogeneous formulations, and phase transitions).[40] Thus, designing materials or preparation methods that limit or eliminate these challenges would be impactful.

B. Recent Progress

Structural determination aided by mechanochemistry. Our group has developed a strategy for synthesizing drug cocrystals when one component is a solid and the other is a viscous liquid at room temperature (Fig. 2).[47] Our attempts to synthesize cocrystals using standard solution-based crystallization methods afforded oils rather than crystalline solids. This is a common outcome for compounds that are oils or generally difficult to crystallize. We, thus, sought to develop a strategy for obtaining cocrystalline solids and implemented mechanochemistry. The solid component was the anti-cholesterol drug, bezafibrate, and the viscous liquids included four pyridine-based compounds (three had never been crystallized).[48] Neat milling of the liquid and solid affords a viscous oil, and subsequent dissolution in an organic solvent yielded single crystals suitable for structure determination by standard X-ray diffraction (Fig. 2). This method was previously used for solid-solid combinations;[49] however, it had not been shown for a solid-liquid/oil combination. Spectroscopy showed structural similarities between the cocrystal and oil after milling, while products from failed solution crystallizations differed. Importantly, single crystals obtained with our method can be used to seed bulk solution crystallization when solids were inaccessible via traditional solution growth.

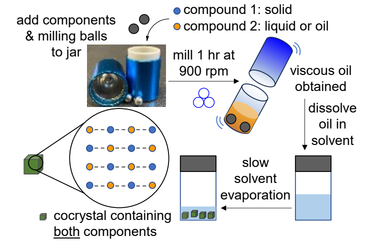


Fig. 2 Mechanochemistry strategy for cocrystallization of liquid/oil-based compounds.

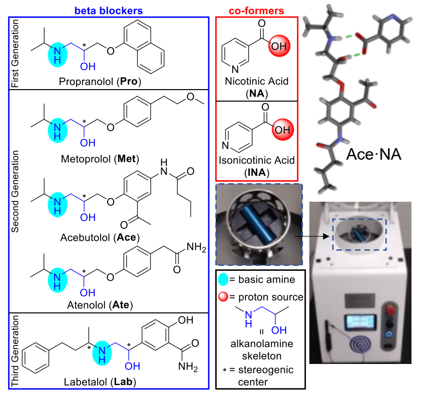


Fig. 3 Structures of beta blockers and coformers (key groups noted), mill, and example X-ray structure.

Our group has also reported a comprehensive study of beta blocker drugs,[50] which have limited known crystal forms and are often sold as HCl salts. We selected five beta blockers (from the three generations, Fig. 3) and demonstrated the first gram-scale mechanochemical neutralizations of commercial salts to afford free bases of the drugs. Neutralization enabled access to single crystals and the structure of one beta blocker for the first time. We further showed successful cocrystallization across the beta blocker series *directly during* liquid-assisted milling. The cocrystalline powder can be used directly, dissolved to grow crystals for structure analysis, or as a crystallization seed. The work revealed that the liquid additive identity plays a substantial role in milling outcomes.

Cocrystalline forms of agrochemicals. Our group has recently begun investigating cocrystallization of the herbicides, 2,4-D and dicamba. Using nitrogen-based heterocyclic compounds as model coformers, several multi-component solids were obtained. Based on SCXRD data, the two components interact through hydrogen bonds between the carboxylic acid of the agrochemical and the nitrogen of the heterocycle (e.g., acridine, Fig.

4, unpublished results). The solids are classified as ionic cocrystals; the hydrogen on one of the herbicides transferred to the nitrogen of the coformer, and there is a second herbicide in the solid that is neutral. The neutral herbicide only engages in hydrogen bonds with the deprotonated herbicide. Thermal data for these two solids with acridine are relatively similar to the parent herbicide, and isothermal studies (at 75 °C) showed no mass loss during a 12 hr hold.

We have also investigated the cocrystallization of 2,4-D and dicamba with a purine-based compound using solution and mechanochemical methods. In this relatively simple system, we have prepared cocrystals (neutral hydrogen bonds), salts (proton transfer), and salt-hydrates, all from the same starting materials (unpublished results). Small amounts (~30 µL) of water and ethanol were added during milling experiments as liquid additives, and changes to the ethanol-water ratio afforded differences in the solid phase obtained from milling.

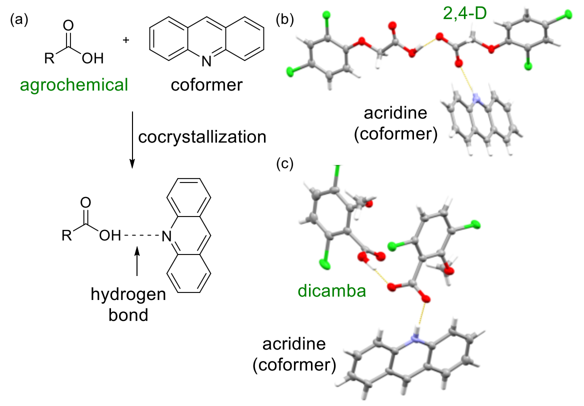


Fig. 4 a) Cocrystallization strategy for agrochemicals and X-ray structures of (b) 2,4-D·acridine and (c) dicamba·acridine. Hydrogen bonds are shown with yellow dashed lines.

C. Overview of Proposed Research

Methods. Milling experiments will be conducted using a FlackTek SpeedMixer 300-100 SE. Milling jars fabricated from stainless steel or teflon, accompanined by stainless steel or zirconia milling balls, respectively, will be used. The jar volume is 5 mL or 15 mL, and the milling ball diameter is 7 mm or 10 mm. Experiments will be conducted at ambient temperature and humidity using a milling speed of ~1000 – 2000 rpm with milling times ranging from 5 min to 2 hr. Synthesized materials and products from milling experiments will be characterized by powder X-ray diffraction (PXRD), nuclear magnetic resonance (NMR) spectroscopy, and Fourier-transform infrared (FTIR) spectroscopy. Cocrystals will be synthesized using methods similar to preliminary results above. Cocrystals will be characterized by IR and NMR spectroscopy, single crystal X-ray diffraction (SCXRD), and PXRD. Thermal properties will be characterized by differential scanning calorimetry and thermogravimetric analysis. Particle sizes will be determined from Scherrer analysis, supported by scanning electron microscopy. Characterization is facilitated with resources in the Department of Chemistry, the MU Materials Science & Engineering Institute, and the MU electron microscopy core, all at the PI's institution.

Objective 1. Behavior of synthetic auxin herbicides under mechanochemical conditions. Synthetic auxins represent one of the most widely used and effective classes of herbicides. Typically, the synthetic auxins are applied as a post-emergent spray, and can be susceptible to loss through rain, wind, and volatilization.[2,3] Post-emergent herbicides can also be applied in a granular form, if the foliage is damp, but this is used less commonly. Strategies that achieve optimal particle size, solid-state form (crystalline or amorphous), and stability for small-molecule organic compounds would be useful for industrial applications. A combination of literature and our recent progress led us to the first hypothesis driving this direction – mechanochemical milling reduces particle size, affords amorphization under long milling times, and enables polymorph conversion with addition of liquid additives. For organic compounds with known polymorphs, only one or two forms are often suitable for production because of differences in solubility/stability. To test the hypothesis of Objective 1, crystalline synthetic auxins obtained via solution crystallization (initial particle size ~50-500 µm) will be subjected to mechanochemical milling with characterization performed at multiple time points throughout the experiment (*ex situ*). Milling time influences the form obtained;[28,51–53] thus, multi-point characterization will enable insight into the species present. Our focus will be synthetic auxins that are: i) most frequently used and ii) polymorphic (ex. Fig. 5). Structural features within an herbicide class are similar; thus, we expect selected auxins to serve as good models and knowledge will be applicable to other herbicides or small molecules.

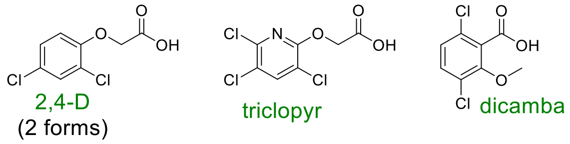


Fig. 5 Chemical structures of common synthetic auxins.

For small molecule organic compounds used in commercial products, some applications require a crystalline phase (single polymorph or mixtures), and in some cases, amorphous solids are preferred. In our own work, many crystalline solids are stable under milling conditions, while some lose crystallinity or undergo polymorph conversion.[50,54] During milling, crystal size is reduced and under different conditions (milling time, solvent additive) polymorph switching[55] can occur due to enhanced stability.[28,55] For the herbicide model systems, we will first investigate milling parameters (time, intensity) that afford particle-size reduction and/or amorphization. The initial conditions will be neat (i.e., dry milling), as the presence of liquid additives frequently assists in crystallization or polymorph conversion. Amorphization is often achieved in organic solids when long milling times (i.e., hours) are used, so time will be an important experimental variable for testing the hypothesis. Lastly, aging studies will be conducted to determine if the milled material is stable after the mechanical force stimulus is removed.

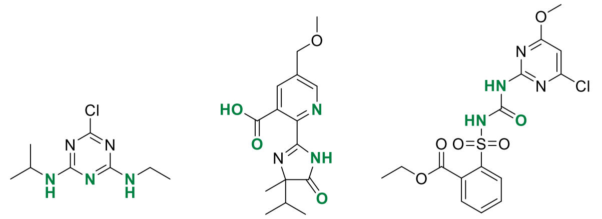
In the field of mechanochemistry, the use of small quantities of liquid additives is common practice because addition of liquid was long assumed to promote reactivity via enhanced molecular diffusion, local solubility, or lowered nucleation energy pathways. A recent study challenged this ideology by demonstrating solvent additives can *promote, inhibit, or reverse cocrystallization in milling*.[56] The work suggested molecular components dictate solvents that fall into each category, and simple DFT-d calculations were unable to rationalize experimental results. Inspired by this work, our most recent study on beta blockers (Fig. 3) clearly shows solvent additive identity influences cocrystallization outcomes in milling.[50] Using 14 solvents, we observed more polar solvents tended to afford full conversion to products and several solvents did not yield cocrystallization. Other researchers have correlated experiment success with solvent parameters (e.g., solubility parameter, polarity), but the role of additives in mechanochemical processes remains far from understood.

The herbicide 2,4-D was discovered in 1941,[57,58] and a second polymorph of 2,4-D was identified just three years ago.[59] The single crystals of form II respond to mechanical force by deforming elastically, and form II converts into form I upon heating. To elucidate mechanism(s) of polymorph conversion under milling conditions, the two polymorphs of 2,4-D will be prepared via known methods then subjected to milling, either dry or with a liquid additive. For most impact/relevance, efforts will focus on industrially-relevant solvents (e.g., water, ethyl acetate, ethanol).[60] PXRD will elucidate crystallinity changes, crystallite size, and polymorph identity at multiple time points. FTIR spectroscopy will afford insight into crystal form(s) present at each stage by monitoring changes in key signals (e.g., shifts, differences in packing arrangements).[61–63] These experiments will provide insight into the stability of herbicide polymorphs under milling conditions, which will be correlated to the structure of the crystalline solid. Structural insight will be gained by examining the intermolecular interaction energies and energy frameworks (using the software CrystalExplorer),[64] wherein the points in the structure most likely to break during application of force can be determined.

Success in Objective 1 requires a suite of characterization methods to interrogate and understand how milling converts crystalline herbicides to smaller particles and affords conversion to other polymorphs and/or amorphous phases. Mechanochemical approaches for particle breakage or crystallization have proven incredibly powerful, but methods and material responses are still far from being understood. *This work will develop fundamental amorphization, crystallization, and phase conversion knowledge for agrochemicals, which can be applied to industrially relevant systems.*

Objective 2. Tunable agrochemical solubility via mechanochemical cocrystallization and post-milling stability.

The solubility of agrochemicals has a significant impact on their delivery to target. Strategies that improve efficacy and delivery of current and future herbicides will be impactful for reducing dosage and loss. Particle-size reduction is a long-standing strategy that has been used to increase solubility.[9,10] However, some agrochemicals exhibit aqueous solubility that is quite high, while others are too low. Based on literature and our recent progress in pharmaceutical-related projects, the hypothesis driving Objective 2 is that cocrystallization of herbicides with non-toxic coformers affords increased or decreased aqueous solubility that depends on coformer structure. To test the hypothesis, herbicides based on synthetic auxins, photosynthesis inhibitors (triazines), and acetolactate synthase (ALS) inhibitors (sulfonylureas and imidazolinones) will be used (Fig. 5 and 6). The herbicides will be cocrystallized with non-toxic coformers containing aromatic or aliphatic skeletons, functionalized with only hydrogen-bond acceptor or both hydrogen-bond donor and -acceptor groups (Fig. 7). Although simple intermolecular interactions like one- and two-point hydrogen bonds are quite controllable[65] and affect physicochemical properties, many herbicides functionalized with triazine, sulfonylurea, and imidazolinone moieties are structurally complex and exhibit more than one site for hydrogen bonding. Thus, design of multi-component solids can be more challenging. Some of the selected herbicides have been crystallized as



atrizine
photosynthesis inhibitor
triazine

imazamox
ALS inhibitor
imidazolinone

chlorimuron-ethyl
ALS inhibitor
sulfonylurea

Fig. 6 Example herbicides within different classes. Key functional groups noted in green, bold.

components of coordination complexes with various metals (e.g., 2,4-D), but the number of organic cocrystals is relatively small (herbicide: number of published cocrystals: 2,4-D: 35; dicamba: 7; triclopyr: 0; atrazine: 4; imazamox: 0; chlorimuron-ethyl: 0).[66]

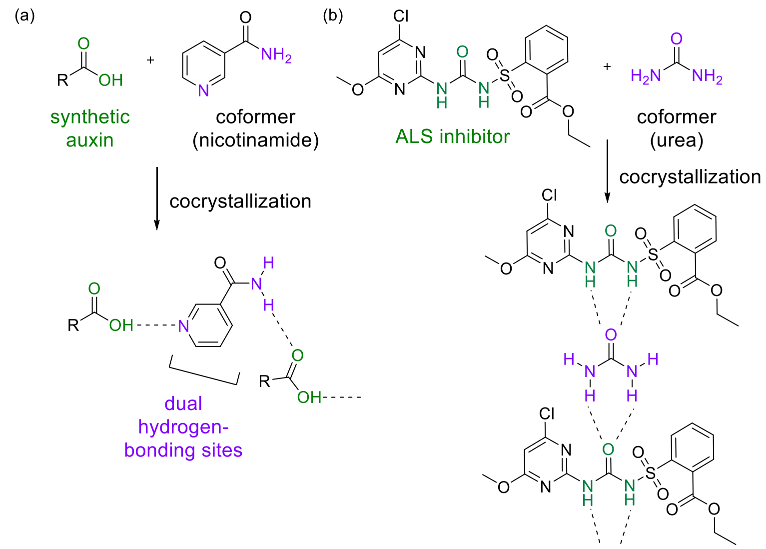


Fig. 7 Cocrystallization approach for (a) auxins and (b) ALS inhibitors.

The selected herbicide will be subjected to milling with a coformer. Coformers will be non-toxic and strategically chosen to form specific noncovalent bonds with the herbicide to facilitate cocrystallization (Fig. 7). Diffraction, spectroscopy, and imaging will be used to characterize presence or absence of cocrystal formation at multiple time points in mechanochemical reactions. If cocrystallization is successful, PXRD clearly differentiates novel phases from physical mixtures, and signals in an FTIR spectrum corresponding to noncovalent bonds will appear (i.e., hydrogen bonds) while individual component signals will shift.[67] In cases where cocrystallization is successful through co-milling, the obtained cocrystalline powder will be dissolved in solution to yield single crystals for structural characterization by SCXRD. Data from SCXRD will be compared to the milled samples to ensure phases are identical.

Solubilities will be measured via the shake-flask method,[68–70] and thermal stabilities quantified with differential scanning calorimetry and thermogravimetric analysis. Solubility and stability data for agrochemical materials will be compared to the individual components to determine if and to what extent cocrystallization modified the properties. Cocrystals with both increased and decreased solubility (compared to the herbicide) will be identified and selected for subsequent post-synthetic milling experiments.

Given that milling organic cocrystals can reduce particle size, afford form conversion, or convert the solid to an amorphous form, cocrystalline solids will be re-subjected to milling under dry conditions with PXRD characterization performed at multiple time points throughout the experiment (*ex situ*). These experiments will provide insight into the mechanical stability of cocrystalline agrochemical formulations when used to reduce particle size or achieve amorphization of the solid. Similar to Objective 1, with SCXRD data, correlation to structure and breakage probability along certain supramolecular interactions[64] will be accomplished.

Success in Objective 2 requires gaining an understanding of the cocrystallization behavior of agrochemicals and its impact on properties. The influence of mechanical force in this area is two-fold, first to facilitate cocrystallization and second as a post-crystallization stimulus. The supramolecular structure of the solids will be correlated to the response of the material in post-crystallization milling. *By using agrochemicals from three different classes of herbicides, this knowledge can be extended to agrochemicals with non-ideal properties (e.g., solubility) that are currently used or in development stages. As mechanochemistry becomes a common, green synthetic alternative, building models to understand the role of force as a stimulus with connection to organic and supramolecular structure will enable rational use of the method in preparing industrially-relevant materials.*

Pitfalls and alternative strategies. Milling may not afford polymorph control, amorphization, or cocrystallization for every herbicide that is used. Reaction conditions relevant to the product outcome including milling time, speed, number of milling balls, and liquid additive volume/identity will be systematically tuned first. If no conditions afford changes in the crystalline solid, structural correlations that afford stability will be garnered. Moreover, this will be contrasted with solids that are less stable under milling conditions, providing chemical understanding of response to force. Molecular level mechanochemical insight is in early stages, so thorough studies, even for select herbicide classes, are useful. Some cocrystalline solids may not exhibit ideal properties (e.g., reduced thermal stability); however, structural characteristics of systems yielding identical or diminished properties are useful in building models to inform coformer choice. To modify properties in such cases, coformers that significantly alter intermolecular interactions and extended supramolecular assembly will be used.

Impact of proposed project on existing research program. The Hutchins group is actively engaged in projects focused on mechanochemistry of pharmaceuticals. Specifically, the group is working on elucidating mechanochemical mechanisms that enable control over drug polymorphism, crystallization, and preparation of novel drug forms for disease treatment. The proposed work focuses on a different class of materials (agrochemicals) that require different material behaviors for industrial use and includes amorphization studies; however, the proposed project could leverage the group's experience with pharmaceuticals and apply it to a different class of materials. Notably, our group has begun projects focused on agrochemicals but has not published or had funding to support the work.

Proposed project outline/timeline:

Project Tasks	**Year 1**	**Year 2**	**Year 3**
1A. Crystallization of herbicides and time-dependent milling experiments	■	■	
1B. Modification of milling experiments to elucidate parameters that afford amorphization or stability of crystalline solids	■	■	
1C. Herbicide polymorph conversion experiments via milling		■	■
2A. Cocrystallization of herbicides and characterization of properties	■	■	
2B. Characterization of solids when re-subjected to milling post synthesis		■	■
2C. Correlation of organic structure to breakage in milling (both Obj 1 and 2)		■	■

IFPRI Support. Objective 1 will benefit from consultation with the IFPRI industrial partners to determine the material phase(s) that are of most interest (e.g., crystalline vs. amorphous) for specific industrial applications. This insight will be used to inform our experimental design and focus our approaches on either achieving ideal materials or preventing transformation to non-ideal forms. Within objective 2, support from IFPRI through provision of model test materials would be of interest. Objective 2 will also benefit from IFPRI insight into test methods that would be most applicable for the post-synthetic milling stability studies.

Three years ahead. Overall, behavior of organic crystalline solids under mechanochemical processes can vary widely depending on structure, polymorphic behavior, stability, and reactivity. We envision the proposed work will generate fundamental knowledge on the behavior of agrochemical solids under milling conditions with correlation to structure. The partnership with the IFPRI will enable our team to target both methods and materials that will be of most interest and use to industry, enabling the broader use of mechanochemical techniques in industrial applications.

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