Mitigation of Chemical and Physical Mechanical Activation Risks of Organic Small Molecule Crystalline Materials by Co-Processing

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Introduction: Many small molecule organic crystalline solids are exposed to high-shear mechanical processes in their use as materials by various industries. Supramolecular changes caused by particle deformation and fracture can result in significant disorder, which increases the molecular mobility enough to drive physical changes (*e.g.*, polymorphic interconversion or amorphization) or regional/global chemical changes (*e.g.*, increased susceptibility to chemical degradation)[1-3]. Crystalline solids used as *active pharmaceutical ingredients* (API) are commonly subjected to high-shear manipulations during the preparation and finishing of drug delivery platforms (*e.g.*, tablets, capsules, *etc*.)[4]. API that are mechanically activated during manufacturing can cause a variety of issues ranging from inefficient downstream processing due to altered materials handling properties[5-7], up to variable therapeutic usefulness, owing to compromised dosage form performance from changes in the chemical and/or physical stability of the drug[2-4, 8-11].

To address these challenges, we propose an experimental framework to establish a means for protecting high-risk API that undergo different types of mechanical activation upon exposure to dry milling. By specifically addressing the relationship between the material functions for both API and excipients, and the physicochemical and mechanical properties that dictate their respective mechanical responses while co-processed, this project will serve as a novel approach to solving a key problem when working with organic small molecule crystalline materials. In this context, we define high-risk API as *organic small molecule crystals that easily convert high-shear mechanical processing energy into surface and/or bulk disorder*. The extent of mechanical activation generally increases with increasing magnitude of the applied stress (process intensity), and its continuous repetition (process duration)[1, 4, 12-21]. To mitigate the risks associated with API mechanical activation, we propose selection of inert ingredients (termed excipients), which will be co-processed with the high-risk API. These excipients are expected to be able to divert a portion of the mechanical energy away from the high-risk API during co-processing, thereby reducing the extent to which the API is mechanically activated. Selection of co-processing excipients will be enabled by determination of their material functions, related to how their physicochemical and mechanical properties allow consumption of milling energy.

Figure 1 illustrates the hypothesis framing this work, which is that ***softer, less brittle co-processing excipients will consume a greater portion of shear energy during co-processing, resulting in less mechanical activation of the high-risk API.*** The complement to this hypothesis is that harder, more brittle co-processing materials will absorb less shear energy during co-processing, offering less protection against API mechanical activation. By identifying physicochemical and mechanical attributes of the co-processing excipients that relate to their energy consumption during dry milling, we can better direct formulation to align high-risk API with materials that offer them protection against mechanical activation within the processing environments that they must encounter. This approach is consistent with the FDA's materials understanding component of the *Quality by Design Initiative*[22] and represents a desirable departure from expensive and inefficient trial-and-error experiments.

Background: Extensive work by our lab has demonstrated that exposure of API to high-shear manufacturing risks at least some degree of mechanical activation. Previously, we showed that consolidation can lead to polymorphic interconversions[15, 19, 20] or disordering[17, 23], the extent of which increased with increasing compaction pressure. Notably, it was the shear component experienced at interparticulate contacts that allowed these conversions, as similar hydrostatic loads did not result in mechanical activation[10]. Key to the proposed work, we investigated how the physicochemical attributes of organic small molecule crystalline solids can be used to predict their risk of physical transformations during high-shear processing. We adapted a model[24] that assumed that when organic

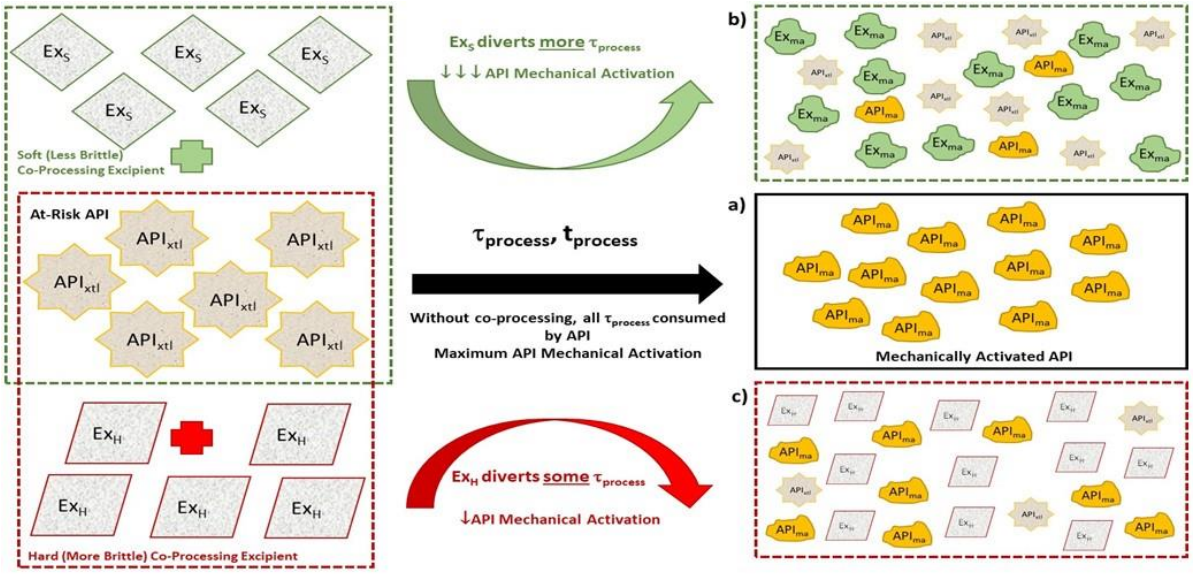

Figure 1. A high-risk crystalline API will be a) mechanically activated (API_{ma}) when exposed to a high-shear processing environment for a certain time. Co-processing with a soft, less brittle (Ex_S) diverts more process energy to excipient activation, b) reducing mechanical activation of the API. Co-processing with a hard, more brittle excipient (Ex_H) diverts less process energy to excipient activation, c) reducing the protection offered against API mechanical activation.

crystalline particles reach their fracture limits, continued application of shear stress results in the generation, movement and entanglement of dislocations. This allowed us to predict that when the energy converted into lattice dislocations (ΔG_d) reached the free energy required to amorphize (ΔG_{am}) the γ-polymorph of indomethacin (IMC), complete disordering due to processing would result[19]. Although originally envisioned in relation to lattice deformation, this mechanism can also apply to the deformation that occurs at propagating cracks, as particles fragment. Expansion to a broader library of organic small molecule crystals revealed a more accurate material function, in which a bivariate model was used to combine the glass transition temperature (T_g) and the molar volume (M_V) of a material to predict the risk for its complete disordering after extensive cryogenic milling[4, 14, 16]. In both cases, the physicochemical properties of IMC revealed its high risk for mechanical amorphization.

In other work related to this proposal, a mechanism for the chemical degradation of gabapentin (GPN) was observed to be accelerated by high-shear processing, due to formation of an activated, unstable GPN* solid-state intermediate[25]. Dry milling GPN led to greater chemical degradation, as evidenced by the increased formation of the lactam degradant. Additionally, exposure of GPN to moisture after processing significantly reduced the effects of mechanical activation[26], suggesting that environmental water can heal the damage caused during milling. We also expanded the initial kinetic model to accurately account for catalytic effects of excipients, as well as their influence on damage produced during compression[27]. In these results, softer excipients (*e.g.*, starch), led to very little additional activation from compression, while harder materials (*e.g.*, DiTab®), significantly accelerated the initial degradation rate, beyond the catalytic effect of the excipient.

The results with GBN seem to complement our earlier work using a relatively unique technique known as compression calorimetry, in which work, heat, and internal energy changes accompanying the compression process are simultaneously measured. Studies using this technique have found that some portion of the mechanical energy introduced into a material during compression remains stored as internal energy, presumably associated with defects or amorphous regions[28]. This residual internal energy due to supramolecular response to

consolidation was subsequently confirmed for lactose monohydrate, using solution calorimetry[29]. Most importantly, the amount of energy stored as disorder in the excipients studied was higher for less brittle materials. Accordingly, these data suggest that *energy introduced during processing, either by milling or compaction, can be absorbed by excipients to varying degrees, based on their mechanical properties, which may reduce the damage done to the API*.

Project Framing: Essentially, there are two factors that contribute to the mechanical activation risk of an organic small molecule crystalline material:

1. *Susceptibility of the lattice and/or particle surfaces to disordering via application of high-shear mechanical energy*[4, 10, 14, 16, 19]
2. *The ability of the mechanically activated material to heal itself by annealing*[1, 3]

We propose that both factors can be affected by co-processing. The first can potentially be manipulated by combining high-risk API with another excipient. Based on literature observations, co-milling materials results in differences in their observed mechanical activation and subsequent stability[11, 27, 30-36]. In the proposed work, we will explore ways in which the *excipient consumes a portion of the high-shear process energy in its own mechanical response, effectively diverting energy away from activation of the API*. In a controlled high-shear process, co-processing excipients that divert more energy will generally offer greater "protection" against mechanical activation for the high-risk API. We expect that the second of these factors can also be mitigated by co-processing, through the intentional use of moisture-containing excipients whose associated water molecules plasticize the T_g of the high-risk API, and help to anneal disorder, particularly at particle surfaces[35]. In the first proposed project period, we will focus on the first of these factors by demonstrating that **the risk of mechanical activation for two high-risk model organic small molecule crystalline materials can be mitigated to different extents by co-processing with anhydrous materials, selected based on their respective material functions related to their physicochemical and mechanical properties**. An extension of this work to explore the second factor is anticipated as the focus for a future project period.

To demonstrate the benefit of mechanochemical protection by co-processing, two model compounds, identified as high-risk API for different types of mechanical activation, have been selected:

1. ***Indomethacin (IMC)*** will be used to assess how co-processing can mitigate risks of *physical transformations* resulting from mechanical activation.
2. ***Gabapentin (GPN)*** will be used to assess how co-processing can mitigate risks of *chemical degradation* resulting from mechanical activation.

Selection of co-processing excipients is directed by our experience with the mechanical activation potential of these materials:

1. ***Sucrose*** is susceptible to rapid amorphization on milling. In our bivariate predictive model[4, 14, 16] this was due to its high T_g (74.65 °C), which offset the increased mobility conferred by the relatively small M_V (212.87 cm^3/mol). Mechanically, sucrose is relatively soft and less brittle.
2. ***β-D Lactose (anhydrous)***, is susceptible to amorphization over a wide range of temperatures, owing to a balance of T_g (82.55 °C) and M_V (215.83 cm^3/mol) consistent with our bivariate predictive model[4, 14, 16]. With stress-strain behavior expected to be intermediate to sucrose and mannitol, we have chosen it to investigate whether the diversion of process energy is linear/nonlinear relative to the material function of the co-processing excipient.

3. ***Mannitol*** is resistant to amorphization, confirmed by our lab owing to its relatively small M_V (122.76 cm^3/mol) and low T_g (34.15 °C)[4, 14, 16]. Mechanically, many grades of mannitol are relatively hard and more brittle.

Aside from the mechanical activation potential of the co-processing excipients, their **ability to divert process energy and affect the activation of high-risk API is hypothesized to be more significant when materials having lower yield pressure (σ_y) and hardness (*H*) are used**. Correspondingly, mannitol is expected to absorb the least energy during co-processing, diverting less away from mechanical activation of the IMC or GPN. In contrast, the softer, less brittle sucrose will offer the most mechanical protection when co-processed with the API, while the anhydrous lactose will offer mechanical protection intermediate to mannitol and sucrose. It is noted that the mechanical properties of excipients can vary, depending on the grade used[37], requiring mechanical characterization of the specific materials used in co-processing, to control for variations dependent on manufacturing history. We will also consider the effect of partial annealing due to loosely bound environmental water, which is not expected to change the extent of mechanical activation, but may affect the kinetics. As such, the hygroscopicity of all materials at ambient relative humidity will be measured.

Trends in mechanical risk mitigation will benefit process development for materials identified as susceptible to different degrees of mechanical activation. Our approach will demonstrate that *the extent of mechanical protection offered by co-processing is fundamentally knowable, based on a material function involving the physicochemical and mechanical properties of the excipients involved*. This will allow creation of a *protective index* for co-processing materials that can allow directed formulation approaches for high-risk API.

Outline of Planned Activities (Years 1-3)

The following outlines the 3-year experimental framework for the <u>first project period</u>:

<u>Year 1</u>: Baseline Mechanical activation of API and Process Energy Consumption of Excipients

Extant material functions for IMC and GPN will be used to predict mechanical activation responses to (i) cryogenic impact milling and (ii) ambient-temperature ball/jar milling. Baseline mechanical activation for the GPN and IMC will be measured for both mill types. For IMC, mechanical activation will be quantified using our in-house suite of characterization techniques (DSC, PXRD, and PLM)[38] to determine amorphization (*%Am*), relative to unprocessed drug. GPN mechanical activation will be determined using HPLC to quantify lactam formation (*%L*), relative to unprocessed drug. Evaluation of applied stress and process temperature will be used to determine how process intensity affects the extent of activation for both drugs and may be incorporated into our extant models. IMC and GPN hygroscopicity will be measured using dynamic vapor sorption (DVS) to evaluate the influence of environmental relative humidity (%RH ranging from ~0-80%) on mechanical activation. The kinetics of progressive activation will be modeled as a function of milling duration for both mill types. Hygroscopicity measurements are expected to inform kinetic models regarding the role of environment %RH on activation and to identify appropriate experimental conditions.

Baseline process energy consumption capacity for sucrose, lactose, and mannitol will be measured using compression calorimetry[28], while work of compression/decompression will be determined using Heckel Analysis[39]. Mechanical characterization of σ_y and *H* will respectively be done using Heckel Analysis[39] and indentation testing[40]. Consistent grades/vendors of each excipient will be used as a control to establish insight regarding how each excipient interacts with energy during controlled deformation. Material functions for the excipients will be investigated using relationships between thermodynamic data (internal energy change/work of compression, work of compression/decompression) and mechanochemical properties, including *H*, σ_y, elastic moduli (*E, G*), and

thermal conductivity (k)[41]. Some degree of work-hardening is expected for these materials during prolonged high-shear processing, which may affect energy diversion during co-processing. Material-dependent strength coefficients (K) and work-hardening exponents (n) will be determined for each co-processing excipient.

Year 1 Critical Unknowns: *Establishing a model that relates* **1.** *API physicochemical and mechanical properties to material size reduction and physical/chemical activation and* **2.** *Excipient physicochemical and mechanical properties to material size reduction and energy diversion/consumption.* **Expected Outcomes: 1.** *Baseline mechanical activation for IMC and GPN,* **2.** *Mechanical characterization of sucrose, lactose, and mannitol, and* **3.** *Evaluation of work-hardening of each co-processing excipient.*

- We expect that Year 1 experiments could be expanded to include materials that are of particular interest to IFPRI members. The model API have been chosen based on internal experience, while the excipients were selected owing to their GRAS status and ubiquitous use in pharmaceutical formulations processing. We are flexible to explore additional/different materials, particularly excipients, if IFPRI members have identified API that specifically require protection against mechanical activation or excipients that might fall outside those listed here.

Year 2: Co-processing of IMC and GPN with Select Excipients

Each drug will be co-processed with sucrose, lactose, or mannitol, in 50:50 ratios, using both cryo- and ambient-temperature milling. Year 1 analytical methods will be used to quantify *%Am* or *%L* and the kinetics for progressive activation, relative to IMC and GPN milled without co-processing excipient. Potential changes in the kinetic reaction order will be evaluated to provide mechanistic insight into the role of co-processing excipient on the mechanical activation of IMC and GPN. Changes in the extent/kinetics of API mechanical activation will be related to the Year 1 excipient material functions based on measurements of energy consumption capacity and mechanical properties. These data will be used to establish a preliminary mechanical activation protective index for co-processing excipients, based on their measured properties.

Evaluation of excipient work-hardening after prolonged exposure to shear stress (Year 1) will be used to direct Year 2 experiments concerning the effects of work-hardening on mechanical activation during co-processing. It is anticipated that excipient work-hardening will change the consumption of energy during prolonged co-processing, potentially altering the extent/kinetics of IMC and/or GPN mechanical activation. For these experiments, pre-milled sucrose, lactose, and mannitol will each be combined in 50:50 ratios with IMC and GPN and co-processed using both mill types. Any observed changes in *%Am* or *%L* and/or the activation kinetics because of co-processing with work-hardened excipients will be used to correct the preliminary protective index. The results, if significant, will be used to create pre-processing guidance for mechanical activation protection, used to direct process and formulation development.

Year 2 Critical Unknowns: *Relating the effect of co-processing to the* **1.** *Extent/kinetics of API mechanical activation and* **2.** *The influence of work-hardening on mechanical protection in prolonged milling;* **Expected Outcomes: 1.** *Evaluation of extent/kinetics of IMC and GPN mechanical activation when co-processed with select excipients,* **2.** *Establish relationships between mechanical activation protection and the material functions of co-processing excipients, and* **3.** *Evaluation of work-hardening on mechanical activation during co-processing.*

- We expect that Year 2 experiments could be expanded in partnership with an IFPRI member institution, to allow modeling at pilot or industrial scales, and/or use of additional mill types unavailable in our lab (*e.g.*, jet milling or other large-scale micronization techniques).

Year 3: Risk Mitigation Evaluation using Different Amounts of Co-processing Excipient

Experiments in Year 3 will focus on changes in the extent/kinetics of mechanical activation when IMC and GPN are co-processed using different amounts of each excipient. Both mill types will be used to co-process IMC and GPN in the presence of excess excipient (70% and 90% w/w). Increased portions of process energy are expected to be diverted by increasing excipients, leading to a reduction in the extent of API mechanical activation. Conversely, we will use both mill types to co-process IMC and GPN with less excipient (30% and 10% w/w), which is expected to provide less protection, and result in more extensive *%Am* or *%L*. Comparisons of the extents of API activation at each drug:excipient ratio will be made, to measure differences in trends related to the quantity of excipient. Relationships between API mechanical activation and the energy consumption/mechanical properties of sucrose, lactose, and mannitol will be evaluated for non-linearity. Variations in mechanical activation kinetics will be evaluated with changing amounts of excipient, particularly in cases where Year 2 studies indicate that the presence of co-processing excipient influences the observed reaction order. For any excipient where Year 2 work-hardening evaluations reveal an impact on the extent/kinetics of API mechanical activation during co-processing, experiments using both mill types will be performed using the different ratios above, replacing unprocessed excipient with a pre-milled sample. Models requiring incorporation of work-hardening will be adjusted to consider the quantities of excipient present, and the extent to which the excipient is hardened during co-processing. Where relevant, the Year 2 preliminary protective index will be adjusted to compensate for different amounts of co-processing excipient.

Year 3 Critical Unknowns: *Relating the quantity of co-processing excipient on the* **1.** *Extent/kinetics of API mechanical activation and the* **2.** *Extent of work-hardening in prolonged milling;* **Expected Outcomes: 1.** *Establish relationships between mechanical activation "protection" and the amounts of co-processing excipient,* **2.** *Extend relationships between material functions to include relative amounts of excipient used for co-processing, and* **3.** *Incorporate relative amounts of co-processing excipient for materials that are work-hardened during extensive milling.*

- We expect that Year 3 experiments could be expanded in partnership with a member institution, particularly by expanding quantification of mechanical activation protection using techniques currently unavailable in our lab, such as ssNMR. Additionally, Year 3 collaboration with a member institution lab can help direct the next phase of research in this area (see below).

Depending on the progression of the proposed work, we envision adding experiments to the first project period that begin to model recovery from mechanical activation in the presence/absence of co-processing. Physical stability during controlled storage will be evaluated for co-processed IMC, relative to unprocessed amorphous IMC and IMC activated without the protection of excipient. Using our in-house characterization suite (DSC, PXRD, and PLM), amorphous relaxation and the extent of recrystallization will be monitored for different samples of mechanically activated IMC. Similarly, chemical degradation during controlled storage will be evaluated for samples of co-processed GPN, relative to unprocessed GPN and GPN activated without the protection of excipient. HPLC will be used for quantification of continued *%L* formation on storage for different samples of mechanically activated GPN. The kinetics of GPN degradation during processing and storage will be compared, allowing potentially separate mechanisms of degradation to be determined. In either case, re-evaluation of excipient hygroscopicity will be used to determine how %RH during controlled storage affects processes related to recovery from activation. Given that these questions are related to annealing/self-healing after disordering, we expect that they will form a major aspect of the second project period, in which questions surrounding co-processing with excipients that contain water (*e.g.*, crystalline hydrates) will be explored.

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