

# International Fine Particle Research Institute

## Project Brief

### Mechanical Activation of Crystalline Organic Materials

Particle breakage of crystalline organic materials is often associated with “mechanical activation” of the material with negative implications for process performance and product properties. Typical issues associated with this behavior are (a) limited throughput, limitations in product fineness and caking in process operations, and (b) particle size growth, solid form transformation, loss in crystallinity, and chemical degradation in manufactured products. This is industrially relevant particularly in dry milling for particle size reduction and powder compression for tablet/pellet manufacturing. The fundamental problem is poorly understood (Descamps and Willart, *Adv. Drug Deliv. Rev.* 100 (2016) 51-66, Iyer et al. *J. Pharm. Sci.* 112 (2023) 1539-1565). Industry handles these issues in most cases through trial and error.

#### Scientific scope

Models of dry milling and powder compression include the mechanics of breakage (typically based on fracture mechanics), and they don't consider (supra)molecular-scale changes to the material near a crack tip or on the surfaces of a growing crack, and related aftereffects. This is especially relevant for organic crystalline materials, which may undergo mechanochemical reaction, disruption of crystalline order (including amorphization), structural relaxation on different timescales, and atmospheric interactions. This scientific scope is an interdisciplinary topic across particle breakage, crystallography, mechanochemistry, organic chemistry and solid-state science. The review by Boldyrev on mechanical activation (Boldyrev *Her. Russ. Acad. Sci.* 88 (2018) 142-150) should be considered as starting point.

Creation of the fundamental understanding on the dynamic material behavior following from the initiation of breakage and addressing the relationship between input material attributes, mechanical stress characteristics/atmospheric conditions and physical and chemical product material attributes would lead to opportunities for early-on risk assessment and guiding directions for process and product improvement in industry. The project should be primarily experimental but may be augmented with computational components.

The objective of this project is to develop an experimental framework for constructing the material function<sup>1</sup> of a crystalline organic material that includes (a) the relevant physical and chemical input material attributes, (b) stress conditions, (c) crack initiation and propagation (e.g. breakage probability), (d) molecular and supramolecular changes that occur in the growing crack, and (e) related aftereffects that may occur intrinsically or by interaction with the atmosphere (e.g. solid state relaxation, chemical degradation).

**Scope:** Organic crystalline materials (aligned with industrial project liaisons) of single, non-agglomerated particles; particle shape as applicable; brittle fracture characteristics of initial solids material. Selection of appropriate model compounds is encouraged.

- Morphology: particle size between 50 to 500  $\mu\text{m}$ ; no restriction on shape
- Stress conditions: relevant to industrial powder compression and dry milling processes
- Atmospheric conditions: Temperature of about -20 to 40°C, rel. humidity of about 0 to 80% in nitrogen or air.

---

<sup>1</sup> In the context of milling, size reduction can be understood by deconstructing the process into a mill function and a material function. The mill function describes how particles are stressed in a particular mill type and geometry (this can be generalized to a process function in other processes in which particles break). The material function describes how a particle of a give material deforms and breaks under stress and strain.