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Review

Role of Crystal Disorder and Mechanoactivation in Solid-State Stability of Pharmaceuticals

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ABSTRACT

Common energy-intensive processes applied in oral solid dosage development, such as milling, sieving, blending, compaction, *etc.* generate particles with surface and bulk crystal disorder. An intriguing aspect of the generated crystal disorder is its evolution and repercussion on the physical- and chemical stabilities of drugs. In this review, we firstly examine the existing literature on crystal disorder and its implications on solid-state stability of pharmaceuticals. Secondly, we discuss the key aspects related to the generation and evolution of crystal disorder, dynamics of the *disordered*/amorphous phase, analytical techniques to measure/quantify them, and approaches to model the *disordering* propensity from first principles. The main objective of this compilation is to provide special impetus to predict or model the chemical degradation(s) resulting from processing-induced manifestation in bulk solid manufacturing. Finally, a generic workflow is proposed that can be useful to investigate the relevance of crystal disorder on the degradation of pharmaceuticals during stability studies. The present review will cater to the requirements for developing physically- and chemically stable drugs, thereby enabling early and rational decision-making during candidate screening and in assessing degradation risks associated with formulations and processing.

Introduction

The crystalline state is the most common form of solid matter in drug substances and excipients. Most active pharmaceutical ingredients (APIs) are isolated/purified in crystalline form (preferably the stable polymorph), unless a non-crystalline state is intended for some specific application, such as the amorphous form to increase aqueous solubility of poorly soluble drugs.[1] Depending on the crystallization process and conditions, the final crystals not only differ in crystallite size/shape but also in surface and/or bulk characteristics such as the degree of *disorder*/(im)perfection, surface roughness, thermal and mechanical properties of surfaces and their anisotropies. During solid dosage manufacturing, surface *disorder* can be produced by solution-mediated processes (precipitation, granulation, drying, coating) and/or through the disruption of the crystalline lattice (milling, desolvation, roller compaction, compression).[2] Unintended *disorder* and surface amorphization can lead to several detrimental physical effects such as particle bridging, particle agglomeration, modification of powder tribocharging, as well as induction/acceleration of chemical degradation of an API or a drug product. This review focuses on the generation of crystal disorder through milling/micronization processes and its impact on the chemical stability of small molecule drugs.

For predominantly crystalline APIs, a potentially useful physical property that relates to the site, extent and kinetics of solid-state degradation appears to be the degree of imperfection/*disorder* of these crystals, including the types, density and size of defects/flaws, surface roughness, inclusions of impurities, and the overall amount of amorphous material. As compared to inorganic matter (metals, metal oxides, salts etc.), research on defects and *disorder* in organic crystalline solids has found relatively little attention, especially where pharmaceutical solids are considered.[3] Also, pharmaceutical product/process design and development discuss mainly amorphous and crystalline states, the two extremes of *disorder* continuum, with respect to the performance. Even given a complete loss of long range order, an emerging notion of 'polyamorphism' has been observed in increasing numbers of pharmaceuticals, showing different compositions of conformational states in amorphous materials as a function of amorphization methods.[4] The API molecules in *disordered* regions, when compared to the crystalline bulk, can be expected to be more

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promiscuous when it comes to chemical reactions due to their higher conformational flexibilities, greater molecular mobility and higher localized moisture sorption. Even small amounts of amorphous material or defects can result in a pronounced increase in chemical reactivity. In particular, powders that have been exposed to process steps involving mechanical stress can feature substantial amounts of imperfections and *disorder*. Sources of mechanical stress include milling, mixing, drying, sieving, fluidization and compaction. Arguably, the most effective route to *disorder* is micronization/milling. There are two major reasons for including a micronization step in formulation: 1) improve process related attributes of the powder such as flowability and ease of blending/compaction (to improve product uniformity),[5] and 2) improve the APIs aqueous solubility/dissolution rate and bioavailability through particle size reduction.[6,7] The majority of drug formulations do require micronization steps which is attained via a diversity of mills such as cone mill, ball mill, air-jet mill etc. at a controlled environment (RH and ambient or sub-ambient cryo-temperature).

In general, the development of solid dosage forms requires an extensive characterization of the API, excipient and product regarding various solid-state properties. For the API portion of the formulation, these properties can include solid-state characteristics (degree of crystallinity, polymorph, morphology/habit, crystal size and distribution), particulate/bulk properties (density, particle size, porosity), and surface properties (surface chemistry, surface composition, energetics, *disorder*, charge). In many cases, only the first two properties are considered as critical quality attributes, and very little attention is given to surface properties, especially with respect to the degree of crystal disorder and the fraction of residual amorphous content. Priemel et al. published a recent review on the various routes of unintended process-induced amorphization of APIs during primary or secondary manufacturing.[8] A recent perspective by Descamps and Willart specifically discusses several aspects of milling-induced amorphization of pharmaceutical materials including prerequisites for amorphization of crystals via milling, nature of the obtained amorphous states and their behavior towards physical- and chemical transformation.[9] Although numerous publications discuss the impact of various processing steps on crystal disorder for simple model systems, little information is available about the degree of *disorder* in formulations of marketed drug products. A possible reason for this knowledge gap is the fact that the process of amorphization/*disordering* introduced by mechanical stress is often reversed during further (post) processing, either through controlled curing/conditioning/annealing, or simply through a (perhaps un-intentional) exposure of the product to temperatures and humidity levels that allow for an extensive recrystallization of *disordered* API material (during granulation, powder transfer, compaction, coating etc.). An additional limitation is the lack of sensitivity of conventional solid-state analytical methods to detect/quantify different types of surface/bulk *disorder*, especially in a low level. While explicit conditioning (using controlled humidity) to prevent amorphization during milling and as a de-amorphization step of milled powders is frequently applied in the case of formulations for pulmonary delivery,[10] this is less common for other solid dosage forms. Even for small inhalable size API crystals (mostly <5 μm) obtained via top-down mechanical dry milling, the post-process conditioning is optimized empirically, although they can feature more surface *disorder* than crystalline APIs intended for solid oral dosage forms.[11] In the case of micronized API manufactured for solid oral dosage, it is often not well established how fast is the recrystallization, how much *disorder* remains entrapped in drug product, and for how long.

A crystal disorder can be defined as a deviation in the arrangement of atoms/molecules from the perfectly ordered state. There are different types of *disorder* in the solid-state.[12] In the approximate order of the relative amount of material affected and the extent of *disorder* these include point defects/vacancies, impurities, lattice dislocations/grain boundaries, rough surfaces, amorphous layers on crystal surfaces, and full amorphization. The continuum of solid-state *disorder* between equilibrium (perfect) crystals to isotropic liquid phase is sketched in Fig. 1. Between physically distinct stable ordered crystal and a fully amorphous phase reside diverse metastable states with intermediate degree of order called mesophases lacking translational, orientational or conformational order up to some supramolecular distances. Mesophases like liquid crystal, conformationally *disordered* (condis) crystal, plastic crystals are some of them.[13]

A perfect crystal is characterized by translational, rotational and conformational order. Depending on the presence of an order/symmetry operator, various types of crystalline mesophases can be defined. Liquid crystals contain orientational order, but lack conformational and translational order. Plastic crystals have translational order, but lack rotational and conformational order. Conformationally *disordered* crystals have translational and rotational order, but partial or no conformational order that implies different conformers of a molecule are distributed randomly throughout the crystal lattice.

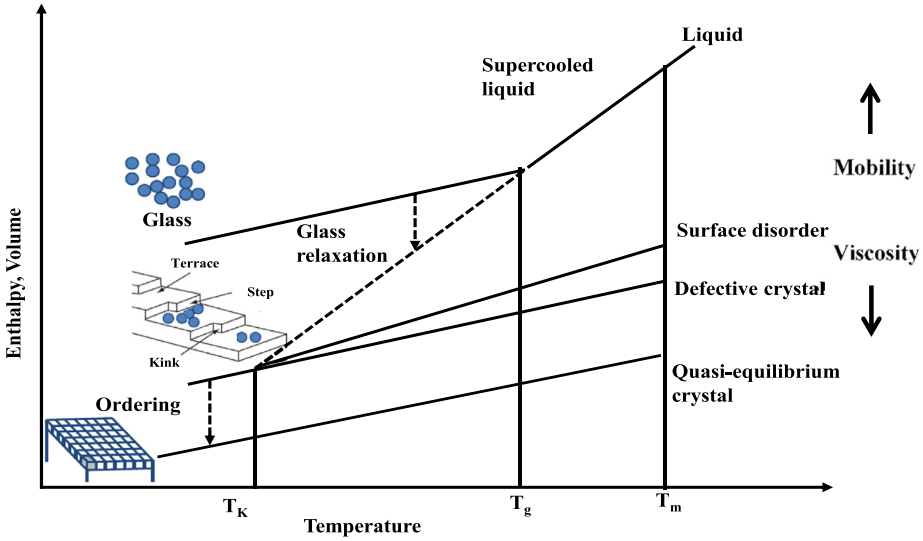

Figure 1. Energy landscape of molecular solids with different degree of orders and schematic presentation of a perfect crystal, different types of surface crystal defect, surface defect with amorphous, bulk amorphous (reported from ref[2,14]) T_K: Kauzmann temperature, *Tg*: glass transition temperature and T_m: melting temperature.

These crystalline mesophases have a higher molecular mobility and reactivity.[15] For example, the end product of solid-state milling of tetra-glycine methyl ester was found to be a *disordered* mesophase phase possessing combined properties of amorphous and crystalline phase.[16] Solid-state thermal degradation of this milled form is mediated via a different mechanism than the neat crystal. A study by Elamin et al. suggests that milling of Griseofulvin crystals leads to the *disorder* in the solid-state structure down to 50 nm from crystal surface.[17] These different types of *disorder* and imperfection, including amorphicity, can therefore be either confounded within the crystal bulk or can propagate up to or originate from the crystal surface. The surface *disorder* possess higher energetics, and the kinetics of relaxation/ordering is usually faster than that of bulk crystals (Fig. 1). At the same time, surface crystal defects are known to be more reactive and serve as the onset of physical and chemical transformations. Recently, in addition to amorphization, formation of various crystalline polymorphs as a result of mechanoactivation was systematically investigated.[18–20] One can assume that the more pronounced *disorder* is in the API, the higher would be the impact on molecular mobilities and, hence, on physical transformation as well as chemical degradation. In order to improve our understanding of the effect of *disorder* on specifically drug degradation and chemical stability, we need to address the following key questions:

- For a given solid-state of an API and a given processing history, what is the typical extent and nature of *disorder*?
- For which solid form of a given API (anhydrous, polymorph, hydrate/solvate, salt, co-crystal, amorphous form), does *disorder* matter more in the context of chemical degradation?
- How much *disorder* in API can recrystallize at ambient conditions and within a negligibly short period as compared to the drugs shelf-life?
- Can one predict the extent of *disorder*, and subsequent recrystallization based on environmental conditions, and on the API's and excipient's physico-chemical properties?
- For a given nature/degree of *disorder*, can one predict its impact on chemical stability of a particular solid form?

In the present review, we have collated non-exhaustive cases from published works about the impact of solid-state disorder on chemical degradation, the degree and the nature of *disorder* we expect to find in typical powder-based drug formulations, and analytical methods for its quantification. The literature analysis leads us to outline the research required for a better understanding of the role of *disorder* in solid-state drug degradation. We also discuss how simulation and modelling can be used to gain complementary insights, and expedite pre-formulation stage and formulation/process development of physically and chemically stable drug product under the quality by design (QbD) principle.

The Impact of Crystal Disorder on Chemical Stability

As mentioned above, more *disorder* is expected to result in a higher molecular mobility, which, in turn, should lead to higher physical and chemical reactivity of samples that feature *disorder* from mechanical activation during processing. The vast majority of published works mentioning about the impact of processing on solid-state properties of pharmaceuticals are concerned with the formulation's physical stability. Although, it is often mentioned as a possibility; the impact of processing on chemical stability in the solid-state is rarely considered explicitly or investigated in mechanistic detail. Also, most of the published work on solid-state degradation of pharmaceuticals dates several decades back, and process-induced *disorder* of inspected materials/formulations is rarely covered.

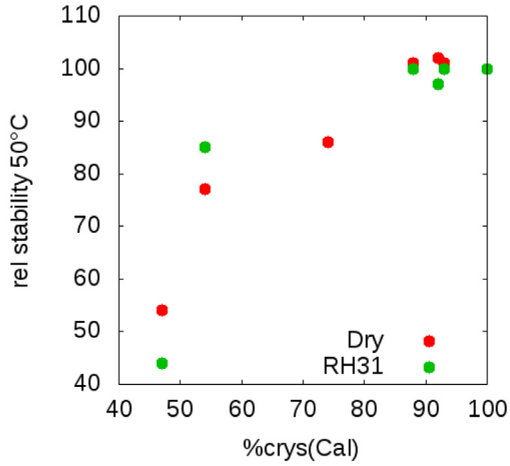

Figure 2. Chemical stability of cephalothin sodium versus the crystallinity of processed solid stored under dry and moist (31 % RH) conditions. Data is reported from Ref.[21]

Pikal et al. investigated solution calorimetry as a method for the quantitative determination of crystallinity in sodium salts of various Cephalosporin antibiotics.[21] They report that the solution calorimetric crystallinity correlates well with chemical stability of cephalothin sodium, provided amorphous and crystalline standards are appropriately chosen. They defined percent crystallinity via stability as $P = 100\ (1\text{-}k_S/k_a)$ where k_S and k_a are the apparent first-order decomposition rates for the sample and amorphous standard, respectively (Fig. 2).

In a number of early contributions, the impact of grinding and drying on various crystalline hydrates were investigated. The studied compounds include sodium Prasterone sulfate,[22] Ampicillin trihydrate,[23] and Cefixime trihydrate.[24] As documented by Hickey et al., it is important to realize that for the electrophilic drug molecules, the hydrate crystalline form show decreased affinity and chemical potential of mobile water towards the reactive site. Thus, preventing dehydration/amorphization of such crystal drug hydrates is crucial for their chemical stability.[25] Next to the interesting effect of water, which will be further discussed in Section 5.1.2, the authors generally observed increased reactivity of samples exposed to longer milling times. In a rather interesting contribution, Grant et al. introduce a so-called *entropy of processing*, ΔS_p, as a quantity for comparing the solid-state disorder of pharmaceutical materials.[26] ΔS_p is defined as the difference between the entropy of the sample and that of the same amount of a conveniently chosen reference material. It can be measured using, for example, conventional differential scanning calorimetry (DSC). Interesting examples of the model systems they consider in their study include Chloramphenicol palmitate polymorphs A and B whose ΔS_p increases after pharmaceutical processing, and correlates for different samples with the dissolution profile, and the rate of hydrolysis; as well as variously dried and/or aged samples of β-lactam antibiotics for which ΔS_p was found to increase with decreasing X-ray crystallinity, chemical stability, and with increasing water absorption. Irwin and Iqbal[27] measured the solid-state decomposition (hydrolysis) of methoxyphenyl amino-acetate hydrochloride in contact with two different excipients. They found that the observed degradation rates not only vary with the type of excipient, temperature and humidity, but also increase with increasing energy input from mechanical activation (gentle mixing vs grinding).

A considerable body of work on solid-state reactions in pharmaceuticals has been published by Stephen Byrn and co-workers.[28,29] Although a large portion of this work is about topo-chemical, intramolecular, or dimerization reactions that do not require any major diffusional motions of the reactants,[30,31] there are cases that are more relevant in the current context. For example, thermally-

induced methyl transfer in Tetraglycine methyl esters was found to proceed in the solid with an apparent auto-catalytic kinetic profile.[32] This is explained as an effect due to the increasing *disorder* in the crystal lattice caused by the formation of a crystalline solid solution of products. Interestingly, reactivity in a freeze-dried solid is considerably faster than that occurring in the milled samples, suggesting that the two processes produce different extents and types of *disorder*. An example that demonstrates the complex relationship between molecular mobility in the solid-state (and particle state) and chemical reactivity is amorphous Quinapril hydrochloride prepared by solvent- and melt-based methods.[33] A temperature dependency of isothermal cyclization kinetics of the compound was found to correlate with that of molecular mobility below the glass transition temperature (*Tg*) and irrespective of preparation methods, but reaction was slower than expected above *Tg*.[33] The observed slower reaction rate in the latter case (above *Tg*) were explained as a consequence of a reduction of the particle surface/volume ratio above *Tg* due to agglomeration/sintering of particles caused by softening of the solid, and a resulting decrease in the rate of removal of the gaseous HCl product.

Studying the acid–base reaction between various solid forms of Indomethacin and ammonia gas, the authors found that amorphous Indomethacin readily reacts.[34] In the metastable α-polymorph, carboxylic acid groups of Indomethacin are exposed on the (100) faces and are accessible to attack by ammonia gas which explains why the reaction was found being anisotropic, propagating along the a-axis of the crystals. The stable γ-polymorph has the reactive groups protected by the 3D arrangement of molecules in the crystal structure, which explains it's close to zero reaction rate. The acid–base reaction between Indomethacin and sodium bicarbonate was studied at different humidity levels. At 80 %RH the reaction was found to proceed faster than at 66 %RH, while at 11 %RH no reaction occurred at all. The kinetics suggested a diffusion controlled reaction.[35] An interesting example is the solid-state Maillard reaction between Metoclopramide-HCl and lactose. Drug powder was milled for various times, mixed with amorphous lactose, and reactivity was found to increase with milling time. For tablets formed from the same mixtures, reactivity was found to correlate with compression pressure.[36] In another study by Byrn and coworkers, the reactivity of Flufenamic acid was investigated. The authors found that the rate of the solid-state transformation from Form I to Form III depends on the size of crystals, being faster for larger than for smaller crystals. This result was rationalized by the finding that larger crystals have a higher defect density than smaller ones, which was also confirmed through atomic force microscopy (AFM) experiments. Although this example does not directly address the effect of mechanical activation and also does not deal with the chemical transformation, it does suggest that the mobility of molecules on crystal surfaces as well as number of reaction sites for a given reaction increase with the increasing defect densities.[37]

Of all the work published to date, the above mentioned study by Qiu et al.[36] is perhaps the most relevant in the current context. Although the authors went to some lengths to discriminate between the effects of different factors, it turned out being difficult to deconvolute the impact of changes in surface area, the amount of amorphous content, and the density of defects in the solid. In fact, these three references[34–36] discuss the three mechanisms which probably provide the most important contributions to chemical degradation in the solid-state: i) crystal/surface structure and exposure of reactive groups, ii) humidity and its impact on mobility, and iii) *disorder* introduced by mechanical activation. However, the total evidence available regarding the role of these three mechanisms, and their relative contributions under varying environmental conditions must still be considered anecdotal. We believe that this is essentially the very point at which further studies need to set in. Here we expect that a judicious combination of experimental techniques with theoretical approaches based on molecular simulation, as discussed in the coming sections, has a potential to provide genuinely new insights.

Structure of Amorphous Phase

The microstructure of an amorphous solid phase of drug has been a subject matter of great interest. As a glassy/amorphous state is an out of equilibrium state, there can be a large number of conformations existing in it that may pack randomly.[38] According to Bates et al., amorphous glasses obtained via melt cooling feature random closed packing of molecules and local interaction through van der Waal forces, and higher range orders are related to the molecular shape, comparable to the molten state.[39] Yang et al. have attempted to develop an atomic electron tomography reconstruction method to determine the 3D atomic position of an amorphous solid using a multicomponent glass forming alloy as model compound.[40] They report that amorphous phase may have some short-range order connected with each other to form crystal-like superclusters and give rise to medium-range order. Solid-state nuclear magnetic resonance (NMR) spectroscopy has been widely used to characterize the amorphous solid. While two-dimensional correlation experiments can be used to identify the intermolecular contacts between atomic pairs, deriving a complete atomic level structure is challenging in amorphous solids. In an interesting work Cordova et al. utilized machine learning model to relate the NMR chemical shifts of a hydrated amorphous drug with the chemical shifts for MD simulations.[41] This was used in identifying the H-bonding motifs and relate them to the local intermolecular complex formation energies. Lu et al. have elucidated the molecular structure of amorphous drug Posaconazole generated by melt quenching the crystalline form, using ^{13}C and ^{19}F magic angle spinning (MAS) NMR spectroscopy. They find that the amorphous variant may possess localized molecular order which closely resembles the crystalline counterpart. Similarly, two-dimensional NMR spectroscopy has been useful for elucidating the drug–polymer molecular interactions in Posaconazole amorphous solid dispersions.[42] Using a variant of $^{19}F-^{13}C$ rotational echo and double resonance (REDOR) technique, the same group of workers also depicted the utility in probing atomic distance measurement that can be used to characterize the drug–polymer interactions in ASDs.[43] Local short-range spatial order of amorphous phase obtained by milling the crystalline counterpart still retains the memory of the original crystalline symmetry. Therefore, the short-range microstructure of melt quench-cooled and mechanoactivated amorphous products essentially differ and possibly so do their reactivity and glassy dynamics.[44,45]

Measurement and Quantification of Crystal Disorder and Molecular Mobility

In this section we outline the existing literature on the assessment of *disorder* and crystal defects in solid-state pharmaceuticals. For a more comprehensive account the readers are referred to these excellent review articles.[46–50]

General Solid-State Analytical Techniques

A range of techniques with different level of resolutions, surface sensitivity and measurement times needs to be considered for the characterization of mechanically activated *disorder*/non-crystallinity.[51] Furthermore, these techniques must often be used in combination to distinguish a real amorphous solid-state from a highly defective crystalline states. Such a combination of analytical methods might be able to provide information of crystal *disorder* at the low quantities that are relevant to pharmaceutical intermediates and/or finished products.

In a relatively early account, Pikal et al. compare estimates for the amorphous content in four different crystalline APIs from solution calorimetry and PXRD.[52] They find that absolute values for crystallinity are difficult to ascertain as they depend on the choice of amorphous and crystalline standards, but for relative crystallinity, the heat of solution obtained by isothermal microcalorimetry is a precise (1%) measure. Saleki–Gerhardt et al. compared numbers for the amorphous content in sucrose samples obtained using water sorption, PXRD, and heat of crystallization. They found that the methods generally agree, but that water vapor sorption measurements provide higher precision (~1%) compared to the other two methods (~10%).[53]

In an attempt to quantify more subtle differences in *disorder*, Ticehurst et al. investigated different batches of α-lactose monohydrate for which variable processing performance had been reported.[54] Using a number of analytical approaches, including FT-Raman spectroscopy, PXRD, DSC, TGA, and surface area measurement, they did not observe any differences between the batches. Only the net retention volume (from IGC) using polar probes showed significant differences. The authors hypothesized that these differences in surface energetics were caused by minor variations in surface crystallinity or purity. Using Salbutamol sulphate as a model compound, Feeley et al. reported that surface energy differences detected by IGC can also be related to other processing properties such as powder flow.[55]

In an account that highlights some of the limitations of commonly used methods, Zimper at al. compare measurements of crystal disorder found in milled Indomethacin and Simvastatin samples from different process conditions. Using PXRD, DSC, and Raman spectroscopy, the authors find that the outcome depends on the analytical method used and the calibration standard chosen as well as on the drug itself.[56] The amorphous content calculated using partial least squares regression (PLS) models showed large differences between the three methodologies. Besides other effects the authors ascribe the observed differences to the impact of particle size (PXRD) and residual short-range order (Raman) on the measurement results. They suggest using complementary analytical methods to fully understand the investigated systems.

Greisdale et al. compared a range of analytical methods for the determination of amorphous content using Salbutamol sulfate as a model compound.[57] The investigated methods include modulated temperature DSC, attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR), PXRD, and DVS analysis. They generally find reasonable agreement for amorphous content determined by different methods provided potential methodological issues, in particular regarding calibration, are accounted for. They also suggest two further methods, one that uses *Tg* and water plasticization to estimate amorphous content, and a method whereby the enthalpy of crystallization is used.

Using Etoricoxib as model compound, Clas et al. compared three analytical methods or the determination of amorphous content.[58] They find limit of detection (LOD) values of 2.0% for Raman spectroscopy, 5.0% for modulated differential scanning calorimetry (MDSC), and 2.5% for dynamic mechanical analysis (DMA). Sheokand et al. used DVS to quantify trace amorphicity of Celecoxib in bulk crystalline powder. [59] The equilibration time for this hydrophobic API was relatively shorter with LOD and limit of quantification (LOQ) of 0.3% w/w and 0.9% w/w, respectively. For the detection of trace *disorder*/amorphicity in a range of APIs that differ in lipophilicity/hygroscopicity using DVS, method optimization requires to select types of probe vapor (moisture as well as organic vapors) and partial vapor pressure range.[60]

Isothermal microcalorimetry can also be used to determine amorphous content by controlling the relative humidity or relative vapor pressure in the sample.[60,61] A suitable plasticizer needs to be available, and, both, method design and data interpretation are not trivial. Especially, (moisture-induced) heat of crystallization in the calibration samples with different levels of amorphicity can show non-linear behavior. Instead, using heat of adsorption obtained by gas perfusion isothermal microcalorimetry is shown to provide detection and quantitation limits of 0.3% and 0.92% of amorphous content, respectively.[62] However, if these requirements are met then the method has been shown to have a quite good sensitivity with a LOD below one percent.

A strategy that can be used to obtain a maximum of information about the amorphicity from PXRD measurements is the calculation of pairwise distribution function (PDF). Bøtker et al. showed that in a characterization of amorphous material applying PDF on FTIR spectra allows for a better discrimination of subtle differences between amorphous samples from different processing routes.[63,64] An even higher precision should be achievable using high-energy X-ray total scattering coupled with PDF analysis as discussed by Billinge et al.[65] However, limits of detection (LOD) for amorphous content are not given there. Terban et al. have implemented PDF (based on X-ray total scattering) analysis over differently milled API differentiating the local structural differences (e.g., packing, conformation, domain size) existing in samples containing crystal disorder from the fully amorphous counterpart prepared by microfluidic injection.[66] The LOD for amorphous content here was shown to be 4% and an obvious limitation of this method is that it requires a high energy source.

While quantitatively analyzing trace *disorder*/amorphicity, it is important to realize that the total percentage often provide almost no information on the distribution of these *disorder*. For example, the technique that can detect/quantify certain amorphous content may not necessarily be sensitive to the equivalent amount if it is 1 wt% of the total sample and is heterogeneously distributed as shown by the IGC results published by Newell et al. on milled lactose monohydrate containing 1wt% amorphous lactose.[67] The progressive and complete amorphization of α-lactose generated using ball milling are characterized and complemented with solid-state analytical techniques (Fig. 3).[68]

The methods mentioned so far are primarily used to determine bulk amorphicity. If one is interested in the impact of micro, or mesoscale structure on degradation rates it is helpful to consider localized *disorder*. Using a combination of IGC with DSC to analyze milled Indomethacin Planisek et al. showed that it is possible to, both, quantify structural changes, and differentiate between transformed structure at the surface and in the bulk of particles.[69] This appears to be a very useful technique in the given context as information about the *disorder's* location will certainly allow for a clearer interpretation of

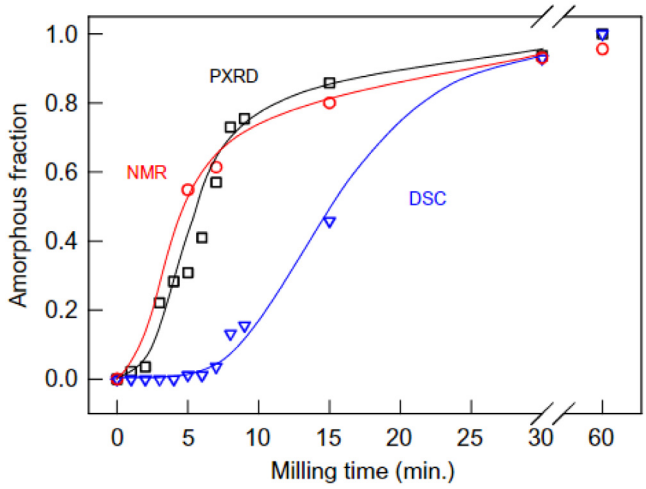

Figure 3. Quantification of amorphous fraction generated by milling using diverse analytical techniques. Reported from Ref. [68]

chemical degradation in the solid-state. The authors state that regardless of the actual underlying amorphization mechanism (quenching or mechanical activation), the increased surface energy and crystallization enthalpy accompanying structural transformations upon milling enables discrimination between surface and bulk structural changes. A variant of IGC-Finite Dilution IGC, can be used to not only measure surface energies of powders, but also the distribution of surface energy values in a heterogeneous sample.[70]

Advanced Amorphous Fraction/Surface Measurements

The combination of chemical specificity of vibrational spectroscopy with the spatial resolution offered by AFM can be realized with the use of recently developed AFM–IR and AFM–Raman techniques for nanoscopic characterization of surface/interface of materials.[71,72] Griesdale et al mapped the local distribution of the amorphous and crystalline form of Salbutamol sulfate on the surface of the compact using AFM–IR technique.[73] A combination of AFM-imaging, nanomechanical measurements, and Raman microscopy 3D profiling can be used for an analysis achieving even higher spatial resolution at the sub-micron level.[74] Using this method Ward et al. investigate the local *disorder* on surfaces of a sorbitol model that was doped with amorphous domains of 1–2 μm diameter.[74] While AFM mechanical measurements were shown to successfully distinguish amorphous and crystalline surface domains through determination of the local nano-scale Young's modulus, Raman microscopy provided complementary information about the 3D-distribution of the amorphous phase. If degradation is studied even in complex composites found in marketed drug products, this level of resolution, in combination with other more quantitative methods might be required.

Other surface-sensitive solid-state analytical techniques such as X-ray photoelectron spectroscopy (XPS), and electron spectroscopy for chemical analysis (ESCA) hold potential in speciation of different *disorders* and their distribution on the surface of milled crystals and in multi-component dosage forms.[75] An interesting technique is time-of-flight secondary-ion mass spectrometry (TOF-SIMS).[76] For example Iuras et al. used this method to map amorphous and crystalline regions on the surfaces of three different crystalline model drug compounds with a spatial resolution in the micrometer range.[77] Eddleston and Jones comprehensively discussed the principles used for the characterization of the crystal defects within particles and at their surface using X-ray topography and AFM techniques. Apart from the use of sophisticated techniques they have also highlighted some of the simple and quick approaches employing chemical etching.[78] Novakovic et al. has systematically investigated the distribution of crystalline and amorphous solid forms of the Indomethacin on the tablet surface using a hyperspectral and narrowband coherent anti-Stokes Raman scattering (CARS) methods combining with sum-frequency generation (SFG) optical imaging.[79]

To summarize, there are methods that allow for the measurement of amorphous content with a limit of detection lower than one percent w/w. However, the most commonly used methods in the industry, DSC and PXRD, unless they are combined with other methodologies, can usually not achieve such accuracies, nor do they provide any kind of spatial resolution. *Disorder* connected to crystal surfaces appears to be ubiquitous, and can make up for less than one percent of the samples total mass, as outlined in the hypothetical example in Section 1. In view of the fact that moderate humidity combined with small amounts of *disordered* material can lead to sections of a solid sample with an extremely high mobility (as discussed in Section 5.1.2) we have to conclude that the most important source of highly mobile API molecules, and the resulting impact on chemical stabilities, are currently not accounted for in applied formulation science.

Analytical Techniques to Measure Molecular Mobility and Nanoscale Density Heterogeneity

Over the last decades, a substantial attention has been paid towards understanding the role of molecular mobility of the *disordered* solid materials and its correlation with the physico-chemical instability.[80] Two types of molecular mobility mode have been identified for the amorphous solids namely, the primary and the secondary. The primary molecular mobility is associated with the *Tg*, is slower in frequency and cooperative in nature (i.e., involves translational diffusion of molecules), hence called as global mobility. On the contrary, the secondary motions are faster, non-cooperative in nature and reported to occur below the *Tg* and it involves diffusion of a part of molecule, hence recognized as local mobility.[81] Here, we briefly review the existing literature of key analytical techniques focusing on the quantitative estimation of molecular mobility in the *disordered* pharmaceuticals covering the primary and secondary (α and $\beta|\gamma|\delta|\varepsilon$-) relaxation processes. In addition to the quantifying *disorder* and crystal defects, estimating molecular mobility of *disordered* solid is a crucial parameter to understand its role towards chemical instability. In Table 1, we enlist various analytical techniques used for measuring the molecular mobilities along with their respective advantages and limitations.

Disordered materials may feature a notable difference in their nano-scale density owing to the presence of distinct domain sizes of the amorphous phase. Scattering-based techniques such as small-angle X-ray scattering (SAXS) and neutron scattering can be useful to measure the changes at the nano-scale density of solids. To what extent does this difference in the density heterogeneity of the *disordered* crystals drives subsequent phenomena such as recrystallization, degradation, annealing etc. poses an interesting question relating to their stability. As illustrated in Fig. 4, the SAXS technique was explored to understand the nano-structural characteristics (linked to the domain sizes of different nanoscale density) of partially crystalline and amorphous phases. The study is verified using a limited number of compounds that were processed through milling and melt-quenching. To complement it, recrystallization tendency was evaluated using wide-angle X-ray diffraction while processing and at storage of the powder material.[103]

The work was extended to the chemical stability context using Simvastatin.[104] This study interrogated the concomitant physical (crystallization) and chemical (autoxidation and hydrolysis) transformation in the solid-state after milling and at storage. Using an amorphous form and partially crystalline form generated by milling, the extent of chemical degradation was found not necessarily linked to the initial bulk crystallinity of the powder. Rather, nanoscale density heterogeneity or the remaining amorphous fraction or both are the main contributing factors.

Crystal Disorder from Mechanical Activation

Having highlighted cases where *disorder* and the resulting increased mobilities can decrease the chemical stability of a crystalline API material, we now turn to the question of how much *disorder* we can expect to find in solid-state drug formulations. Most API powders are exposed to micronization and/or other types of mechanical stress at some point during various conventional unit operations in the manufacturing process, and will therefore feature a certain amount of unintentional/unwanted *disorder* (in excess of the limited *disorder* on pristine crystal surfaces). The recent trend of mechano-activation towards solubility/dissolution rate enhancement of poorly soluble actives will only increase this effect. As mentioned above, how much of this *disorder* is propagated to the final dosage form and remains thereafter in the finished drug product is not well-established, but there is a considerable body of work looking at *disorder* as

Table 1
Overview of the analytical techniques used for measuring and quantifying the molecular mobility.

Technique	Advantages	Limitations/challenges	References
Thermally stimulated depolarization current spectroscopy	• Distinguishes local and global mobilities (co-operative and non-cooperative relaxation processes) • High resolution power • Provides simultaneous information about the dielectric and thermal properties	• Frequency cannot be changed to study time/temperature-dependent relaxations • Sensitive to sample preparations, reproducibility is an issue • Limited to the static electric field • Post analysis processing is time consuming	82–86
Solid-state NMR spectroscopy	• Provides collective information for dynamic mobility, dynamic heterogeneity and (chemical) structural properties	• Instrumental and operational cost • Technical/operation skills required	45,87,88
Broadband dielectric spectroscopy	• Uses the dynamic (adjustable) electric field • Sensitive to low enthalpy transitions & captures unique dielectric properties	• Lower resolution • Cooperative relaxation processes are not always resolved • Limited to samples having dielectric properties	89,90
Differential scanning calorimetry	• Simple and fast • Provides ample of information about global mobility (primary relaxations)	• Does not provide enough information about the local mobility (secondary relaxations)	91–94
Quasi-elastic neutron/ light scattering	• Determination of crossover between faster and slower relaxations is possible	• Specialized expertise needed to curate the data • Expensive analysis	95–97
Dynamic mechanical analysis	• Ideal to characterize secondary relaxations along with the mechanical properties • Sensitive to low enthalpy transitions	• Involves complex sample preparations • Does not capture all solid-state transitions	92,98
Isothermal microcalorimetry	• Measures fast modes of relaxations, enthalpy relaxations and recovery • Extremeley sensitive to small amorphous contents	• Not a routine technique • Transitions due to physical change can confound the signal interpretation	99,100
Terahertz Time domain spectroscopy	• Insensitive to thermal interferences • Time resolved study is possible in sub picosecond timescale • Low energy minimizes sample degradation	• Not sensitive to small amorphous content • Relatively new technique	101,102

a transient/intermediate phase or as an end product during milling of one component crystalline materials (API or excipient) as an immediate consequence of various types of mechanical activation of molecular solids, and some reviews are available.[14,105] Below, we discuss what we consider particularly relevant.

As milling is the most common process with a high energy input, this type of mechanical activation is considered in most publications, including the recent perspective published by Descamps and Willart,[9] but we expect most of the conclusions found there to apply also to other types of mechanical activation such as mixing or compaction. In the case of compaction, plastic deformation of bulk crystal is evidenced during tableting above the percolation threshold in API fraction-dominated formulations. Various phenomenological approaches exist to model/predict such compaction induced-deformation. This is accompanied by various concerted physical processes occurring on different length scales. The fracturing (and attrition) of the particles leading to the generation of crystal defects and/or formation of predominant amorphous phase is exemplified through the mechanical milling.[106]

Influence of Different Factors on Crystal Disorder and Degradation

Temperature

A competition between *disordering* and recrystallization appears to be a feature that is frequently observed in crystalline systems under mechanical stress. In particular, the speed of recrystallization can be expected to depend on the mobility of molecules in the *disordered*/amorphous phase. Thus, it is not surprising that the glass

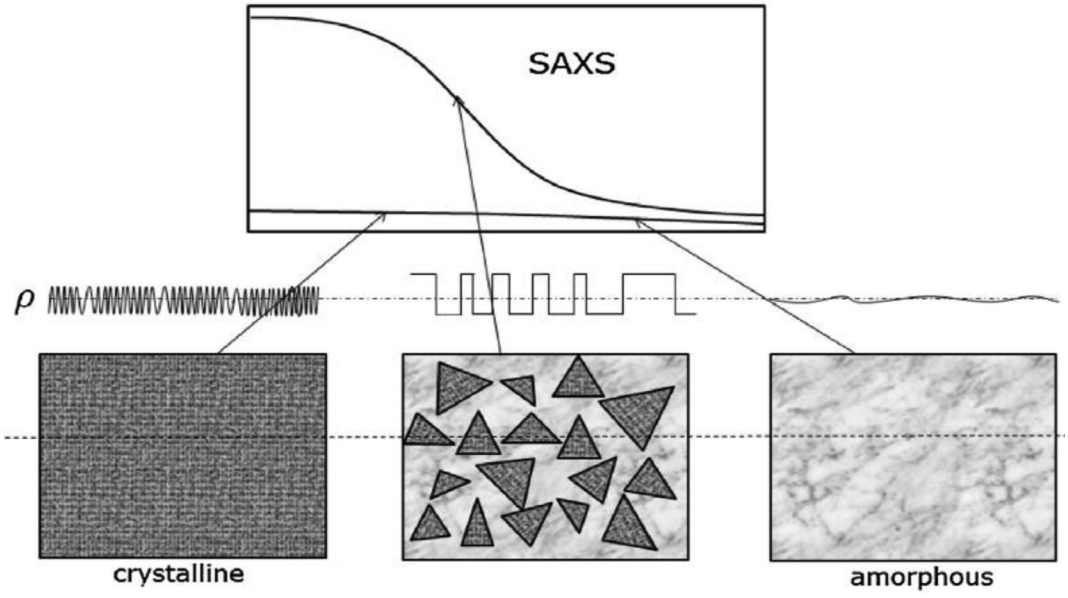

Figure 4. Schematics of SAXS intensity for crystalline, partially crystalline (middle) and amorphous powder samples. Reported from Ref.[103]

transition temperature, the temperature at which amorphous matter transforms from a super-cooled liquid to a dynamically frozen glassy state, with a resulting change in molecular mobilities, is related to the amount of *disordered* material and its nature. In a rather comprehensive study, discussing the consequences of milling for several compounds under different conditions, Descamps et al. conclude that *disorder* in crystals exposed to mechanical stress can proceed to encompass the entire sample (full vitrification), provided the milling temperature is well below *Tg*, and the milling intensity is high enough.[107] Apparently, the relative position of the milling temperature with respect to the *Tg* of the amorphized material is particularly relevant.[108] This mechanism of amorphization was found being fundamentally different from thermal quenching of the melt, as suggested, for example, by the absence of mutarotation in amorphous lactose obtained by milling.[109] Above *Tg*, a transition to a different (often metastable) polymorph can occur, but any *disorder* has the character of crystal defects rather than that of truly amorphous material.[107] Gusseme et al., studying the physical transformations of Forms III and IV of Fananserine (*Tg*≈19°C) upon milling, come to a similar conclusion.[110] They indicate that the nature of the transformation induced by milling does not depend on the initial polymorphic state, but on the milling temperature.[110] Both forms undergo a polymorphic transformation toward the metastable Form I upon milling at room temperature while amorphization is observed upon milling at 0°C. The change in the nature of the transformation with the milling temperature occurs in the temperature range around *Tg*.

Another illustrative example for the impact of *Tg* is provided by Willart et al., who compared the results of milling three different crystalline sugar hydrates.[111] The authors find that lactose monohydrate, like the three anhydrates, amorphizes upon milling while trehalose dihydrate and glucose monohydrate, remained structurally invariant. For the two latter compounds, the plasticization due to the structural water shifts the *Tg* down to values below the milling temperature, while for lactose monohydrate, as for the anhydrates, *Tg* lies above the milling temperature. Dujardin et al.[112] compared the response of crystalline α-glucose (*Tg* ≈30°C) to ball milling at different temperatures. They found that at −15°C the crystals reach a limiting size of about 20 nm, while at room temperature this size limit is about 60 nm. At the lower temperature the stationary size appears to be determined by the fact that crystals below a critical size of about 20 nm undergo spontaneous amorphization. At room temperature, due to the higher mobility of the molecules in the amorphous state, an equilibrium between mechanical fragmentation and recrystallization of an amorphous surface layer is reached.

Recently, Shah et al. showed for Brivanib alaninate that milling temperatures (cryogenic versus ambient) have opposing effects on surface energy and on surface area of the resultant particles.[113] Cryogenic milling led to a five fold increase in the suraface area as compared to room temperature (RT) milling. However, the average contribution of surface energy on the cohesivity of milled particles was higher for that obtained by milling at RT. Decoupling the surface energy and surface area contributions experimentally on the properties of milled pharmaceutical materials is an emerging area of research.[114]

Moisture Content and Extraneous Humidity

The catalytic role of water for chemical reactions is well studied and is beyond the scope of present context. Here, we focus on its role as a plasticizer. If we consider a crystalline system with a certain amount of *disorder*, be it fully amorphous regions, or *disordered* molecules, both inside the crystals or on their surfaces, we can make the assumption that nearly all the water adsorbed by the powder will reside locally in the *disordered* regions. If the total amount of *disorder* is small, this means that the concentration of localized water in these *disordered* regions can be significant, even at a very low degree of ambient humidity or low moisture content in the powder. Molecules in the amorphous phase already have a higher mobility compared to the crystalline phase, and the presence of water can further increase the mobility which is reflected by a substantial lowering of the *Tg*. For example, for sucrose Ahlneck et al. estimated that a total of 0.5% moisture in a sample with 0.5% amorphous material will result in a moisture content of 1 mg H_2O per mg solid in the amorphous phase, lowering the *Tg* from 52°C down to −72°C.[115] Even for an intrinsically non-hygroscopic (hydrophobic) drug compound, solid-state degradation in the milled crystals with certain degree of *disorder* was shown to be due to the trace level of water molecules incorporated in powder during milling itself.[116] For more details on the effect of water molecules on the chemical instability of amorphous small molecule pharmaceuticals, readers are referred to the review by Ohtake and Shalaev.[117]

In principle, this increase in molecular mobility can be expected to increase reactivity of a given compound in the solid-state. For example, in a study on freeze dried Methylprednisolone sodium succinate, it was found that water decreases the *Tg* of the amorphous phase resulting in an increased rate of reaction.[118] The degradation of amorphous Quinapril HCl through a cyclization reaction was found to be accelerated at higher humidity. Using solid-state nuclear magnetic resonance (NMR) spectroscopy, it was shown that this effect of water was due to its impact on molecular mobilities.[29]

In milled samples, humidity can have two effects causing opposite trends with respect to chemical stability: i) through the plasticizing effect of water, the mobility of molecules in *disordered* regions increases, ii) due to the same effect recrystallization of *disordered* regions is accelerated, thereby re-introducing order and eventually lowering the mobility. A case in which the latter effect dominates is discussed in a study by Zong et al. in a study involving solid-state degradation of Gabapentin.[119] The authors found that increased humidity decreases the degradation rate of the compound, and they provide evidence for their hypothesis that the predominant effect of moisture is on annealing of crystal defects. Similar results were obtained in two early studies on sodium Prasterone sulfate[22] and Ampicillin trihydrate.[23] In both cases, storage at high, rather than low, RHs was found to decrease the degradation rates, in spite of the actual degradation reaction being a hydrolysis. The results were explained through an accelerated repair of crystal defects in the presence of water. A surprising case of the humidity-mediated progressive loss of crystallinity of poorly water soluble small molecule API crystals in the mixture with polyvinylpyrrolidone (PVP) was noticed by Malaj et al.[120] The authors attribute this behavior to the physicochemical interactions of drug crystals with PVP, while water molecules lead to favorable conformations of PVP. It is important to note that there are cases showing translational mobility of water molecules in a composite in the glassy state, irrespective of their function as plasticizer.[117] Therefore, diffusion-controlled degradation cannot be ruled out entirely in these cases.

Mechanical Properties of Crystals

To consider the *disordering*-induced instabilities in crystals more directly (and quantitatively), we need to establish the mechanical properties of a crystalline material, that determine its resistance towards deformation or fracture. Interestingly, the answer to the question that which out of several possible mechanical properties or combinations thereof, to use as a measure for the resistance of a crystal towards fragmentation by forces typically encountered during milling is not straight-forward.

Perkins et al. investigated the response of three different carbamazepine polymorphs to jet-milling under identical conditions.[121] AFM measurements were performed to determine indentation hardness, Young's modulus and surface energies of the crystals. The authors report a correlation between the ratio Hardness/Young's

modulus (H/E) and micronization behavior, both, in terms of particle size reduction and surface energy change. The physical interpretation of the parameter H/E is not straight forward. However, it might be a useful semi-empirical parameter in the given context. Between Young's (E) and shear modulus (G) a linear relation exists, with a factor including Poisson's ratio. If we replace E by G in H/E we obtain the Gilman–Chin parameter, which can be calculated based on the energetics of lattice defects, and has been shown to allow for a prediction of Hardness based on the shear modulus.[122,123] The quantity H/E has also been successfully used in related contexts, such as compaction,[124] or wear and abrasion.[125,126]

Using nano-indentation experiments, Chen et al. determined Young's Modulus (E) and hardness (H) for crystals of two different pharmaceuticals.[127] In this case, both quantities suggested the same trend regarding hardness (H) and stiffness (E). Samples from milling of the two compounds at identical milling times and intensities were analyzed using high energy X-ray scattering measurements followed by a calculation of Total Scattering PDF. Comparison of the resulting PDF of un-milled and milled samples for the two compounds revealed that the compound with the harder crystals featured considerably less *disorder* than the other compound.[121,127] Further to this, a comparison between samples that were milled down to the same particle size would be meaningful.

In a quite comprehensive study, Wildfong et al. proposed a model for the prediction of the amorphization tendency of a given crystal.[128] A model, previously developed for inorganic materials, was adapted for organic molecular crystals. It is based on a comparison of the free enthalpy of the amorphous and of the defective crystalline phase for a material, as a function of the number of dislocations in the lattice.[52] The required input parameters of this model include the elastic shear modulus (G), Burgers vector magnitude (b), molar volume, melting temperature, and heat of fusion. Among seven compounds, two were predicted to become fully amorphous upon extended mechanical activation by the model, and these predictions were confirmed by experiment for six out of the seven compounds.

Using a different, but conceptually similar model that is based on a calculation of the critical size of a hypothetical amorphous nucleus (r_c), Lei et al. attempted to provide a more quantitative estimation of amorphization based on mechanical, structural, and thermodynamic properties of the material.[129] The model was tested using four compounds, a subset of the set used by Wildfong et al.[128] A correlation between the ratio r_c/b, where b is the Burgers vector, and amorphization propensity was found.

An open question regarding the models mentioned above concerns the role of recrystallization. The relation between mechanical properties of compounds in the crystalline state on one side, and the crystallization kinetics in the amorphous phase as evidenced by the *Tg* of these compounds on the other side is unclear. Wildfong et al.[128] state: "initial development and application of this theory will use temperatures sufficiently below the glass transition to stabilize any *disordered* solids as they are formed. Such persistence will permit isolation of the *disordering* phenomenon from its kinetic counterparts". Indeed, the compounds in this study were cryo-milled, immersed in liquid nitrogen, at temperatures that are probably below even the lowest *Tg* value. However, a cursory look at the numbers reveals that those two compounds that are predicted to fully amorphize by the model are also the two compounds that, by some margin, have the highest *Tg* values. This in turn suggests that exactly those two compounds whose amorphous phases have the lowest mobilities become (or rather stay) fully amorphous upon milling, which is exactly what a simple univariate model based on the *Tg* would predict. One might argue that all compounds were milled at temperatures well below their respective *Tg* values. Yet, as reported in the literature, the glass transition is not an absolute threshold, as materials even well below *Tg* can retain a considerable mobility through diverse secondary molecular motions.[130] Also temperature dependencies of the mechanical moduli are to be considered here to establish them as predictive towards mechanically activated-*disordering* propensity with respect to milling temperature.

The work discussed so far suggests that various mechanical properties, including hardness, Young's modulus, shear modulus, or a quantity H/E are related to the amorphization propensity of crystalline materials under mechanical stress. In how far these correlations hold for a wider range of compounds is unclear, though. Whether these properties can be approximated for a given material from first principles will be discussed in Section 7.

The Solid-State of Starting Materials

Mechanically-induced order–*disorder* transitions, as explained in the preceding section, have some relation with the resistance towards fragmentation that is inherent to the structural (crystallographic, molecular and supra-molecular) components of a particular solid-state. In addition, thermodynamic stability and competing kinetics, which are related to different solid forms need to be accounted towards predicting their *disordering* tendencies.

Enantiotropic polymorphs have distinct thermodynamic transition temperature and direct crystal-to-crystal (reversible) transition can commence without the absolute necessity of an intermediate *disordered* phase. However, milling of enantiotropic crystals is sometimes accompanied by partial amorphization before completely transforming to a new crystalline form.[131] This is exemplified for Ribavirin, where unprocessed samples of the metastable form did not convert to the stable form when held isothermally above the transition temperature; however, the milled crystals transformed to the stable form within 15 min upon storage at that temperature. Latter indicates that the defects sustained during the milling process reduced the energy barrier for transformation, allowing it to occur.[132] Thermodynamically, direct crystal-to-crystal transition is hard to realize between monotropic polymorphs of molecular solids, which occurs through a transient amorphous or *disordered* phase generated during milling. This has been exemplified for the low temperature milling of API monotropes such as Fananserine[110] or Indomethacin.[9] The crystalline *disorder* generated in monotropes via sub-*Tg* milling can live long enough to stay (partially) *disordered* for time-scales relevant to product shelf-life.

Hydrate crystals generally show intrinsically a reduced tendency towards milling-induced *disordering*/amorphization compared to their anhydrate counterparts. This is because, the free water molecules liberated from crystal structure during milling can instantaneously plasticize (decrease *Tg*)/heal the generated non-crystalline fraction, eventually recovering the lost crystallinity. The extent/kinetics of *disordering*/ordering during milling at a particular temperature evidently depends upon the *Tg* of the anhydrous amorphous form and water molecules of hydration. For example, during sub-*Tg* milling, lactose monohydrate (with a single water molecule per unit cell and *Tg* of 110°C) shows tendency of amorphization, while it was not the case with trehalose dihydrate (two water molecules per unit cell, *Tg* = 38°C) and glucose monohydrate.[111] Of course, milling well-below the *Tg* of pure water (e.g. cryo-milling) can even lead to an amorphization of trehalose as well.[133] Besides the plasticizing role of water in re-ordering, hydrates possess a higher plasticity than anhydrates, as water molecules in the crystal structure of hydrates act as space fillers and thereby, increase interlayer slip during mechanical stress.[134,135] In another study, the kinetics of amorphization and dehydration of diaqua-bis(Omeprezolate)-dihydrate was shown to be exponential (i.e. a faster initial process followed by a plateauing).[136] The thermal analyses of this compound indicated that upon ball-milling under ambient conditions, the amorphization progresses with a loss of water molecules. A glass transition or recrystallization event corresponding to the presence of amorphous phase was interestingly not observed; however, the melting endotherm became

broader and shifted to lower temperatures upon continued milling. A progressive loss in crystallinity was also confirmed with PXRD and FTIR analyses. It can be speculated that in the initial minutes of ball milling, a competition between dehydration, particle size reduction and crystal disordering must proceed; however, full amorphization (by accumulation of such crystal defects) only occurred upon considerably longer milling.[136] Sheth et al. found that cryo-milled Piroxicam Form I recrystallizes back to Form I, while amorphous material obtained from milling Form II recrystallizes to Form III.[44,137] Pair distribution functions (PDF) from analysis of powder X-ray diffraction (PXRD) data show subtle differences between the structures of the two amorphous samples, suggesting that amorphous material that originates from Form I crystals retains a structural memory of the original form. The authors argue that amorphous forms prepared by grinding can contain nuclei representing the original polymorph, in particular, if this polymorph features strong inter-molecular interactions, and are therefore susceptible to recrystallize back to the polymorph from which they were prepared. The fact that this behavior is observed with Piroxicam Form I, but not with Form II as starting material is in accordance with Form I being the thermodynamically stable form.[138] This suggests that, the strength of intermolecular interactions between molecules in a crystal influences the extent of its amorphization for a given degree of mechanical stress.

In case of some anhydrates with poor plasticity, mechanical force induces interlocking of zigzag layers inhibiting the slip between planes and therefore, they preferentially undergo brittle fracture. The superior mechanical properties of hydrated compared to anhydrate counterparts have been shown for APIs like Chlorpromazine HCl, p-hydroxybenzoic acid and others.[139,140] *Disordering* tendency of multi-component co-crystals has not been explored so far. However, it is reasonable to imagine the contribution to the amorphization potential in terms of mechanical properties and possible plasticizing effect of co-formers, as in case of hydrates.

Crystalline states of molecular salts require separate considerations as their strong ionic bonds result in more negative/favorable lattice energies, and higher melting temperatures. Therefore, mechanically-induced *disordering* propensity in salts can be relatively lower than it is for free-acid or base counterparts. Typical point defects occurring in crystalline salts are a vacancy of an anionic–cationic pair (Schottky defect) or smaller ionic species moving towards the structural voids (Frenkel defect).[3] The extent of *disorder*/disproportionation depends upon the counter ion present in the salt[141] and its hydration state. Another aspect to consider here is the relative stability of non-crystalline states of salts generated during milling. The *Tg* values of amorphous salts increase with the increase in charge density (therefore the strength of electrostatic interaction) of cations as shown for various salts of Indomethacin.[142] Also, *Tg* depends upon the hygroscopicity, relative solubility, and microenvironment pH of the dissociated form of salt.

It is difficult to appreciate the *disorder* in the non-crystalline solids, especially due to the ambiguity of the reference amorphous state, while for crystalline bodies a perfect crystal acts as clear reference. An important phenomenon observed in a range of amorphous materials is mechanical rejuvenation. The milling process has shown to rejuvenate the aged amorphous glass of both, small and large molecules, thus recovering a large fraction of the lost enthalpy through usual molecular relaxation processes.[143,144] Several potential energy-based formalisms through molecular modeling have been published to evidence strain rate dependency of molecular reorganization (accelerate or decelerate nucleation rate) in amorphous glass under shear strain which support the observed mechanical rejuvenation.[145,146]

Besides the internal structure of solid-state material, morphological aspects are also important to account for the *disordering* propensity. The anisotropy in relevant properties such as attachment energy, presence or absence of slip planes, thermal expansion coefficient for crystals with different aspect ratios is important. Ball milling of a crystal form of Paracetamol (Form I) is accompanied by the fracture along the (010) face of the crystal which bears the lowest attachment energy, thereby increasingly exposing a hydrophobic surface of the crystal upon progressive decrease in the crystal size.[147] This new surface chemistry leads to an increase in dispersive surface energy by 20% compared to the initial single crystals (with 011 as abundant face). To what extent does the increased surface free energy of an amorphous phase contribute to its recrystallization remains interesting to explore, as the latter may have an important repurcussion on the chemical stability of the amorphous phase. Likewise, Ho et al. has shown the dependencies of fracture axes of β-mannitol crystals during milling on the aspect ratios of the resulting crystals and their surface energy distribution.[148]

Energetics of Milling Process and Mechano-Transitions

Even though several solid oral and inhalation drug product manufacturing routes involve solid-state (or dry) milling as a primary particle size reduction/engineering step, it is still a poorly understood and unpredictable process. Literature reports Rumpf's particle fracture theory (initiation, growth and branching of cracks,[149] Vogel and Peukert breakage probability theory (that accounts resistance against impact–fracture and specific impact energy)[150] and Roberts–Rowe's brittle–ductile transition,[151] as examples to study particle energetics during milling. However, none of existing methods can predict the behavior of particles during milling. Milling, as such, is an energy intensive and inefficient process. Only a small portion of the input process energy is consumed in creating new surface and comminution, while a large fraction of process energy is utilized for various elastic and inelastic deformation processes of particles (and equipment), particle–particle and particle–machine friction, heat/vibration and noise. Despite existence of different classical laws (of Rittinger, Kick and Bond), there is still a significant gap in understanding the relation of input process energy (power) to the energy actually required for the particle breakage/fracture.[152] The energy required for size reduction is strongly material dependent (e.g. initial particle size, shape, density, hardness, mechanical moduli etc.)

Different multi-scale numerical methods and population balance models have been employed to analyze non-linear particle breakage during milling.[153,154] However, material properties driven prediction of different kinds of stressing mechanisms (particle-to-particle impact), and mechanical impact (residence time, energy) in different types of milling are yet to be thoroughly investigated. Recently, different experimental methodologies for screening of grindability and pulverization parameters were developed in combination with the computational methods.[155,156]

Coming back to the focus of current contribution i.e., the impact of process intensity on mechanoactivation related process-induced *disorder* and parallelly evolving solid solid-states, the relation is complex. One might assume that the amount of *disorder* in a powder that has been exposed to micronization, should primarily depend on the length and intensity of the milling operation. With the milling process extended for a long enough time and/or with an energy input that is high enough the milling should, in principle, be able to disintegrate the material down to the molecular scale, resulting in a fully amorphous sample. The kinetics and the extent of *disorder* highly depends upon the milling conditions, milling intensity at a specific temperature being the key aspect. Exact and physically meaningful comparative values for milling intensity are difficult to derive for mills operating in different principles. However, it is clear that the increase in milling intensity leads to an increase in the kinetics and the extent of *disordering*. For example, the end products of room temperature ball-milling of γ-Indomethacin crystals are found to be a mixture of γ-Form and amorphous form, the metastable α-Form and

complete amorphous form when milled under low, medium and high intensities, respectively.[108] Interestingly enough, milling amorphous Indomethacin (generated via quench cooling of melt) at *Tg* − 20°C follows the path of partial crystallization into γ-Form at lower intensity, full transformation into α-Form at medium intensity and full amorphization at higher intensities.[157] This clearly points towards the fact that the kinetics of competing transitions (thermodynamically stable to metastable crystal form through transient amorphization versus the kinetics of *disordering*/amorphization) changes across different milling intensities. At lower milling intensity, milling energy dissipation is found to be accompanied by spontaneously aging the intermediate amorphous glass and thereby inducing concomitant recrystallization.[158] A recent work highlighting the transient amorphization in sorbitol was proposed based on the formation of a molecular alloy generated by comilling sorbitol with amorphous Hydrochlorothiazide. The stable crystalsof sorbitol initially underwent amorphization upon milling for 9–10 h, and later transformed to the metastable Form upon extended milling.[159]

It has been suggested that the transition of ordered crystals to amorphous or *disordered* solid-state via milling proceeds through local thermal melting at so-called "hot spots" generated by inter-particle friction followed by rapid quenching.[160] However, various experimental findings of sub-ambient amorphization (e.g. by cryo-milling) contradict the mechanically induced *disordering* based on hot-spot hypothesis, instead suggest direct crystal to glass transformation.[107,161,162] Descamps and Willart in their recent review[9] cited a seminal work published by Martin and Bellon (MB) on phenomenological theories of driven alloys and underlying path of activated phase-transformation that seems to be applicable for milling-induced *disordering* as well.[163] According to MB model, two dynamic factors concomitantly contribute to the molecular material undergoing mechano-active *disordering* (against the energy landscape for evolution/transition), eventually leading to a particular solid-state of the end product of milling at a given temperature and intensity. One is usual (but, enhanced) thermal motion towards thermodynamic equilibrium (usually associated with milling temperature) and another the temperature-independent dynamic mechanical ballistic jump for point defects. The latter ballistic regimen is explicitly associated with the milling intensity and play the decisive role on the relative stability of different evolving solid-states through modification of various configurational populations of molecules. With this model, a stable solid form (polymorph, *disorder*, amorphous etc.) yielded through milling at a particular temperature (T) is the form existing at so called "effective temperature" (T_{eff}) under no mechanical intervention such that: ($T_{eff}/T - 1 = D_{bal}/D_{th}$). "$D_{bal}$" and "$D_{th}$" are ballistic and thermal diffusion coefficients, respectively, and related to milling intensity and temperature. In case of high milling temperature and low milling intensity, $D_{th}>D_{bal}$ which leads to the lesser *disordered* or metastable end product. In contrary, milling at high intensity and not very high temperature leads to relative increase in defect flux and slower mobility of the resulting defects ($D_{bal}>D_{th}$, therefore $T_{eff}>>T$) thereby leading to *disorder*/defect supersaturating in the end product.

Apart from the isolated treatments, evolution of particle size and solid-states with different degree of defect should certainly have some degree of rational convergent relation with the milling intensity and kinetics which is not necessarily straightforward. Frequently micronization of crystalline powders is found to proceed up to a certain limit only. As an example, Voriconazole has been reported to be a drug that is difficult to micronize below 9 μm owing to the plasticity of the crystal. Cleavage along the (00l) plane (identified as the slip plane) was energetically favorable. Yet upon milling, exposure of the (001) plane led to the generation of 2D molecular sheets, rendering plasticity to the crystal, thereby disallowing further size reduction of the crystal.[164] There is a common agreement on the particle size regimen of materials undergoing milling that shows brittle to ductile transition.[165] Before reaching this critically small size range (for brittle/ductile transition), crystals typically undergo fracture during milling and entering the size regimen below this leads to a compressive deformation over fractural comminution. For Propranolol HCl, it was shown that dispersive surface energy increases through milling and reaches a plateau at the size of brittle/ductile transition.[166] However, the increase in surface amorphization/*disordering* can further continue with the increase of mechanoactivation time without necessarily yielding a decrease in particle size, as shown for Griesofulvin.[167]

Kaneniwa at al. found that for Sulfadimethoxine powder the sample's total surface area reached a limiting value after ball milling for about five hours.[168] Re-analysis of the published data suggests that the limiting size was smaller than 2.5 μm. Hüttenrauch et al. applied various types of mechanical activation to Ergocalciferol powder. They found that in each case the same limiting amount of activation energy was stored in the material, corresponding to an excess free enthalpy of about 4 kJ/mol. The authors state: "at this point a thermodynamic equilibrium existed that was characterized by the same amount of defect formation and healing".[169] The literature data suggests that a value of about 20 nm for the minimum crystal size appears to be a fairly general limit, applying to metals, inorganic, and organic compounds.[112]

The Extent and Nature of Crystal Disorder

So far, we primarily discussed what could be called generic *disorder* in crystalline materials. However, as briefly mentioned above, *disorder* can come in different forms and can affect different parts of a material. One recurrent issue with studies of milling-induced *disorder* is the fact that most analytical methods for the measurement of *disorder* require standards that are usually prepared as physical mixtures of amorphous and crystalline material at varying ratios. This assumes the presence of fully amorphous, rather than a defective crystalline material. In an attempt to discriminate between amorphization versus the introduction of defects in milled material, Chamarthy and Pinal studied the structures of cryo-milled Felodipine (*Tg* = 45°C) and Griseofulvin (*Tg* = 85°C). Analyzing DSC data and thermal polarization profiles they find that both drugs lose crystallinity upon milling, but none of the two becomes amorphous.[170] Thus, the observed loss of crystallinity is due to defects and surface *disorder*, rather than a transition to an amorphous phase. Interestingly, the authors find that, for both compounds, the surface energies of un-milled, amorphous, and milled samples increase in the order amorphous<unmilled<milled. This is rationalized by the assumption that, due to the higher molecular mobilities, surface bound molecules on amorphous particles find it easier to rearrange and minimize the surface energies, compared to milled particles. This might be a general attribute of milled versus amorphous materials as the same phenomenon has been reported for Indomethacin.[171]

Given that they observe no amorphous content in their two selected drugs, Chamarthy and Pinal conclude that, a one-phase model provides an appropriate description of crystallinity change.[170] However, this result might be a consequence of the relatively short milling times and dry condition used by these authors. Luisi et al., upon cryo-milling D-Salicin (*Tg* = 60°C) and γ-Indomethacin, (*Tg* = 45°C) observe the formation of, both, amorphous and defective crystalline phases.[172] Using solid-state NMR techniques, they interpret the observed chemical shift changes in the ^{13}C spectra for both compounds as a discrete phase transformation. They propose a model that includes a phase transition separating two continuous one-phase systems, defective crystalline and amorphous.

Feng et al. studied cryo-milled Griseofulvin using PXRD, DSC and FT-Raman spectroscopy.[173] They attribute the exothermic event observed in the DSC below *Tg* to a recrystallization of defects rather

than amorphous material. In contrast to this finding Trasi et al., also studying Griseofulvin, employ modulated DSC (mDSC) and find glass transition event, and consequently claim that the cryo-milled samples do contain a fully amorphous fraction. The observed bimodal exotherm in the DSC thermograms is explained by crystallization of nuclei that form on the surface of particles, followed by crystallization of the bulk amorphous material.[174] Otte et al. took another look at the Griseofulvin amorphous systems.[175] They claim that the bimodal exotherms observed for, both melt-quenched, i.e., fully amorphous, and for cryo-milled material correspond to different mechanisms. Using mDSC analysis they find a *Tg* only for the melt quenched sample, but not for the milled sample. Consequently, they come to the same conclusion as Feng et al., stating that the reduced crystallinity observed in milled griseofulvin using XPRD data, is due to crystal defects rather than a truly amorphous material.

Ito et al. compared the thermal responses of several different, but structurally similar, compounds (*Tg* ≥78°C) to cryo-milling.[176] For two out of six compounds showed double exotherms below, or around *Tg* in DSC thermograms, similar to the response found with Griseofulvin.[174,175] They find that the two compounds that show these double exotherms are the ones with the lowest heats of fusion and melting points. Based on this, they speculate that the compounds showing unimodal exotherms might have the potential to accumulate and maintain more energy compared to the others, suggesting that intermolecular interactions in the crystalline phase determine the DSC response. However, this might only hold for a homologous series of compounds. Trasi et al. compared six structurally different compounds, and no such correlation with heat of fusion or melting point was apparent.[177] Instead, compounds that feature a double exotherm showed a higher surface crystal growth rates.

Planisek et al. studied the milling-induced amorphization of Indomethacin.[69] The surface amorphization rate, calculated based on inverse gas chromatography (IGC) data, turned out being an order of magnitude higher than the bulk amorphization rate from DSC/PXRD data. However, accumulation of *disorder* on surfaces with milling time might be reversible to some extent, even in the short run. Otte and Carvajal investigated *disorder* in cryo-milled Ketoconazole and Griseofulvin using PXRD, DSC, and IGC.[178] Compared to the work by Chamarthy and Pinal, discussed above,[170] here the authors obtain results at a range of different milling times (0–30 min). For Ketoconazole, as opposed to the other compound they find that initial reduction of particle size due to attrition is followed by particle growth upon extended milling. Scanning electron microscopy (SEM) images reveal that this effect is due to a fusion of particles with fines, which starts at the point when IGC finds a maximum in the free energy of adsorption for various probes. The maximum in the surface energy which is observed as a function of milling time is explained as a consequence of, both, this mechano-fusion of fines onto surfaces, and an increased molecular mobility in the samples with subsequent healing of the surfaces.

To summarize this section, the *disordered* material in milled samples can represent truly amorphous or defect crystalline matter, depending not only on the milling temperature relative to the *Tg*, and on the milling time/intensity, but apparently also on the molecular structure of, and interactions in the amorphous and the crystalline phases. The exact nature of *disorder* in milled powders, amorphous versus defect crystalline, still appears to be a matter of debate.[4,179,180] Furthermore, surface (hydrated) and bulk (dry) amorphicity in completely amorphous Salbutamol sulfate has been proposed by Griesdale et al. based on an anomalous observation of two distinct glass transition events.[181] Independent of the presence of fully amorphous material, *disordered* layers on crystal surfaces form readily upon milling. This type of *disorder* might be the one that is most relevant here, as i) defects in the interior of crystals will usually not come into contact with any reactants, and ii) fully amorphous material will, in most cases recrystallize upon storage. Whether the second assumption holds, is subject of the next section.

How Fast is Recrystallization?

Usually, molecules in the crystalline state have a lower free enthalpy compared to the amorphous state. Thus, amorphous/*disordered* material is physically unstable, and its recrystallization is only a matter of time. However, due to the low global molecular mobility (α-relaxation) in the solid-state below *Tg*, the transition from an amorphous/glassy to a crystalline state can be slow. The question here is, whether the resulting recrystallization rates are fast enough to ensure healing, i.e., exhaustive recrystallization, of the involved materials at a time scale that is short compared to a drug's shelf life. In many publications, the investigation of non-isothermal recrystallization of amorphous material relies on DSC data, usually considering events well above room temperature.[173,177,178,182] Whether the described events can also occur at room temperature, given enough time, is often not clear. A body of work on diffusion-less nucleation/crystal growth in the glassy state (in sub-*Tg* regions) occurring through faster secondary (local) and non-cooperative molecular mobility has been reported.[81,183,184] Especially, relaxation time of Johari–Goldstein (β) process (the precursor secondary motion of α-relaxation) has been shown to be directly related to the onset of crystallization below *Tg*.[185] Understanding the kinetics and mechanism of such sub-*Tg* perfectioning of crystal imperfections (crystallization from mechanically active glasses) in milled crystals is important in the current context. Further, the impact of moisture on different molecular mobilities and subsequently on the crystallization kinetics of amorphous materials needs to be taken into account. In a recent comprehensive review, Newman et al. elaborated the important factors that contributed to the crystallization of amorphous API from the glassy state for 78 studies reported previously. Two factors were known to be majorly common for inhibiting crystallization: i. the degree to which diffusional molecular mobility is reduced, and ii. degree of interaction between API and polymer. It was also referenced that hydrogen bonding, proton transfer interactions, disruption of API–API self-association (e.g. dimerization) and $\pi-\pi$ stacking were the major molecular factors that influenced the recrystallization.[186] At the particle level it has been shown that the recrystallization of milled solids can depend on the particle size and the surface area.[20] Another factor to consider is the higher surface mobility of the amorphous solid as compared to the mobility at the bulk level. The isothermal crystallization kinetics of several amorphous drugs (Indomethacin, Griseofulvin, Felodipine, Acetaminophen) follows a two staged behavior with an initial faster recrystallization rate (occurring at the surface) followed by a much slower recrystallization rate (plateau) occurring at the bulk.[187]

Tsukushi et al. studied the behavior of nine different molecular crystals after mechanical activation through grinding in a vibrating mill at room temperature, which, in all cases, was below *Tg*. Using PXRD[188] they did not observe amorphization for three of the compounds. Using a number of assumptions, they calculate the free energy difference between glassy and crystalline states for all materials and find no correlation between this number and amorphization tendencies. They state: "it may be that they (the three compounds) were actually amorphized, but recrystallized immediately after the amorphization", suggesting that recrystallization might proceed fast even below *Tg*.

In a study using air jet micronized Albuterol sulfate (*Tg* = 65°C), Ward et al. concentrate on the effect of humidity on the amorphous content in the material.[189] Results from water vapor sorption analysis suggest that exposure to humidity above a certain threshold leads to an irreversible recrystallization of small amounts of amorphous material in the samples within less than an hour exposure time.

Somewhat unexpectedly, they also find that the surfaces of un-milled material show a higher water sorption than those of milled samples. They assign this effect to capillary condensation in cracks and fissures that are numerous on the unmilled material. As evidenced by SEM images, the milled material, albeit smaller, has smoother surfaces and perhaps also a higher degree of agglomeration. Here, the water vapor sorption technique used to measure amorphous content results in an effective conditioning of the samples, and this process appears to be more efficient for milled compared to un-milled crystals. This example suggests that there might be cases in which *disorder* introduced by milling is, in fact, over-compensated for by subsequent conditioning. However, macroscopic cracks formed through the non-crystalline regions in milled crystal surface can further enhance the rate of crystal growth.[190–192]

MacFhionnghaile et al. performed a study similar to that discussed in Section 5.1.1 with Sulfamerazine (*Tg* = 62°C) and find that cryo-milling far below the *Tg*, leads to complete amorphization while milling still below, but close to, the *Tg* did not.[193] Recrystallization of amorphous samples stored under vacuum took hours (at RT) to days (at 4°C).

Most of the above examples consider recrystallization at temperatures not far below *Tg* and the presence of humidity might still lower the difference between the storage temperature and *Tg*. Willart et al. micronized Linaprazan (*Tg* > 100°C) at RT to produce amorphous material. They found that amorphous Linaprazan obtained by milling is stable against recrystallization at ambient conditions (20°C, 50%RH) for at least two months.[194]

In their study attempting to understand the best possible conditioning/annealing technique Brodka–Pfeiffer et al. stored freshly micronized Salbutamol sulfate (*Tg* = 54°C) at 21.5°C/42 %RH and measured the amorphous content using isothermal micro-calorimetry. Over four weeks storage the amorphous content, starting at 7.7%, decreased to 6.5% (1 week), over 5.4% (2 weeks), down to 4.5% (4 weeks). The authors state that when samples were stored in a container with reduced moisture permeability "recrystallization was significantly minimized" although a quantitative figure was not reported.[195]

In a study already mentioned in Section 5.1.3 Perkins et al. micronized, under identical conditions, three different crystalline polymorphs of Carbamazepine.[121] (*Tg* = 56°C) After storage at ambient conditions for four weeks all samples showed a reduction of the initially increased surface energies. This is attributed to a reordering/recrystallization of the *disordered* regions as they revert to lower surface energy states. However, the level of relaxation varied widely between the polymorphs with Form I relaxing almost back to its original surface energy and Form II displaying almost no relaxation at all.

Qi et al. studied the recrystallization of cryo-milled Etravirine (*Tg* ~100°C).[196] In isothermal crystallization experiments at 70°C and 90°C starting with fully amorphous material, the amorphous content plateaued at values of 65% and 85% respectively. This was confirmed using, both, spectroscopic and thermal approaches, and indicates that, even at temperatures close to the *Tg*, where mobility would still be reasonably high, the material may retain a significant portion of amorphous content following crystallization.

Depasquale et al. investigated surface properties and amorphous content of micronized Fluticasone propionate (*Tg*≈16°C).[197] They stored samples at 25°C/77 %RH and 25°C/33 %RH, as well as at 60°C/44 %RH for up to 90 days. Unlike high temperature, humidity-conditioning was found to be incapable to eliminate *disorder*. Measured using micro-calorimetry, the amorphous content, starting at 5% was still above 1% after 90 days at, both, 33 and 66 %RH. These numbers are noteworthy if we consider the fact that, given the relatively high RHs, the compounds resulting *Tg* is probably well-below the storage temperature, and the mobility of any *disordered* molecules in the sample would be rather high.

Lim et al. determined the amorphous content of an undisclosed crystalline API post-micronization using dynamic vapor sorption (DVS).[198] They compared samples from cryo-milling and from jet-milling at three different intensities stored at conditions of 40°C/75 %RH and 25°C/55 %RH. The amorphous content in the freshly milled samples varied from 100% (cryo-milled) to 15% (jet-milling at the lowest intensity). After storage for 13 weeks, these numbers decreased to 44% (cryo-milled sample) and 1.6% (jet milled sample) respectively at 40°C/75 %RH. At 25°C/55 %RH the amorphicity was reduced to 57% and 8%, respectively. The identity of the compound and it's *Tg* are not provided, and the analytical method used cannot be expected to discriminate between bulk- and surface-bound amorphous material. Nevertheless, this example demonstrates that drug-like molecules are likely to take several months to recrystallize at ambient conditions, even when starting at a small amount of total amorphous content after milling at a relatively low intensity.

Although a detailed characterization of the nature of the amorphous phase is not provided in all cases, the above examples clearly show that the speed of recrystallization of amorphous content or *disorder* introduced through mechanical activation can vary widely. In some cases, it can take a long time, even in comparison with a drugs shelf-life (≥ 2 years). Non-negligible amounts of *disordered* material can remain for months even when the storage temperature is well above the *Tg*. Glasses obtained directly by solid-state milling of the crystal often have specific recrystallisation properties owing to their (proto-crystalline) short-range order as that of precursor crystals; therefore, crystallization kinetics can strongly differ from those of the obtained from solution/melt. While amorphous mobility and crystallization being prevalent, the current information on relaxation dynamics and sintering of different types of non-amorphous *disorder* is rare, although it might be equally important for micronized materials.[199]

Which Solid form is Liable to Disorder-*Induced Degradation?*

Given the range of *disorder* attained via milling, some solid forms of a given molecule are certainly more susceptible than others to *disorder*-induced degradation. In some cases, mechanically-induced crystal disorder are also reported to remain intact for longer duration in drugs, making them inherently susceptible to degradation upon storage. Also, solid forms that feature *disorder* preferentially at surfaces are readily approachable by chemical reactants, and surface *disorder* usually shows higher molecular mobility than its bulk equivalent.[187] However, the diversity of solid forms found among pharmaceutical materials, and their complex mutual relationships make it difficult to draw any general conclusions.

Hydrates, often more resistant to mechanically-induced *disorder*, are rather liable solid forms for solid-state degradations originating at their defect sites. The water molecules, otherwise homogeneously distributed in the unperturbed hydrates, tend to concentrate in much higher amounts at the sites of milling-induced local imperfection/amorphization. This can provide abundant hydrolytic micro-environment, even at very low levels of *disorder*. Especially, non-stoichiometric hydrate often contains mobile or loosely bound water in its crystal structure that can often participate in solid-state degradation or drug–excipient reactions.[200]

Any amorphous content in such hydrates can increase the risk of solid-state degradation.[201] Likewise, isomorphic dihydrates behave as a molecular vacuum and are highly susceptible to solid-state oxidation and other topochemical reactions. The vacant channels, that are occupied by water in parent molecules, favor diffusion of reactants to the reactive sites deep inside crystal lattice.[202,203] Therefore, trace disorder in these solid forms can provide an environment that facilitates degradation.

Mechanically-induced *disorder* in multi-component molecular crystals adds another risk factor for degradation, and therefore it deserves more a mechanistic assessment beyond the state of the art. For example, free or mobile counter-ions at the *disordered* sites of

Table 2
Reported studies relating pharmaceutical solid-state *disorder* and chemical degradation.

Compound	Processing operation	*Tg* (°C)	T_m (°C)	Major degradation mechanism	References
Tetraglycine ester	Ball milling	30.3±5.7	190	Demethylation, polycondensation	16,32
BMS-561388	Compression, granulation, blending (with MCC)	–	–	Hydrolysis	207
DMP-754	Blending, granulation	–	–	Hydrolysis	208
Piroxicam	Milling	0.2±0.9	200	Proton transfer (Mechanochromism)	209
Praziquantel	Milling, comilling	37.7	201.9	Diverse	210, 211
Furosemide	Cryo-milling	53.0	206	Hydrolysis, oxidation	212
Metoclopramide HCl	Milling and compression	99.7±0.2[213]	180–182[213]	Maillard reaction	36
Simvastatin	Cryo-milling	32.8±0.7	136.7±0.1	Autoxidation, hydrolysis	104
Simvastatin	Ball milling	32.8±0.7	136.7±0.1	Autoxidation, hydrolysis	214
Cephalothin sodium	Grinding	70.0	204–205	Decomposition	215
Cefixime trihydrate	Grinding	–	220.6	Decomposition	216
Indomethacin	Milling with polymers	42[217]	160.7[218]	Decomposition	219
Cinnarizine		6.8[218]	119.6[218]	Decomposition	219
Fenofibrate		−22.4[220]	81.1[220]	Decomposition	219
Naproxen		−6.7[221]	153		219
Merck API	Cryo-milling	–	–	Oxidation	222
CP-448-187 (Pfizer)	High shear blending	–	–	Autoxidation	223
CS-758 (Daiichi-Sankyo)	Grinding	–	–	Oxidation	224
KW-2581	Jet milling	–	–	Oxidation, Hydrolysis	116
Δ9-tetrahydrocannabinol	Hot melt amorphization	–	–	Oxidation	225
Sirolimus	Hot melt extrusion	87–93	189	Autoxidation	226
GENE-A (Genentech)	Spray drying	–	–	Oxidation	227
SX-3228 (Dainippon Sumitomo Pharma)	Grinding, compression	–	–	Methyl shift, diverse	228
TAK-599 (Ceftaroline fosamil)	Synthesized as amorphous	–	–	Hydrolysis	229
TAT-59 (Taiho Fine chemical co. ltd.)	Compression	–	–	Hydrolysis	230
Quinapril Hydrochloride	Grinding, solvent evaporation	91.0	120–130	Cyclization and hydrolysis	33
Gabapentin	Milling	–	165–167[231]	Lactamization	119
Candesartan cilexetil	Compression	–	163[232]	Desethylation, ethyl rearrangement	233
Ziprasidone	Cyclodextrin complexation	70–71[234]	300[235]	Oxidation	236
Quetiapine fumarate	Hot melt extrusion	47.0	174	Oxidation	237
Dipyridamole	Spray drying (enteric polymers)	37.4–43.3[238]	165–166	Oxidation	239
Compound A (phyenylalanine complex)	Blending (compatibility studies)	–	–	Oxidation	240

crystalline salts can take part in reactions with the parent molecule, catalyze reactions with other components in formulations, or enhance moisture sorption. Some of the effects relevant for chemical instability of salts depend on counter-ion types.[204,205] Co-crystal formation of API with a suitable co-former is one of the approaches towards improving solubility, processability, stability etc.[206] The *disorder*/amorphicity generated via milling of these co-crystals can increase the proximity between the API and co-former molecules to trigger undesired chemical reactions which is not possible when they are ordered in crystal lattice. Table 2 enlists selected case studies where *disorder*/amorphous content has led to chemical instabilities in pharmaceuticals.

What is Known and What Do We Miss?

Below, we summarize in a short list what we know about the extent and the nature of *disorder* from mechanical activation of pharmaceutical compounds in the solid-state, about the factors that impact the relative amount of observed *disorder*, and what must be considered open questions at this point.

1. The degree of *disorder* can depend on the difference between the compound's *Tg*, and the experimental (e.g. milling) temperature. Above *Tg*, the molecular mobility is high, and accordingly recrystallization is fast. Below *Tg*, mobility and recrystallization tend to be so slow that micronization due to mechanical activation can result in a fully amorphous material. However, the *Tg* is not an absolute threshold. If interpreted carefully, and if other factors are accounted for, it can be used to indicate trends, but not for quantitative predictions.
2. Given the amorphization of a solid upon milling below *Tg*, the impact of storing the solid may result in diverse outcomes. If the molecular mobility is not high enough at the stored conditions, annealing of the crystal defects can occur resulting in a reduced surface energy of the solid. Also, storage in the presence of humidity can result in the plasticization of the amorphous phase with a subsequent recrystallization. Given either of these situations pervade, their implications on the degradation is still unknown. One might expect that annealing of the crystal defects results in a solid with a lower energy (static charge); however, storage under conditions which do not result in recrystalliztion can lead to accelerated dergadation of the amorphous phase.
3. The degree of *disorder* depends on humidity in a non-trivial way. Water, as a plasticizer, can increase mobility of *disordered* material and lower the *Tg*. At the same time the increased mobility can accelerate recrystallization, and thus improve the chemical stability. The threshold at which the plasticizing effect of water, and its consequences for a sample's physical and chemical stabilities' are reversed by recrystallization is poorly understood. Deconvolution of these effects and the general catalytic effect that water has on many reaction types is not yet explored.
4. Mechanical properties of crystalline materials have been shown to correlate with the amount of *disorder* introduced through mechanical activation. However, which of the several properties (hardness, shear modulus, etc.) is best suited for this purpose is not well-established. The number of cases where experimental results were compared to predictions of the resulting models are limited, and the available evidence supporting any such models is anecdotal at this point.

In spite of a good number of publications, our understanding of this field does not seem to go far beyond these principal insights. The impact and the interpretation of *Tg* values appear to be trivial, but

the few examples discussed in Section 5.1.2 should suffice to demonstrate the highly ambiguous role that humidity can play in this context. Also it is not clear to what extent the residual mobility left below *Tg* varies, depending on the physico-chemical properties of a given compound.[130] The relative impact of, and the relation between, mobility and mechanical properties, as discussed in Section 5.1.3, are poorly understood.

Another unresolved issue is about how the relative impact of the discussed factors changes when considering *disorder* in the long-term rather than in the short-term. The relative amount of *disorder* in the long-term, i.e., during storage for months or years, obviously depends on i) the amount in the sample immediately post-micronization, as well as on ii) the speed of recrystallization. The former is determined by, both, the mechanical properties of the crystalline phase and the molecular mobility in the amorphous phase. The latter will depend on the energy difference between *disordered* and crystalline phases, and on kinetics (affected by mobility, humidity, and *Tg*).

We have to assume that among all factors discussed so far, the environmental conditions, temperature and humidity, as well as material properties, will play a role in the response of an API powder to mechanical stress, and on the transformation kinetics of any *disorder* that is generated. To our knowledge, no systematic study of the interplay between all these factors has been performed to date.

Formulation Development – Practical Considerations

Depending on the compound and on the experimental conditions, the response of a crystalline powder to mechanical activation can obviously range from a barely measurable activation of the crystal surfaces to full amorphization. How much *disorder* one can expect to observe under typical conditions used in processing of drug formulations is difficult to tell, but the numbers might show a wide variation, depending on the physico-chemical properties of each compound, and on the desired particle size. Obviously for a powder that needs to be micronized down to the nano-meter size range in order to improve bioavailability, one might run a risk of observing substantial amounts of *disorder* in the product. On the other hand, we can expect that milling conditions that lead to a large degree of amorphization that is not counteracted immediately by recrystallization, will generally be avoided unless a fully amorphous product is aimed at. Micronization is frequently performed at room temperature, and a substantial portion of drug-like molecules have *Tg* values close to or below the room temperature **(**Fig. 5**).** The data shown in the figure suggests that the numbers of APIs with a *Tg* above and those with *Tg* below room temperature are comparable.

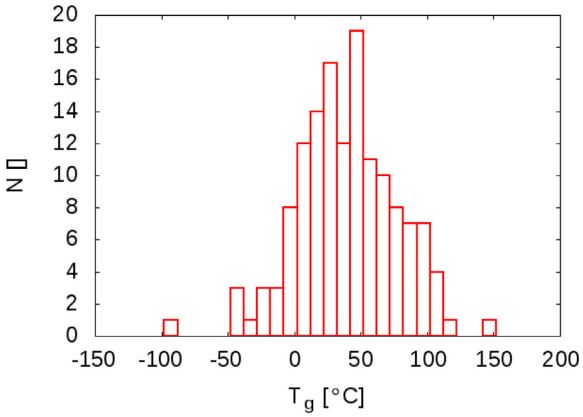

Figure 5. Histogram of glass transition temperatures, *Tg*, of 140 pharmaceuticals, compiled from literature data.[241,242]

That is, at RT, mobility in the amorphous phase is high, and recrystallization can be fast, leaving only small amounts of *disorder* that are of little interest to the formulation scientist, and not measured unless we use specific tools and methodologies for this purpose. Thus, we have to assume that the amorphous content of an API in a powder-based formulation is usually small, but *how* small it really is, and for *how* long it will persist, is not known at this point.

This being said, even small amounts of *disorder* might have a substantial effect on chemical stability. If we consider a drug's chemical degradation in the solid (crystalline) state we can make the assumption that, unless a noticeable fraction of the API is fully amorphous, chemical reactions will happen predominantly at crystal surfaces, or a thin layer of *disordered* molecules on top of the surface.[1] If, for example, we consider a cubic crystal of 5 μm side length, and assume that the topmost 10 nm of the surfaces, i.e., a few molecular surface layers, are *disordered*, then about one percent of the total volume or mass will be *disordered*. For larger crystals, this percentage can be considerably smaller. If the reaction increases *disorder*,[32] under humid conditions,[243] or if the product can migrate away from the surface and crystallize[244,245] the reaction might become auto-catalytic to a certain degree. Thus, a relatively small percentage of *disordered* material might suffice to allow for a non-negligible degree of chemical degradation over the course of a drug's shelf life. This has to be seen in the context of the fact that commonly used analytical tools for solid-state characterization are often not sensitive enough to detect such small amounts amorphous content or elevated crystal defect densities as discussed in Section 4.1. At present, the information on small amounts of (unintended) amorphous content in final dosage forms of crystalline API are rather inferred than analytically confirmed.

Besides the pharmaceutical industry, several interesting findings in the field of metallurgy/inorganic catalysis, polymer engineering have evidenced the utility of milling/mechanoactivation as a technique to synthesize a variety of chemical products.[246–249] It was shown that bond scission/cleavage and rupture alongside the high energy involved in the reaction vessel during milling can contribute to the generation of free-radicals, gases and breakdown products or intermediates directly in the solid-state, attributed to the (reactive) amorphous form.[250] Since, the reaction proceeds without the requirement of a solvent, i.e. in the solid-state, mechanoactivation/mechanochemical synthesis is regarded as a "neat and green technique".[251] Mechano-induced alteration of physiochemical and mechanical properties in the presence of excipients can have a significant impact on the quality of a final drug product. The intentional *disordering* by mechanoactivation is one of the commonly resorted processes to achieve the desired (bio) pharmaceutical properties of the solid formulations.[252–254] This is especially relevant to pulmonary drugs that are micronized to achieve the desired particle size required for deposition in lungs.[11] Very commonly, techniques such as comilling a poorly water-soluble drug with a highly water soluble polymer has been resorted to generate amorphous formulations such as amorphous solid dispersions, nano-amorphous, or co-amorphous forms. The key challenge to consider in this aspect is regarding the storage stability of such solids. Studies supplemented with electron spin resonance (ESR) spectroscopy have revealed the formation of free-radicals after milling/mechanical treatments. This has been the case for certain amino acids such as cystine,[255] alanine, arginine,[256] and excipients like sacharides,[257] celluloses,[258] and povidones,[259] etc. It would be therefore expected that manufacturing operations involving the generation of such free-radicals with a susceptible API would lead to stability concerns. Of particular concern would be the autoxidation of drugs that are processed or co-processed with such

[1] Unless the drug crystal features large pores, or in special cases like topo-chemical/photo-chemically induced reactions.

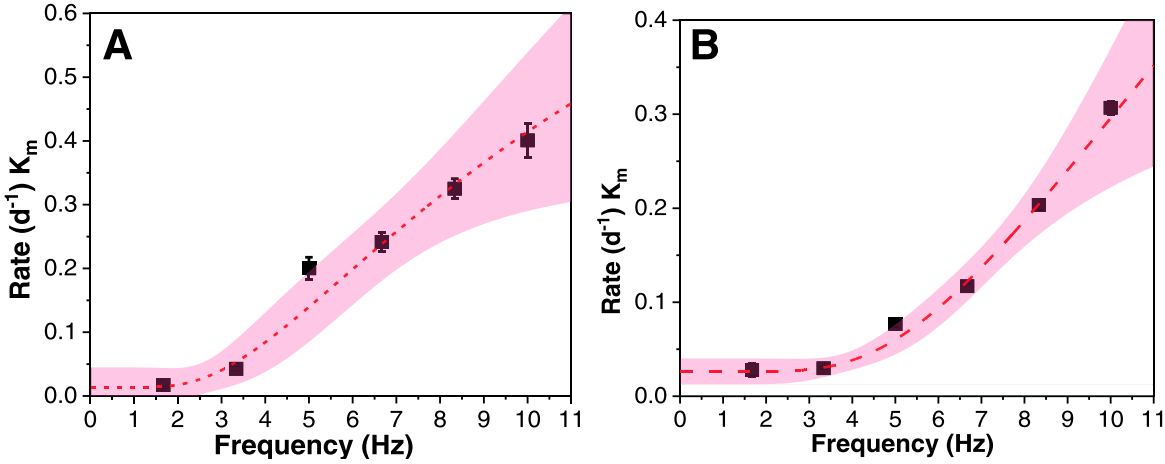

Figure 6. Plots depicting an relationship between milling frequency and degradation rate K_m for (A) amorphous Mifepristone:PVPVA (1:10) and (B) amorphous Olanzapine:PVPVA (1:10) systems. Black squares denote the average rates ±error. The confidence interval across the fitted data points is indicated in the pink band.[262]

excipients as the reaction mechanism results from the reaction involving free-radicals and molecular oxygen. In addition, it is recognized that processing steps that induce transient amorphization or crystal defects in the API may exacerbate the (in)stability even under gentle sieving or blending operations.[222,223] In their article named as how to handle small amorphous fractions in early clinical development, Petzoldt et al. have highlighted the utility of a ^{19}F ssNMR spectroscopy in probing and remediating small amorphous fraction arising during early clinical development of a candidate by the choice of a different milling technique.[260]

Looking from another perspective, comilling an oxidation sensitive API with excipients that enrich free-radicals can be an efficient way to perform autoxidative stress in solid-state. An existing investigation considering the impact of comilling an oxidatively labile drug with povidone excipient at different milling frequencies was undertaken at the author's site. The work indicates an exponential relationship between the milling frequency and degradation (autoxidation) rate of amorphous drugs which is analogous to that reported for mechanoactivation reactions.[261] A complete similarity between the resulting degradants with the reaction carried out in azo-bis-isobutyronitrile (AIBN) suggested autoxidation as the reaction mechanism. The exponential trend was fitted by an extended Arrhenius equation which allowed for a back extrapolation at zero milling frequencies to yield the degradation rate that could be compared to the reaction rate of (non-mechanoactivated) amorphous APIs under stability storage conditions. It was therewith concluded that mechanoactivation could be useful as a novel (in)stability/autoxidation prediction tool (shown in Fig. 6).[262] Also, the later could be useful to assess the efficiency of antioxidant thereby enabling rational selection and development.

Besides, the role of crystal disorder on the formation of organic impurities/degradation products one of the most crucial aspect is to understand the role of crystal disorder/mechanoactivation on the formation of nitrosamines and genotoxic impurities in drug products. A recent study[263] has indicated that processing steps used in the manufacture of solid dosages can induce the formation of nitrosamines. The formation of nitrosamines in the pharmaceuticals poses strict concerns regarding the safety, tolerability and stability due to a number of reasons.[264] First, the analytical methods required for detecting nitrosamines are quite limited and sophisticated, highly sensitive techniques are required. Secondly, the recommended limits of nitrosamine levels in the drug product is very low (below *parts per billion*) making its stricter control challenging. Thirdly, a number of marketed drugs have been required to be recalled as they were found to contain high levels of nitrosamines especially "sartan drugs" and drugs with tetrazole or nitrate groups).[265,266]

Sometimes pharmaceutical processing may induce the structural collapse of particles leading to undesired effects during formulation development or at scale-up. Upon milling, Pazesh et.al. observed the differences in the compaction behavior of the α-lactose monohydrate due to increased particle plasticity of the *disordered* particles. This led to the formation of core-shell particles

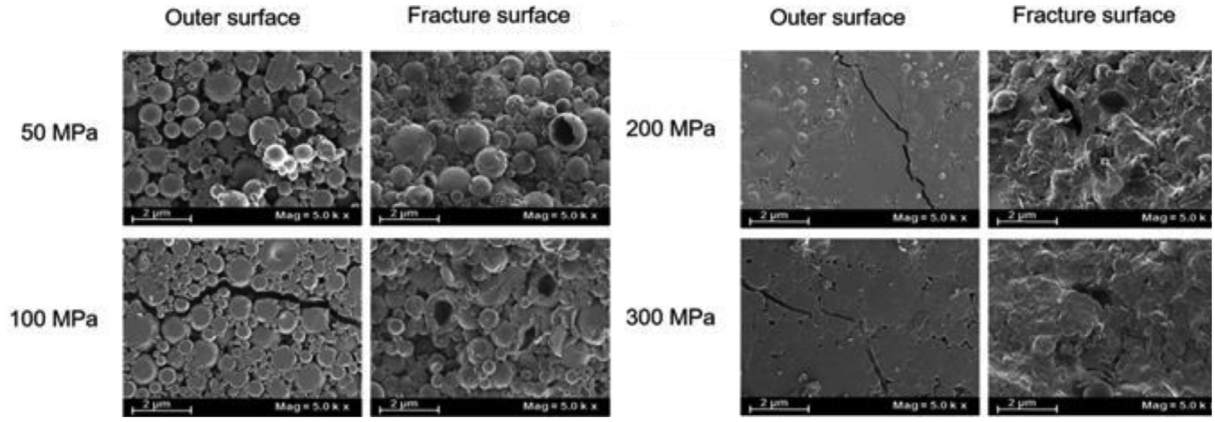

Figure 7. SEM images depicting the compaction behavior of *disordered* lactose particles at different compaction pressures (Reported from[267]).

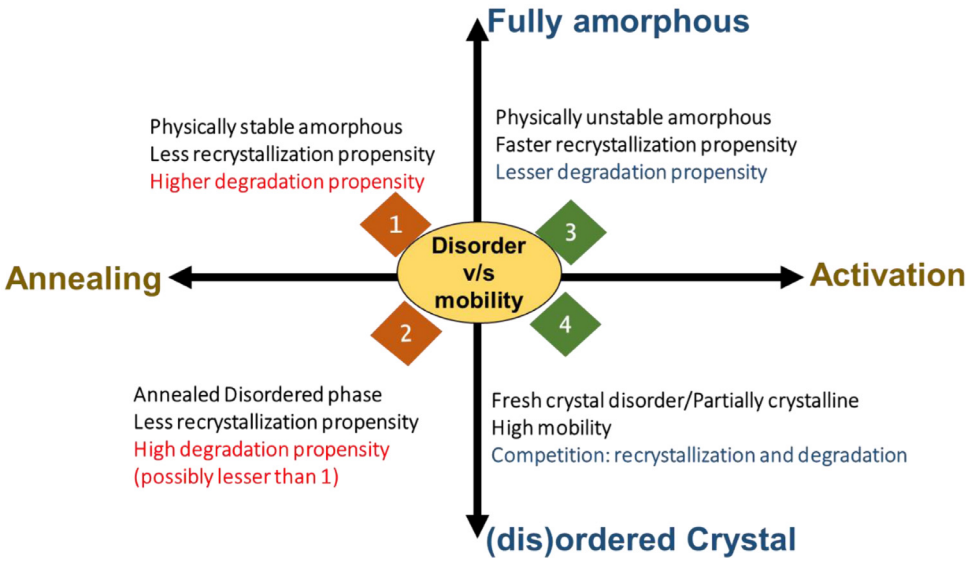

Figure 8. Proposed classification chart for *disordered* materials based on the extent of *disorder* and molecular mobility indicating the physical and stability implications of a *disordered* solid phase.

with an amorphous outer shell housing a defective crystalline core.[267] (Fig. 7)

Huang et. al. presented a case study showing compression induced changes in the solid-state behavior of Posaconazole in the presence of excipients in the tablet formulation. By utilizing finite element analysis (FEA) and ^{19}F solid-state NMR (ssNMR), the stress distribution profile during processing and amorphous form quantification is performed.[268] Moseson et al evaluated different formulation and processing strategies that can be useful to determine matrix crystallization in amorphous solid dispersions.[269]

In summary to the discussions made above, one of the outcomes of a *disordered* phase on the physical- and chemical stabilities of material can be expected, depending on the storage conditions and the transformation path the solid phase undertakes. One can classify the possible consequence of a *disordered* solid phase on its stability implication, as shown in the Fig. 8. In the vertical axis is the degree of crystal disorder; moving from low to high, the *disorder* content increases to a stage that the solid becomes fully amorphous. On the horizontal axis is the molecular mobility in the given solid-state material, that may reduce from annealing, curing, recrystallization etc. (left direction) or increase due to processing such as milling, tableting etc. (mechanical rejuvenation), moisture sorption etc. (right direction). For a fully amorphous solid phase that has undergone marked annealing (quadrant-1), it is expected that the solid would be physically stable and resist to recrystallize under accelerated and long-term stability storage. However, depending on the higher accelerated storage, (temperatures) the solid would likely be chemically reactive, hence show a higher degradation propensity. Likewise, for a solid that is not fully amorphous, yet features crystal defects (quadrant-2), it is expected that annealing would markedly reduce the recrystallization propensity (due to so called "rigid amorphous fraction" within crystalline matrices); however, make the solid phase reactive to an extent lesser than class-1. On the other side, for a fully amorphous solid with a higher molecular mobility (quadrant-3) generated via processing or moisture sorption, the propensity to undergo recrystallization would be much faster. Hence, the degradation propensity for this class can be expected to be much reduced, due to the rapidly reducing amorphous fraction at a given timescale. Of the most interesting, is the quadrant-4, where a crystal featuring predominant surface defects containing a much higher mobility may undergo a competition between the recrystallization and degradation phenomena depending on the storage condition and the dynamics of the *disordered* phase. One would anticipate, more commonly that processing stages like milling, compression, drying etc. leads to the generation of a fresh *disordered* phase that would likely behave as quadrant-4.

While Fig. 8 depicts a simplified classification, the authors acknowledge that a combination of quadrant 1–4 behavior may also exist depending on the time evolved, temperature/storage and the molecular mobility/dynamics, which may be complex to decouple.

Can We Predict Crystal Disorder from First Principles?

If we re-consider the factors discussed in Sections 5.1.1 and 5.1.3, we find that two conceptually different criteria for the potential of a crystalline solid to become fully amorphous upon mechanical activation have been proposed. One is based on mechanical properties of the crystalline phase,[128,129] the other one is based on *Tg*, i.e. the competing kinetics and thermodynamics in the amorphous phase.[107] Since both factors have been proposed in the context of pharmaceutical materials, we have to assume that both do influence, to a non-negligible extent, the fate of such materials under mechanical stress. The question is whether both factors provide the same or opposing trends for *disordering* in the solid-state of different materials, or whether they are un-related.

The model discussed by Wildfong et al.[128] suggests that a higher shear modulus increases the free energy of the *disordered* crystalline solid for a given dislocation density, allowing for this free energy to approach the corresponding value of the amorphous solid, which in turn can lead to full amorphization. On the other hand, if the *Tg* of a material is high then this indicates that the molecular mobility in the amorphous (glassy) phase is relatively low. This in turn can lead to a situation in which the *disordered* material generated through mechanical activation cannot recrystallize fast enough to compensate for the mechanical attrition, leading again to full amorphization. Of the seven compounds studied in this work the two which become fully amorphous are those two which have the highest values of, both, *Tg* and shear modulus. Interestingly, both, the *Tg*[270] and the shear modulus[271] are known to correlate with the cohesive energy density (CED). This would lead to the seemingly paradoxical conclusion that a high CED, i.e., strong and energetically favorable intermolecular interactions in the crystalline solid, lead to increased amorphization. However, the energy of the crystalline solid used in this model[52,128] is only the energy originating in dislocations. Unlike

the CED, it does not include the electrostatic and Van der Waals interactions between the molecules in the ordered crystalline phase, but is an approximation for the difference between the lattice energy of the perfect crystal and the true energy of the defective solid. In the model, this energy difference is compared to an approximation of the energy difference between the perfect crystal lattice and the fully amorphous phase. That is, here we essentially consider the difference between the average energy of a molecule in the defect crystalline solid as a function of the dislocation density and the energy of molecule in the amorphous solid. This energy difference, in turn, does not necessarily correlate with the CED. Thus, the relative energetic and mechanical properties of two compounds might indeed provide a trend regarding its potential for the generation of *disorder* that is different from the trend suggested by kinetics.

To progress from here, we need to establish the relative importance of mechanical and energetic properties versus kinetics for the residual *disorder* in samples that are stored at ambient conditions for a duration corresponding to a drugs shelf-life (months to years). The nature and distribution of short-range order, conformational compositions in given amorphous states are crucial in understanding their temporal physical and chemical manifestations. Furthermore, (pro-crystalline) memory effect, precursor moieties of various local and global molecular motions on mechanically generated amorphous materials can deeply be associated to the competing nucleation/crystal growth and degradation reactions. In the following, we discuss methods for the calculation of some of these factors from first principles.

Kinetics: Glass Transition and Molecular Mobility

The most obvious candidate for a material property that needs to be included in a model for the prediction of *disorder* in milled powders is the glass transition temperature, *Tg*, or more precisely the relation between *Tg* and i) the experimental (e.g., milling) temperature (*Tm*), as well as ii) the storage temperature (*Ts*). At the time of formulation development, the *Tg* for a particular API is probably known. If this is not the case, it can be estimated from the melting temperature, *Tm* using the simple empirical relationship *Tg* = 0.7 x T*m*, calculated using QSPR models,[241] or calculated from first principles using molecular dynamics (MD) simulations.[272–279] Usually, the calculated *Tg* values are overestimated by MD simulation due to the cooling rates that are faster than those used in experiment by several orders of magnitude,[280] but trends and relative numbers can be predicted with some confidence.

As discussed above, the *Tg* is not an absolute threshold, and even below *Tg* some mobility is left in glasses for several small molecule APIs that typically undergo sub-*Tg* nucleation/crystal growth. In principle, it is possible to calculate α-relaxation, i.e., diffusional motion of molecules, directly from MD simulations of glasses at arbitrary temperatures. Knowledge of the residual mobility, α and β-relaxation, of a given drug at the actual storage temperature (usually RT) might be more informative than the *Tg*. We have in-house data suggesting that, these numbers can be calculated using MD simulation (although can be demanding in terms of the required computational resources). Depending on the chemistry of the molecules and time scale distributions of various molecular motions; relaxation times for amorphous phase can be experimentally determined using various techniques, including dielectric relaxation spectroscopy, NMR relaxometry and DSC.[281] The relationship between local and global mobility and chemical stability of amorphous materials has to be seen in the context of the length scale of the mobility of the molecule or the part of it potentially involved in a particular chemical reaction.[282] Although, when extraneous reactants (excipients, water) are involved, the chemical reactivity of *disordered* solids does not necessarily have to correlate with molecular motions of the reacting entities.

Mechanical Properties

As discussed in Section 5.1.3 mechanical properties that might be related to the amount of *disorder* resulting from mechanical activation of a crystalline powder include hardness (H), Young's Modulus (E), shear modulus (G), and the ratio H/E. The models discussed in literature[121,127–129] require as input mechanical as well as thermodynamic properties of crystalline materials that were determined experimentally, usually through nano-indentation.[283] As such, they are of limited use for a quantitative prediction of *disorder*. However, the estimation of these properties from first principles for a given micro-crystalline material appears to be possible. Of particular relevance here is a series of publications by Roberts, Rowe, and co-workers.[271,284–289] Using a conceptually simple model the authors observed a good correlation between Young's modulus and cohesive energy densities (CED) for a range of different drugs and excipients,[271] Later similar relations were also established for other mechanical properties.[286,288] For perfect crystal structures, i.e., defect free material, the Young's and the shear modulus can be determined using atomic scale models to calculate second derivatives of the lattice energy with respect to lattice parameters. Using this method surprisingly accurate numbers could be obtained for Aspirin and two different Primidone polymorphs.[290] Interestingly even for the Hardness of organic molecular crystals a semi-empirical model, has been proposed, and shown to provide semi-quantitative predictions for pharmaceuticals.[285] The required input for this model includes, the unit cell parameters, the Burgers vector and the CED the latter can be readily calculated from first principles.[291]

The literature cited above suggests that determination of mechanical properties from first principles with reasonable accuracy is straightforward. In practice, we might encounter limitations, though. The hardness, the resistance of a material to localized deformation, is essentially an empirical parameter that depends on the measurement setup and geometries as well as the reference states (between amorphous to crystalline continuum).[292] If we wanted to reproduce, e.g., nano indentation measurements from first principles we would need to simulate the dynamics in a geometry including a sample with dimensions of, at least, micrometers, and the exact shape and mechanical response of the indenter tip.[293] Obviously such a simulation is barely feasible with atomic resolution. An alternative would be the use of semi-empirical meso-scale models like, e.g., discrete elements methods (DEM).[294,295] However, this would defeat the purpose of the exercise as such methods require as input the experimental determination of empirical parameters for each new compound. A difficulty that applies to both Hardness and the elastic modulus, is the fact that the mechanical response of macroscopic crystalline materials down to, and below, the micrometer size range is expected to not only depend on the (perfect) crystal structure, but also, and often more so, on the density and character of lattice dislocations.[296] The relationship is, in fact quite complex, with the mechanical strength of materials showing a minimum at intermediate dislocation densities. This field has been extensively studied for metals, semiconductors and some inorganic materials, but very little research has been published for organic molecular crystals. As for their response to mechanical stress the latter might differ from metals or inorganic crystals on a fundamental level.[297] This might be the reason why attempts to obtain, at least, approximate numbers for mechanical properties of organic molecular crystals from first principles have been successful to some extent, as discussed in the previous paragraph. An example demonstrating the impact of primary crystallization conditions, and thereby of lattice defects and dislocations, on mechanical properties was discussed by Kubavat et al.[298] The authors produced batches of crystalline Fluticasone propionate using different anti-solvents and found that the Young's modulus of the resulting crystals ranged from 0.6 to 12.4 GPa. The model by Wildfong et al.

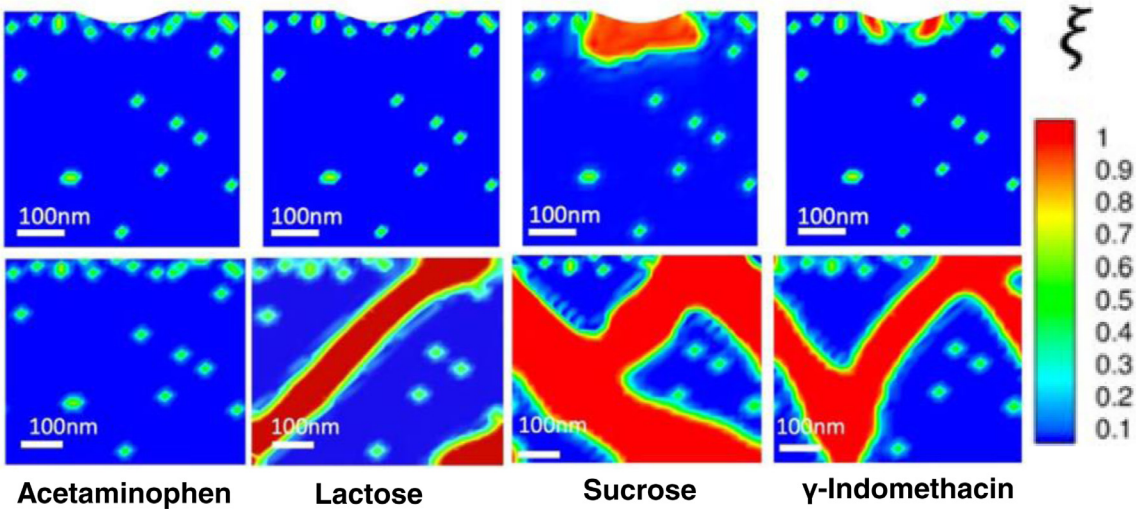

Figure 9. Simulated *disordered* and amorphous regions of the surfaces of four organic crystals after an applied displacement of 25 nm (top) and 85 nm (bottom) obtained via multi-scale modeling. Adapted from Ref. [300] The ξ is a variable related to the free energy density, where $\xi = 0$ is for fully crystalline and $\xi = 1$ is for fully amorphous phase.

implicitly accounts for this variation by using as input a shear modulus that was determined experimentally rather than theoretically based on the perfect crystal structure. Thus, the methods cited above need to be validated for a wider range of materials, and the relation between calculated (ideal) mechanical properties and the mechanical properties of the real material including dislocations/defects needs to be established before these methods can be incorporated in a model for prediction of processing-induced disorder. Lei and Koslowski performed mesoscale simulation of plastic deformation of Paracetamol and sucrose using 3D phase field dislocation dynamics model (PFDD) and stated that the model includes domain size that are relevant of typical crystal size range of pharmaceuticals that undergo milling/compaction.[299] The simulation reproduces the crystal anisotropy and yield stress when compared to the experimental values obtained via indentation. Another interesting work from Koslowski group deploys a multiscale framework to predict mechanically-induced amorphization in small molecule organic crystals (Fig. 9).[300] The model requires the chemical structure of the molecule and performs MD simulations to calculate the elastic constants, melting temperature, crystal −amorphous interfacial energy and the energy density difference between crystalline and amorphous phases. The amorphization model was validated by using sucrose, lactose, acetaminophen and γ-indomethacin and a good agreement was observed between the predicted for two new pharmaceutical compounds.

Furthermore, any models that represents explicitly crystal surface related descriptors to account for the deformation/*disordering* potential can possibly bring better prediction of the extent of milling-induced surface disorder. As an example, generalized stacking fault (GSF) energy surfaces has been studied using MD simulation in a highly energetic organic molecular crystal, namely hexahydro-1,3,5-trinitro-s-triazine (α-polymorph RDX) to predict cleavage/slip plane observed experimentally.[301]

Thermodynamics

As stated above the CED, a thermodynamic property, not only correlates with certain mechanical properties as discussed in Section 7.1.2 but also with the glass transition temperature, chemical potential, solubility parameters and (surface) energies. The latter correlation is weak but significant; at least for polymers this has been shown.[270,302,303] We cannot expect that a model based on thermodynamics (energy) alone can incorporate effects due to, both, kinetics (*Tg*, mobility), and mechanics (H, E). In particular for the latter the correspondence with CED is limited as elastic constants are tensor quantities, and usually anisotropic, while the CED is just a simple number. However, the usage of CED values or related parameters ought to provide complementary information that can be used to improve the accuracy of a given model. The CED for a given material can be readily calculated from first principles, and this can be done for the material in, both, its crystalline and its amorphous state. The latter, in combination with calculations of the molecular mobility, can be used as an input for a model towards glass forming ability (fragility) of a compound, a parameter that might be instrumental for the long-term stability of *disorder*. We ought to stress that in the early work mentioned above the CED was usually calculated from solubility parameters. We expect that CED values obtained from direct MD simulations of the materials will be more accurate, because i) here specific/directional interactions are accounted for explicitly, and ii) the last two decades witnessed considerable improvements in the force fields[304,305] used in MD simulations.

Another thermodynamic quantity that is relevant in particular for the impact of humidity on *disorder* is the aqueous solubility of a given compound. Like the *Tg*, this parameter is usually known for a given drug, except for APIs with exceedingly poor aqueous solubility, at the onset of formulation development. If required, it can also be calculated, using either statistical/semi-empirical models,[306–309] or from first principles.[310,311] Combined with more empirical models for dehydration of hydrates,[312] and water uptake/recrystallization[181] such calculations have the potential to provide quantitative predictions for the distribution of water in solid samples.

If a crystalline drug is embedded in an amorphous matrix, e.g., some polymer, the drug molecule's free energy in the crystal versus the amorphous matrix can provide a descriptor for the energetic driving force towards amorphization. Results of first principle calculations of free energies of drug like molecules in a glassy polymer matrix,[313–319] as well as in the crystalline solid[310,320,321] have been published, but this type of calculations is at an early stage of development, and the methodologies might require some improvements to become applicable to a wide range of compounds and conditions.

Components of a Predictive Model

An examination of the relevance of each of the physico-chemical properties discussed above, a combination of these properties into a model for the prediction of *disorder* from mechanical activation, and finally on the impact on chemical stability is obviously beyond the

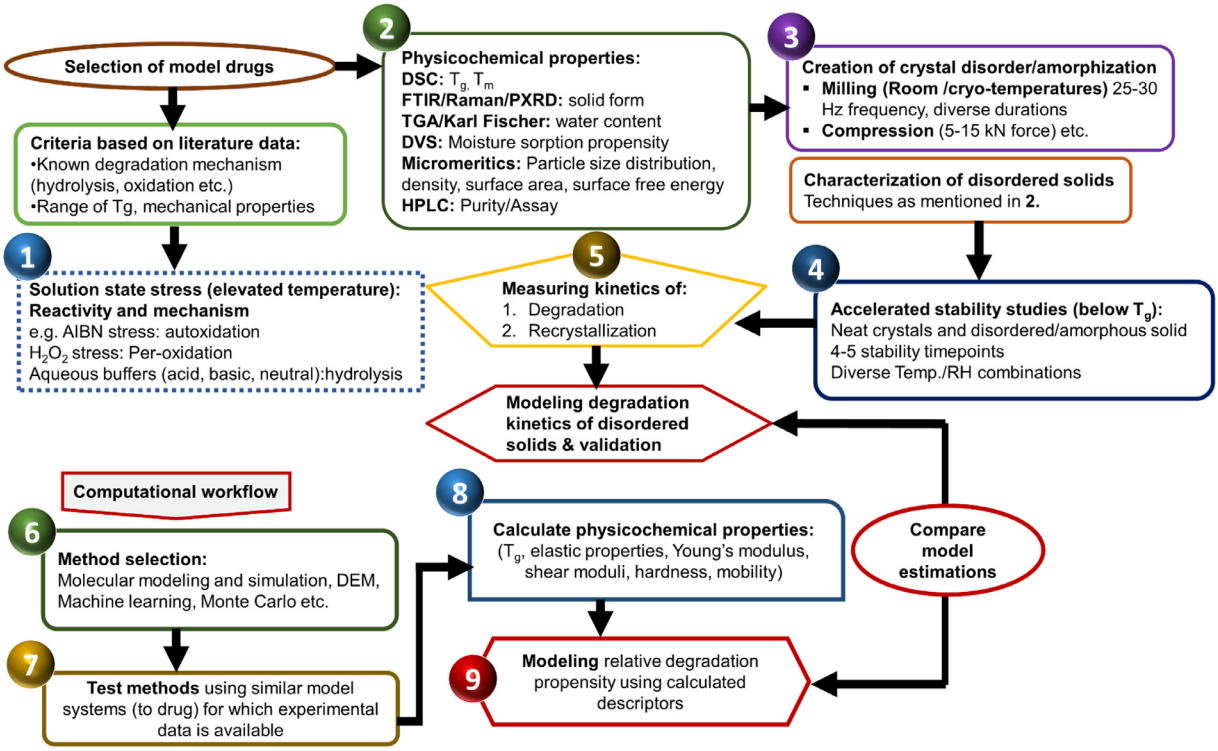

Figure 10. Proposed workflow for modeling *disorder*-induced degradation using experimental and computational (First principles) approaches. Points 1–5 represent the experimental work, while 6–9 indicate the computational modeling and simulations work.[300] Abbreviations: H_2O_2: hydrogen peroxide, DEM: discrete element modeling, HPLC: high performance liquid chromatography, kN: kilo Newton, Temp.: Temperature.

scope of this document. A comprehensive study published by Lin et al. directly addresses this question.[322] The authors subjected 23 different crystalline solids to extensive comminution under controlled temperature conditions, and measured the resulting *disorder*. A number of physico-chemical properties of each compound were measured or calculated, and based on this data logistic regression models for the prediction of *disorder* were generated. The properties found to have a significant impact on *disorder* were the *Tg*, the melting temperature, heat of fusion, crystallographic density, Young's modulus, molar volume and attachment energy. Interestingly, a univariate model based on *Tg* only appeared to explain most of the observed variations. Two avenues for further research can be taken from the point where this publication concludes. First, a limitation of this work in the current context is the fact that only *disorder* obtained immediately post micronization, and not long-term stability is considered. Second, the authors state: "One of the goals of further informatic explorations of this topic should be to create a model that does not require experimental measurements beyond structure". Combining such modelling approaches with experimental work towards the impact of various factors on long-term stability of drug formulations, we expect not only to provide a means to save time and money by reducing the required experimental work, but also additional fundamental insights into the physical basis of the generation of *disorder* in the solid-state, and its ramifications for chemical stability. A generalized model to extrapolate the accelerated stability data to long term storage might necessitate the activation energies estimation for solid state degradation versus that for relaxation and diffusion processes in the disordered solid.

Summary & Suggestions for Further Work

The relative amount of *disorder* in crystalline powders exposed to mechanical stress depends on the experimental conditions, most importantly, milling type, milling intensity and duration, temperature, and humidity. Under identical experimental or storage conditions we can assume that the degree of *disorder* that develops, and the life time of this *disorder*, depend on material properties only. The latter include mechanical, (B, H, etc.) thermodynamic (crystal lattice energy, CED, aqueous solubility), and kinetic (*Tg* of the amorphous phase) properties. Literature data suggests that a model including all these parameters will be overdetermined.[322] A model based on few, judiciously chosen parameters might provide at least semi-quantitative predictions for *disorder* and its impact on chemical stability. To progress from here, we suggest the following approach as shown in Fig. 10.

An important fundamental question is whether the rejuvenation at *disordered* sites initiated post-milling really restore the molecular order to passivate the activated chemical reactivity or it rather misaligns the crystal surface structure further to persistently/increasingly expose the reactive moeity.[323] Development of predictive tools than can help to better control the generation of *disorder* during milling, exhaustive exploration of the routes that amorphous phase passes through during diverse transitions under mechanical perturbation and quantitation of characteristic intermediate and final phases are necessary for a wide diversity of APIs. Such experiments should explicitly include the impact of water activity as well as temperature. An important point here is to choose appropriate methods of experimental characterization that can provide quantitative numbers for all of bulk dislocation densities, surface *disorder*, and fully amorphous content (see Section 4). Whether storage conditions are dry, or under humidity will depend on the reaction type. In a first phase it would probably be helpful to choose degradation reactions and storge conditions that minimize the impact of water/humidity.

Routinely used solid dosage manufacturing can lead to the generation of crystal disorder. The implication of such *disorder* or amorphous content has been widely explored in the context of physical instabilities (e.g., recrystallization, polymorphic conversion) in the literature. In contrast, limited information is inferred about the

chemical (in)stability. This review focused on firstly describing reported principles of crystal disordering followed by emphasizing the need to investigate and predict the degradation space of such *disordered* solids. Recent advances in the solid-state analytical techniques that cater to detect and quantify mechanically-induced crystal disorder, molecular mobility and associated solid-state transformations are highlighted. Lastly, based on the existing literature collection, we propose herein a generic workflow that could systematically explore the relationship between amorphization/crystallization propensity and degradation of drugs during storage. Such an information will be pertinent in addressing formulation and drug stability challenges such as batch recalls and inter-batch variabilities encountered throughout development and commercialization stages, thereby setting an impetus for stability by design paradigm.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Williams HD, Trevaskis NL, Charman SA, et al. Strategies to address low drug solubility in discovery and development. *Pharmacol Rev*. 2013;65(1):315–499. https://doi.org/10.1124/pr.112.005660.
2. Hancock BC, Zografi G. Characteristics and significance of the amorphous state in pharmaceutical systems. *J Pharm Sci*. 1997;86(1):1. https://doi.org/10.1021/js9601896.
3. Catlow CRA. An introduction to disorder in solids. *Defects and Disorder in Crystalline and Amorphous Solids*. Netherlands: Springer; 1994:1–23. https://doi.org/10.1007/978-94-011-1942-9_1.
4. Hancock BC, Shalaev EY, Shamblin SL. Polyamorphism: a pharmaceutical science perspective. *J Pharm Pharmacol*. 2002;54(8):1151–1152. https://doi.org/10.1211/002235702320266343.
5. Williams D. Particle engineering in pharmaceutical solids processing: surface energy considerations. *Curr Pharm Des*. 2015;21(19):2677–2694. https://doi.org/10.2174/1381612821666150416100319.
6. Parrott EL. Milling of pharmaceutical solids. *J Pharm Sci*. 1974;63(6):813–829.
7. Loh ZH, Samanta AK, Sia Heng PW. Overview of milling techniques for improving the solubility of poorly water-soluble drugs. *Asian J Pharm Sci*. 2015;10(4):255–274. https://doi.org/10.1016/j.ajps.2014.12.006.
8. Priemel PA, Grohganz H, Rades T. Unintended and in situ amorphisation of pharmaceuticals. *Adv Drug Deliv Rev*. 2016;100:126–132. https://doi.org/10.1016/j.addr.2015.12.014.
9. Descamps M, Willart JF. Perspectives on the amorphisation/milling relationship in pharmaceutical materials. *Adv Drug Deliv Rev*. 2016;100:51–66. https://doi.org/10.1016/j.addr.2016.01.011.
10. Vemuri NM, Brown AB, Authelin J-R, Hosek P. Milling process for the production of finely milled medicinal substances. Published online June 1999.
11. Depasquale R. Mechanical activation of secondary processed orally inhaled active pharmaceutical ingredients. Published online 2015.
12. Woodruff DP. How does your crystal grow? A commentary on Burton, Cabrera and Frank (1951) “the growth of crystals and the equilibrium structure of their surfaces. *Philos Trans R Soc A Math Phys Eng Sci*. 2015;373(2039): 20140230. https://doi.org/10.1098/rsta.2014.0230.
13. Shalaev E, Wu K, Shamblin S, Krzyzaniak JF, Descamps M. Crystalline mesophases: structure, mobility, and pharmaceutical properties. *Adv Drug Deliv Rev*. 2016;100:194–211. https://doi.org/10.1016/j.addr.2016.04.002.
14. Newman A, Zografi G. Critical considerations for the qualitative and quantitative determination of process-induced disorder in crystalline solids. *J Pharm Sci*. 2014:1–10. https://doi.org/10.1002/jps.23930. Published online.
15. Levine H, Shalaev E, Zografi G. The concept of ‘structure’ in amorphous solids from the perspective of the pharmaceutical sciences. *Amorphous Food and Pharmaceutical Systems*. The Royal Society of Chemistry; 2002:11–30. https://doi.org/10.1039/9781847550118-00011.
16. Shalaev E, Shalaeva M, Zografi G. The effect of disorder on the chemical reactivity of an organic solid, tetraglycine methyl ester change of the reaction mechanism. *J Pharm Sci*. 2002;91(2):584–593.
17. Elamin AA, Ahlneck C, Alderborn GG, Nyström C, Nystroem C. Increased metastable solubility of milled griseofulvin, depending on the formation of a disordered surface structure. *Int J Pharm*. 1994;111(2):159–170. https://doi.org/10.1016/0378-5173(94)00132-4.
18. Oliveira PFM, Willart JF, Siepmann J, Siepmann F, Descamps M. Using milling to explore physical states: the amorphous and polymorphic forms of dexamethasone. *Cryst Growth Des*. 2018;18(3):1748–1757. https://doi.org/10.1021/acs.cgd.7b01664.
19. Elisei E, Willart JF, Danède F, Siepmann J, Siepmann F, Descamps M. Crystalline polymorphism emerging from a milling-induced amorphous form: the case of chlorhexidine dihydrochloride. *J Pharm Sci*. 2018;107(1):121–126. https://doi.org/10.1016/j.xphs.2017.07.003.
20. Schammé B, Monnier X, Couvrat N, et al. Insights on the physical state reached by an active pharmaceutical ingredient upon high-energy milling. *J Phys Chem B*. 2017;121(19):5142–5150. https://doi.org/10.1021/acs.jpcb.7b02247.
21. Pikal MJ, Lang JE, Gaines K. Quantitative crystallinity determinations for P-lactam antibiotics by solution calorimetry: correlations with stability. *J Pharm Sci*. 1977;67(6):767–773.
22. Nakagawa H, Takahashi Y, Sugimoto I. The effects of grinding and drying on the solid state stability of sodium prasterone sulfate. *Chem Pharm Bull*. 1982;30(1):242–248.
23. Takahashi Y, Nakashima K, Nakagawa H, Sugimoto I. Effects of grinding and drying on the solid-state stability of ampicillin trihydrate. *Chem Pharm Bull*. 1984;32(12). 1984;32(12):4963-4970.
24. Kitamura S, Miyamae A, Koda S, Morimoto Y. Effect of grinding on the solid-state stability of cefixime trihydrate. *Int J Pharm*. 1989;56(2):125–134. https://doi.org/10.1016/0378-5173(89)90005-7.
25. Hickey MB, Peterson ML, Manas ES, Alvarez J, Haeffner F, Almarsson Ö. Hydrates and solid-state reactivity: a survey of β-lactam antibiotics. *J Pharm Sci*. 2007;96(5):1090–1099. https://doi.org/10.1002/jps.20919.
26. Grant DJW, York P. Entropy of processing: a new quantity for comparing the solid state disorder of pharmaceutical materials. *Int J Pharm*. 1986;30(2-3):161–180. https://doi.org/10.1016/0378-5173(86)90076-1.
27. Irwin WJ, Iqbal M. Solid-state stability: the effect of grinding solvated excipients. *Int J Pharm*. 1991;75(2-3):211–218. https://doi.org/10.1016/0378-5173(91)90195-T.
28. Byrn S. Mechanisms of solid-state reactions of drugs. *J Pharm Sci*. 1976;6(1):1–22.
29. Byrn SR, Xu W, Newman AW. Chemical reactivity in solid-state pharmaceuticals: formulation implications. *Adv Drug Deliv Rev*. 2001;48(1):115–136.
30. Paul IC, Curtin DY. Thermally induced organic reactions in the solid state. *Acc Chem Res*. 1973;6(7):217–225. https://doi.org/10.1021/ar50067a001.
31. Kaupp G, MR Naimi-Jamal. Mechanically induced molecular migrations in molecular crystals. *CrystEngComm*. 2005;7:402. https://doi.org/10.1039/b503208n.
32. Shalaev EY, Shalaeva M, Byrn SR, Zografi G. Effects of processing on the solid-state methyl transfer of tetraglycine methyl ester. *Int J Pharm*. 1997;152(1):75–88. https://doi.org/10.1016/S0378-5173(97)00068-9.
33. Guo Y, Byrn SR, Zografi G. Physical characteristics and chemical degradation of amorphous quinapril hydrochloride. *J Pharm Sci*. 2000;89(1):128–143.
34. Chen X, Morris KR, Griesser UJ, Byrn SR, Stowell JG. Reactivity differences of indomethacin solid forms with ammonia gas. *J Am Chem Soc*. 2002;124(50):15012–15019.
35. Chen X, Griesser UJ, Te RL, et al. Analysis of the acid-base reaction between solid indomethacin and sodium bicarbonate using infrared spectroscopy, X-ray powder diffraction, and solid-state nuclear magnetic resonance spectroscopy. *J Pharm Biomed Anal*. 2005;38(4):670–677. https://doi.org/10.1016/j.jpba.2005.02.017.
36. Qiu Z, Stowell JG, Cao W, Morris KR, Byrn SR, Carvajal MT. Effect of milling and compression on the solid-state Maillard reaction. *J Pharm Sci*. 2005;94(11):2568–2580. https://doi.org/10.1002/jps.20448.
37. Li H, Wen H, Stowell J. Crystal quality and physical reactivity in the case of flufenamic acid (FFA). *J Pharm Sci*. 2010;99(9):3839–3848. https://doi.org/10.1002/jps.
38. Zografi G, Newman A. Interrelationships between structure and the properties of amorphous solids of pharmaceutical interest. *J Pharm Sci*. 2017;106(1):5–27. https://doi.org/10.1016/j.xphs.2016.05.001.
39. Bates S, Zografi G, Engers D, Morris K, Crowley K, Newman A. Analysis of amorphous and nanocrystalline solids from their X-ray diffraction patterns. *Pharm Res*. 2006;23(10):2333–2349. https://doi.org/10.1007/s11095-006-9086-2.
40. Yang Y, Zhou J, Zhu F, et al. Determining the three-dimensional atomic structure of an amorphous solid. *Nature*. 2021;592(7852):60–64. https://doi.org/10.1038/s41586-021-03354-0.
41. Cordova M, Balodis M, Hofstetter A, et al. Structure determination of an amorphous drug through large-scale NMR predictions. *Nat Commun*. 2021;12(1):2964. https://doi.org/10.1038/s41467-021-23208-7.
42. Lu X, Huang C, Lowinger MB, et al. Molecular interactions in posaconazole amorphous solid dispersions from two-dimensional solid-state NMR spectroscopy. *Mol Pharm*. 2019;16(6):2579–2589. https://doi.org/10.1021/acs.molpharmaceut.9b00174.
43. Lu X, Li M, Huang C, et al. Atomic-level drug substance and polymer interaction in posaconazole amorphous solid dispersion from solid-state NMR. *Mol Pharm*. 2020;17(7):2585–2598. https://doi.org/10.1021/acs.molpharmaceut.0c00268.
44. Sheth AR, Bates S, Muller FX, Grant DJW. Local structure in amorphous phases of piroxicam from powder X-ray diffractometry. *Cryst Growth Des*. 2005;5(2):571–578. https://doi.org/10.1021/cg049757i.
45. Cadars S, Lesage A, Pickard CJ, Sautet P, Emsley L. Characterizing slight structural disorder in solids by combined solid-state NMR and first principles calculations. *J Phys Chem A*. 2009;113:902–911. https://doi.org/10.1021/jp810138y.
46. Shah B, Kakumanu VK, Bansal AK. Analytical techniques for quantification of amorphous/crystalline phases in pharmaceutical solids. *J Pharm Sci*. 2006;95(8):1641–1665. https://doi.org/10.1002/jps.
47. Royall PG, Woodhead B, Tang SJ, Martin GP, Stockton BM, Murnane D. Formation and measurement of process induced disorder during the manufacture of inhalation medicines. *J Drug Deliv Sci Technol*. 2011;21(4):311–318. https://doi.org/10.1016/S1773-2247(11)50048-6.
48. Madsen IC, Scarlett NVY, Kern A. Description and survey of methodologies for the determination of amorphous content via X-ray powder diffraction. *Zeitschrift für Krist*. 2011;226(12):944–955. https://doi.org/10.1524/zkri.2011.1437.

49. Einfal T, Planinšek O, Hrovat K. Methods of amorphization and investigation of the amorphous state. *Acta Pharm*. 2013;63(3):305–334. https://doi.org/10.2478/acph-2013-0026.
50. Kaur A, Kale DP, Bansal AK. Surface characterization of pharmaceutical solids. *TrAC - Trends Anal Chem*. 2021;138: 116228. https://doi.org/10.1016/j.trac.2021.116228.
51. Erdemoğlu M, Baláž P. An overview of surface analysis techniques for characterization of mechanically activated minerals. *Miner Process Extr Metall Rev*. 2012;33(1):65–88. https://doi.org/10.1080/08827508.2010.542582.
52. Tromans D, Meech J a. Enhanced dissolution of minerals: stored energy, amorphism and mechanical activation. *Miner Eng*. 2001;14(11):1359–1377. https://doi.org/10.1016/S0892-6875(01)00151-0.
53. Saleki-Gerhardt A, Ahlneck C, Zografi G. Assessment of disorder in crystalline solids. *Int J Pharm*. 1994;101(3):237–247. https://doi.org/10.1016/0378-5173(94)90219-4.
54. Ticehurst MD, York P, Rowe RC, Dwivedi SK. Characterisation of the surface properties of alpha-lactose monohydrate with inverse gas chromatography, used to detect batch variation. *Int J Pharm*. 1996;141(1-2):93–99.
55. Feeley JC, York P, Sumby BS, Dicks H. Determination of surface properties and flow characteristics of salbutamol sulphate, before and after micronisation. *Int J Pharm*. 1998;172(1-2):89–96. https://doi.org/10.1016/S0378-5173(98)00179-3.
56. Zimper U, Aaltonen J, McGoverin CM, Gordon KC, Krauel-Goellner K, Rades T. Quantification of process induced disorder in milled samples using different analytical techniques. *Pharmaceutics*. 2010;2(1):30–49. https://doi.org/10.3390/pharmaceutics2010030.
57. Grisedale LC, Jamieson MJ, Belton PS, Barker SA, Craig DQMM. Characterization and quantification of amorphous material in milled and spray-dried salbutamol sulfate: a comparison of thermal, spectroscopic, and water vapor sorption approaches. *J Pharm Sci*. 2011;100(8):3114–3128. https://doi.org/10.1002/jps.22484.
58. Clas S, Lalonde K, Khougaz K, Dalton CR, Bilbeisi R. Detection of a minor amorphous phase in crystalline etoricoxib by dynamic mechanical analysis: Comparison with raman spectroscopy and modulated differential scanning calorimetry. *J Pharm Sci*. 2012;101(2):558–565. https://doi.org/10.1002/jps.22774.
59. Sheokand S, Modi SR, Bansal AK. Quantification of low levels of amorphous content in crystalline celecoxib using dynamic vapor sorption (DVS). *Eur J Pharm Biopharm*. 2016;102:77–86. https://doi.org/10.1016/j.ejpb.2016.03.006.
60. Müller T, Scherließ R, Schiewe J, Smal R, Weiler C, Steckel H. Applicability of the one-step DVS method for the determination of amorphous amounts for further different hydrophilic and hydrophobic drugs. *Eur J Pharm Biopharm*. 2015;94:333–341. https://doi.org/10.1016/j.ejpb.2015.06.004.
61. Gaisford S. Isothermal microcalorimetry for quantifying amorphous content in processed pharmaceuticals. *Adv Drug Deliv Rev*. 2012;64(5):431–439. https://doi.org/10.1016/j.addr.2011.11.001.
62. Alam S, Omar M, Gaisford S. Use of heat of adsorption to quantify amorphous content in milled pharmaceutical powders. *Int J Pharm*. 2014;459(1-2):19–22. https://doi.org/10.1016/j.ijpharm.2013.11.052.
63. Bøtker JP, Karmwar P, Strachan CJ, et al. Assessment of crystalline disorder in cryo-milled samples of indomethacin using atomic pair-wise distribution functions. *Int J Pharm*. 2011;417(1-2):112–119. https://doi.org/10.1016/j.ijpharm.2010.12.018.
64. Boetker JP, Koradia V, Rades T, Rantanen J, Savolainen M. Atomic pairwise distribution function analysis of the amorphous phase prepared by different manufacturing routes. *Pharmaceutics*. 2012;4(1):93–103. https://doi.org/10.3390/pharmaceutics4010093.
65. Billinge S, Dykhne T, Juhas P, et al. Characterisation of amorphous and nanocrystalline molecular materials by total scattering. *CrystEngComm*. 2010;12(5):1366. https://doi.org/10.1039/b915453a.
66. Terban MW, Russo L, Pham TN, et al. Local structural effects due to micronization and amorphization on an HIV treatment active pharmaceutical ingredient. *Mol Pharm*. 2020. https://doi.org/10.1021/acs.molpharmaceut.0c00122. Published online May 22:acs.molpharmaceut.0c00122.
67. Newell HE, Buckton G, Butler DA, Thielmann F, Williams DR. The use of inverse phase gas chromatography to study the change of surface energy of amorphous lactose as a function of relative humidity and the processes of collapse and crystallisation. *Int J Pharm*. 2001;217(1-2):45–56. https://doi.org/10.1016/S0378-5173(01)00589-0.
68. Caron V, Willart JF, Lefort R, Derollez P, Dande F, Descamps M. Solid state amorphization kinetic of alpha lactose upon mechanical milling. *Carbohydr Res*. 2011;346(16):2622–2628. https://doi.org/10.1016/j.carres.2011.09.004.
69. Planinsek O, Zadnik J, Kunaver M, Srcic S, Aljaz G. Structural evolution of indomethacin particles upon milling: time-resolved quantification and localization of disordered structure studied by IGC and DSC. *J Pharm Sci*. 2009;99(4):1968–1981.
70. Jefferson AE, Williams DR, Heng JYY. Computing the surface energy distributions of heterogeneous crystalline powders. *J Adhes Sci Technol*. 2011;25(4-5):339–355. https://doi.org/10.1163/016942410X525506.
71. Eifert A, Kranz C. Hyphenating atomic force microscopy. *Anal Chem*. 2014;86(11):5190–5200. https://doi.org/10.1021/ac5008128.
72. Tejedor MB, Nordgren N, Schuleit M, et al. Determination of interfacial amorphicity in functional powders. *Langmuir*. 2017;33(4):920–926. https://doi.org/10.1021/acs.langmuir.6b03969.
73. Grisedale LC, Moffat JG, Jamieson MJ, Belton PS, Barker SA, Craig DQM. Development of photothermal FTIR microspectroscopy as a novel means of spatially identifying amorphous and crystalline salbutamol sulfate on composite surfaces. *Mol Pharm*. 2013;10(5):1815–1823. https://doi.org/10.1021/mp300605s.
74. Ward S, Perkins M, Zhang J, et al. Identifying and mapping surface amorphous domains. *Pharm Res*. 2005;22(7):1195–1202. https://doi.org/10.1007/s11095-005-6027-4.
75. Paudel A, Meeus J, Van den Mooter G. *Structural Characterization of Amorphous Solid Dispersions*. New York, NY: Springer; 2014:421–485. https://doi.org/10.1007/978-1-4939-1598-9_14.
76. a Prestidge C, TJ Barnes, Skinner W. Time-of-flight secondary-ion mass spectrometry for the surface characterization of solid-state pharmaceuticals. *J Pharm Pharmacol*. 2007;59(2):251–259. https://doi.org/10.1211/jpp.59.2.0011.
77. Iuraş A, Scurr DJ, Boissier C, Nicholas ML, Roberts CJ, Alexander MR. Imaging of crystalline and amorphous surface regions using Time-of-Flight Secondary-Ion Mass Spectrometry (ToF-SIMS): application to pharmaceutical materials. *Anal Chem*. 2016;88(7):3481–3487. https://doi.org/10.1021/acs.analchem.5b02621.
78. Eddleston MD, Jones W. Observation and characterization of crystal defects in pharmaceutical solids. *Disord Pharm Mater*20162016:103–134. https://doi.org/10.1002/9783527652693.ch4. Published online.
79. Novakovic D, Saarinen J, Rojalin T, et al. Multimodal nonlinear optical imaging for sensitive detection of multiple pharmaceutical solid-state forms and surface transformations. *Anal Chem*. 2017;89(21):11460–11467. https://doi.org/10.1021/acs.analchem.7b02639.
80. Shamblin SL, Hancock BC, Pikal MJ. Coupling between chemical reactivity and structural relaxation in pharmaceutical glasses. *Pharm Res*. 2006;23(10):2254–2268. https://doi.org/10.1007/s11095-006-9080-8.
81. Bhattacharya S, Suryanarayanan R. Local mobility in amorphous pharmaceuticals—characterization and implications on stability. *J Pharm Sci*. 2009;98(9):2935–2953. https://doi.org/10.1002/jps.21728.
82. Antonijević M. Applications of thermally stimulated current spectroscopy in pharmaceutical research. *Eur Pharm Rev*. 2012;17(3):1–12.
83. Moura Ramos JJ, Diogo HP. Thermal behavior and molecular mobility in the glassy state of three anti-hypertensive pharmaceutical ingredients. *RSC Adv*. 2017;7(18):10831–10840. https://doi.org/10.1039/c7ra00298j.
84. Galop M, Collins GL. Thermally stimulated currents observed in pharmaceutical products. *Thermochim Acta*. 2001;367-368:37–41. https://doi.org/10.1016/S0040-6031(00)00700-0.
85. Diogo P, Pinto S, Moura JJ. Slow molecular mobility in the crystalline and amorphous solid states of pentitols : a study by thermally stimulated depolarisation currents and by differential scanning calorimetry. 2007;342:961-969. https://doi.org/10.1016/j.carres.2007.01.016.
86. Rachel Forcino, Brum J, Galop Marc SY. Using thermally stimulated current (TSC) to investigate disorder in micronized drug substance produced at different milling energies. *Pharm Res*. 2010;27(10):2234–2241. https://doi.org/10.1007/s11095-010-0230-7.
87. Geppi M, Borsacchi S, Carignani E. Study of disorder by solid-state NMR spectroscopy. *Disord Pharm Mater*. 20162016:427–466. https://doi.org/10.1002/9783527652693.ch14. Published online.
88. Yuan X, Sperger D, Munson EJ. Investigating miscibility and molecular mobility of nifedipine-PVP amorphous solid dispersions using solid-state NMR spectroscopy. *Mol Pharm*. 2014;11(1):329–337. https://doi.org/10.1021/mp400498n.
89. Smith G, Hussain A, Bukhari NI, Ermolina I. Correlation between molecular dynamics and physical stability of two milled anhydrous sugars: lactose and sucrose. *Int J Pharm*. 2018;551(1-2):184–194. https://doi.org/10.1016/j.ijpharm.2018.09.027.
90. Kaminski K, Adrjanowicz K, Wojnarowska Z, et al. Molecular dynamics of the cryomilled base and hydrochloride ziprasidones by means of dielectric spectroscopy. *Joiurnal Pharm Sci*. 2011;100(7):2642–2657. https://doi.org/10.1002/jps.
91. Liu J, Rigsbee DR, Stotz C, Pikal MJ. Dynamics of pharmaceutical amorphous solids: the study of enthalpy relaxation by isothermal microcalorimetry. *J Pharm Sci*. 2002;91(8):1853–1862. https://doi.org/10.1002/jps.10181.
92. Thayumanasundaram S, Venkatesan TR, Ousset A, et al. Complementarity of mDSC, DMA, and DRS techniques in the study of T g and sub-T g transitions in amorphous solids: PVPVA, indomethacin, and amorphous solid dispersions based on indomethacin/PVPVA. *Mol Pharm*. 2022;19(7):2299–2315. https://doi.org/10.1021/acs.molpharmaceut.2c00123.
93. Surana R, Pyne A, Rani M, Suryanarayanan R. Measurement of enthalpic relaxation by differential scanning calorimetry - effect of experimental conditions. *Thermochim Acta*. 2005;433(1-2):173–182. https://doi.org/10.1016/j.tca.2005.02.014.
94. Hancock BC, Shamblin SL, Zografi G. Molecular mobility of amorphous pharmaceutical solids below their glass transition temperatures. *Pharm Res*. 1995;12(6):799–806. https://doi.org/10.1023/A:1016292416526.
95. Pajzderska A, Jenczyk J, Embs JP, Wąsicki J. Exploring molecular reorientations in amorphous and recrystallized felodipine at the microscopic level. *RSC Adv*. 2020;10(61):37346–37357. https://doi.org/10.1039/d0ra07266d.
96. Paradossi G, Cavalieri F, Chiessi E, Telling MTF. Supercooled water in PVA matrixes: I. An incoherent quasi-elastic neutron scattering (QENS) study. *J Phys Chem B*. 2003;107(33):8363–8371. https://doi.org/10.1021/jp034542p.
97. Marc Descamps. In: Descamps M, ed. *Disordered Pharmaceutical Materials*. Wiley-VCH; 2016.
98. Jones DS, Tian Y, Abu-Diak O, Andrews GP. Pharmaceutical applications of dynamic mechanical thermal analysis. *Adv Drug Deliv Rev*. 2012;64(5):440–448. https://doi.org/10.1016/j.addr.2011.12.002.
99. Miller DP, Lechuga-Ballesteros D. Rapid assessment of the structural relaxation behavior of amorphous pharmaceutical solids: Effect of residual water on molecular mobility. *Pharm Res*. 2006;23(10):2291–2305. https://doi.org/10.1007/s11095-006-9095-1.

100. Bhugra C, Shmeis R, Krill SL, Pikal MJ. Different measures of molecular mobility: comparison between calorimetric and thermally stimulated current relaxation times below Tg and correlation with dielectric relaxation times above Tg. *J Pharm Sci*. 2008;97(10):4498–4515. https://doi.org/10.1002/jps.
101. Sibik J, Zeitler JA. Direct measurement of molecular mobility and crystallisation of amorphous pharmaceuticals using terahertz spectroscopy. *Adv Drug Deliv Rev*. 2016;100:147–157. https://doi.org/10.1016/j.addr.2015.12.021.
102. Sibik J, Löbmann K, Rades T, Zeitler JA. Predicting crystallization of amorphous drugs with terahertz spectroscopy. *Mol Pharm*. 2015;12(8):3062–3068. https://doi.org/10.1021/acs.molpharmaceut.5b00330.
103. Laggner P, Paudel A. Density fluctuations in amorphous pharmaceutical solids. Can SAXS help to predict stability? *Colloids Surf B Biointerfaces*. 2018;168:76–82. https://doi.org/10.1016/j.colsurfb.2018.05.003.
104. Modhave D, Laggner P, Brunsteiner M, Paudel A. Solid-state reactivity of mechano-activated simvastatin: atypical relation to powder crystallinity. *J Pharm Sci*. 2019;108(10):3272–3280. https://doi.org/10.1016/j.xphs.2019.05.032.
105. Colombo I, Grassi G GM. Drug mechanochemical activation. *J Pharm Sci*. 2009;98 (11):3961–3986. https://doi.org/10.1002/jps.
106. Pinal R, Carvajal MT. Integrating particle microstructure, surface and mechanical characterization with bulk powder processing. *KONA Powder Part J*. 2020;37 (June):195–213. https://doi.org/10.14356/kona.2020008.
107. Marc Descamps JF, Willart E, Dudognon VC. Transformation of pharmaceutical compounds upon milling and comilling: the role of Tg. *J Pharm Sci*. 2007;96:1398–1407. https://doi.org/10.1002/jps.20939ABSTRACT.
108. Descamps M, Willart JF, Dudognon E, Lefort R, Desprez S, Caron V. Phase transformations induced by grinding: what is revealed by molecular materials. Mater. Res. Soc. Symp. Proc. *Vol 979*. Cambridge University Press; 2007:116–131. https://doi.org/10.1557/PROC-979-0979-HH06-06.
109. Willart JF, Caron V, Lefort R, Danède F, Prévost D, Descamps M. Athermal character of the solid state amorphization of lactose induced by ball milling. *Solid State Commun*. 2004;132(10):693–696. https://doi.org/10.1016/j.ssc.2004.09.007.
110. De Gusseme A, Neves C, Willart JF, Rameau A, Descamps M. Ordering and disordering of molecular solids upon mechanical milling: the case of Fananserine. *J Pharm Sci*. 2008;97(11):5000–5012. https://doi.org/10.1002/jps.21472.
111. Willart JFF, Dujardin N, Dudognon E, Danède F, Descamps M. Amorphization of sugar hydrates upon milling. *Carbohydr Res*. 2010;345(11):1613–1616. https://doi.org/10.1016/j.carres.2010.04.014.
112. Dujardin N, Willart JF, Dudognon E, Danède F, Descamps M. Mechanism of solid state amorphization of glucose upon milling. *J Phys Chem B*. 2013;117(5):1437–1443. https://doi.org/10.1021/jp3069267.
113. Shah UV, Wang Z, Olusanmi D, et al. Effect of milling temperatures on surface area, surface energy and cohesion of pharmaceutical powders. *Int J Pharm*. 2015;495(1):234–240. https://doi.org/10.1016/j.ijpharm.2015.08.061.
114. Shah UV, Olusanmi D, Narang AS, et al. Decoupling the contribution of surface energy and surface area on the cohesion of pharmaceutical powders. *Pharm Res*. 2015;32(1):248–259. https://doi.org/10.1007/s11095-014-1459-3.
115. Ahlneck C, Zografi G. The molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state. *Int J Pharm*. 1990;62:87–95.
116. Aoki M, Nishimura H, Mimura A, Kita S, Yasuzawa T, Terada K. Identification of the degradation products of the steroid sulfatase inhibitor KW-2581 in jet milled micronized powder. *J Pharm Sci*. 2013;102(6):1760–1772. https://doi.org/10.1002/jps.
117. Ohtake S, Shalaev E. Effect of water on the chemical stability of amorphous pharmaceuticals: I. Small molecules. *J Pharm Sci*. 2013;102(4):1139–1154. https://doi.org/10.1002/jps.23440.
118. Herman BD, Sinclair BD, Milton N, Nail SL. The effect of bulking agent on the solid-state stability of freeze-dried methylprednisolone sodium succinate. *Pharm Res*. 1994;11(10):1467–1473. https://doi.org/10.1023/A:1018908326074.
119. Zong Z, Qiu J, Tinmanee R, Kirsch LE. Kinetic model for solid-state degradation of gabapentin. *J Pharm Sci*. 2012;101(6):2123–2133. https://doi.org/10.1002/jps.23115.
120. Malaj L, Censi R, Mozzicafreddo M, et al. Influence of relative humidity on the interaction between different aryl propionic acid derivatives and poly (vinylpyrrolydone) K30: evaluation of the effect on drug bioavailability. *Int J Pharm*. 2010;398(1-2):61–72. https://doi.org/10.1016/j.ijpharm.2010.07.024.
121. Perkins MC, Bunker M, James J, et al. Towards the understanding and prediction of material changes during micronisation using atomic force microscopy. *Eur J Pharm Sci*. 2009;38(1):1–8. https://doi.org/10.1016/j.ejps.2009.05.004.
122. Gilman JJ. Hardness of pure alkali halides. *J Appl Phys*. 1973;44(3):982–984. https://doi.org/10.1063/1.1662382.
123. Sirdeshmukh D. Hardness of crystals with NaCl structure and the significance of the GILMAN-CHIN parameter. *Cryst Res Technol*. 1995;30(6):861–866.
124. Duncan-Hewitt WC, Weatherly GC. Evaluating the hardness, Young's modulus and fracture toughness of some pharmaceutical crystals using microindentation techniques. *J Mater Sci Lett*. 1989;8(11):1350–1352. https://doi.org/10.1007/BF00721518.
125. Ni W, Cheng Y-T, Lukitsch MJ, Weiner AM, Lev LC, Grummon DS. Effects of the ratio of hardness to Young's modulus on the friction and wear behavior of bilayer coatings. *Appl Phys Lett*. 2004;85(18):4028. https://doi.org/10.1063/1.1811377.
126. Pintaude G. Introduction of the ratio of the hardness to the reduced elastic modulus for abrasion. *Tribology - Fundamentals and Advancements*. InTech; 2013:217–230. https://doi.org/10.5772/55470.
127. Chen S, Sheikh AY, Ho R. Evaluation of effects of pharmaceutical processing on structural disorders of active pharmaceutical ingredient crystals using nanoindentation and high resolution total scattering pair distribution function analysis. *Pharm Drug Deliv Pharm Technol Eval*. 2014;103:3879–3890. https://doi.org/10.1002/jps.24178.
128. Wildfong PLD, Hancock BC, Moore MD, Morris KR. Towards an understanding of the structurally based potential for mechanically activated disordering of small molecule organic crystals. *J Pharm Sci*. 2006;95(12):2645–2656. https://doi.org/10.1002/jps.
129. Lei L, Carvajal T, Koslowski M. Defect-induced solid state amorphization of molecular crystals. *J Appl Phys*. 2012;111(7). https://doi.org/10.1063/1.3698500.
130. Hancock BC, Shamblin SL. Molecular mobility of amorphous pharmaceuticals determined using differential scanning calorimetry. 2001;380.
131. Shakhtshneider TP, Boldyrev VV. Phase transformations in sulfathiazole during mechanical activation. *Drug Dev Ind Pharm*. 1993;19(16):2055–2067. https://doi.org/10.3109/03639049309069341.
132. Vasa DM, Wildfong PLD. Solid-state transformations of ribavirin as a result of high-shear mechanical processing. *Int J Pharm*. 2017;524(1-2):339–350. https://doi.org/10.1016/j.ijpharm.2017.04.002.
133. Megarry AJ, Booth J, Burley J. Amorphous trehalose dihydrate by cryogenic milling. *Carbohydr Res*. 2011;346(8):1061–1064. https://doi.org/10.1016/j.carres.2011.03.011.
134. Khankari RK, Grant DJW. Pharmaceutical hydrates. *Thermochim Acta*. 1995;248 (C):61–79. https://doi.org/10.1016/0040-6031(94)01952-D.
135. Sheth AR, Grant DJW. Relationship between the structure and properties of pharmaceutical crystals. *KONA Powder Part J*. 2005;23(March):36–48. https://doi.org/10.14356/kona.2005008.
136. Abouhakim H, Quayle MJ, Norberg ST, et al. Mechanically induced amorphization of diaqua-bis(omeprazolate)-magnesium dihydrate. *Cryst Growth Des*. 2020;20 (9):6057–6068. https://doi.org/10.1021/acs.cgd.0c00770.
137. Sheth AR, Bates S, Muller FX, Grant DJW. Polymorphism in piroxicam. *Cryst Growth Des*. 2004;4(6):1091–1098. https://doi.org/10.1021/cg049876y.
138. Vrečer F, Vrbinc M, Meden A. Characterization of piroxicam crystal modifications. *Int J Pharm*. 2003;256(1-2):3–15. https://doi.org/10.1016/S0378-5173(03)00057-7.
139. Sun C, Grant DJW. Improved tableting properties of p-hydroxybenzoic acid by water of crystallization: a molecular insight. *Pharm Res*. 2004;21(2):382–386.
140. Wong MWY, Mitchell AG. Physicochemical characterization of a phase change produced during the wet granulation of chlorpromazine hydrochloride and its effects on tableting. *Int J Pharm*. 1992;88(1-3):261–273. https://doi.org/10.1016/0378-5173(92)90324-U.
141. Guerrieri P, Rumondor ACF, Li T, Taylor LS. Analysis of relationships between solid-state properties, counterion, and developability of pharmaceutical salts. *AAPS PharmSciTech*. 2010;11(3):1212–1222. https://doi.org/10.1208/s12249-010-9499-4.
142. Tong P, Taylor LS, Zografi G. Influence of alkali metal counterions on the glass transition temperature of amorphous indomethacin salts. *Pharm Res*. 2002;19 (5):649–654. https://doi.org/10.1023/A:1015310213887.
143. Descamps M, Aumelas A, Desprez S, Willart JF. The amorphous state of pharmaceuticals obtained or transformed by milling: Sub-Tg features and rejuvenation. *J Non Cryst Solids*. 2015;407:72–80. https://doi.org/10.1016/j.jnoncrysol.2014.08.055.
144. Ayenew Z, Paudel A, Van den Mooter G. Can compression induce demixing in amorphous solid dispersions? A case study of naproxen–PVP K25. *Eur J Pharm Biopharm*. 2012;81(1):207–213. https://doi.org/10.1016/j.ejpb.2012.01.007.
145. Lacks DJ, Osborne MJ. Energy landscape picture of overaging and rejuvenation in a sheared glass. *Phys Rev Lett*. 2004;93(25): 255501. https://doi.org/10.1103/PhysRevLett.93.255501.
146. Frey MM, Lacks DJ. Shear-induced changes of the potential energy landscape underlying n -butane liquids and glasses. *J Chem Phys*. 2000;112(6):2909–2915. https://doi.org/10.1063/1.480863.
147. Heng JYY, Thielmann F, Williams DR. The effects of milling on the surface properties of form I paracetamol crystals. *Pharm Res*. 2006;23(8):1918–1927. https://doi.org/10.1007/s11095-006-9042-1.
148. Ho R, Naderi M, Heng JYY, et al. Effect of milling on particle shape and surface energy heterogeneity of needle-shaped crystals. *Pharm Res*. 2012;29(10):2806–2816. https://doi.org/10.1007/s11095-012-0842-1.
149. Rumpf H. Physical aspects of comminution and new formulation of a law of comminution. *Powder Technol*. 1973;7(3):145–159. https://doi.org/10.1016/0032-5910(73)80021-X.
150. Vogel L, Peukert W. Breakage behaviour of different materials - construction of a mastercurve for the breakage probability. *Powder Technol*. 2003;129(1-3):101–110. https://doi.org/10.1016/S0032-5910(02)00217-6.
151. Rowe RC, Roberts RJ. 1 The mechanical properties of powders. Advances in Pharmaceutical Sciences. *Vol 7*. Academic Press; 1995. https://doi.org/10.1016/S0065-3136(06)80003-8. 1-IV.
152. Rhodes M. *Introduction to Particle Technology*. Wiley; 2008. https://doi.org/10.1002/9780470727102.
153. Capece M, Bilgili E, Davé RN. Formulation of a physically motivated specific breakage rate parameter for ball milling via the discrete element method. *AIChE J*. 2014;60(7):2404–2415. https://doi.org/10.1002/aic.14451.
154. Capece M, Davé RN, Bilgili E. On the origin of non-linear breakage kinetics in dry milling. *Powder Technol*. 2015;272:189–203. https://doi.org/10.1016/j.powtec.2014.11.040.
155. Bonakdar T, Ali M, Dogbe S, Ghadiri M, Tinke A. A method for grindability testing using the Scirocco disperser. *Int J Pharm*. 2016;501(1-2):65–74. https://doi.org/10.1016/j.ijpharm.2016.01.052.

156. Zbib MB, Parab ND, Chen WW, Bahr DF. New pulverization parameter derived from indentation and dynamic compression of brittle microspheres. *Powder Technol*. 2015;283:57–65. https://doi.org/10.1016/j.powtec.2015.04.066.
157. Desprez S, Descamps M. Transformations of glassy indomethacin induced by ball-milling. *J Non Cryst Solids*. 2006;352(42-49):4480–4485. https://doi.org/10.1016/j.jnoncrysol.2006.02.130.
158. Jones W, Eddleston MD. Introductory Lecture: Mechanochemistry, a versatile synthesis strategy for new materials. *Faraday Discuss*. 2014;170(0):9–34. https://doi.org/10.1039/C4FD00162A.
159. Dupont A, Guerain M, Danède F, Willart JF. Evidence of transient amorphization during the polymorphic transformation of sorbitol induced by milling. *Int J Pharm*. 2022;623(March). https://doi.org/10.1016/j.ijpharm.2022.121929.
160. Willart JF, Descamps M. Solid state amorphization of pharmaceuticals. *Mol Pharm*. 2008;5(6):905–920. https://doi.org/10.1021/mp800092t.
161. Delogu F, Cocco G. Weakness of the "hot spots" approach to the kinetics of mechanically induced phase transformations. *J Alloys Compd*. 2008;465(1-2):540–546. https://doi.org/10.1016/j.jallcom.2007.11.024.
162. Okamoto PR, Lam NQ, Rehn LE. Physics of crystal-to-glass transformations. Solid State Physics. *Vol 52*. Academic Press; 1999:1–135. https://doi.org/10.1016/S0081-1947(08)60018-1.
163. Martin G, Bellon P. Driven Alloys. *Vol 50*. Academic Press; 1996. https://doi.org/10.1016/S0081-1947(08)60605-0.
164. Kaur A, Yadav JP, Sathe RY, Puri V, Bharatam PV, Bansal AK. Understanding poor milling behavior of voriconazole from crystal structure and intermolecular interactions. *Mol Pharm*. 2022;19(3):985–997. https://doi.org/10.1021/acs.molpharmaceut.1c00978.
165. Atkins AG, Mai Y-W. Deformation transitions. *J Mater Sci*. 1986;21(4):1093–1110. https://doi.org/10.1007/BF00553238.
166. York P, Ticehurst MDD, Osborn JCC, Roberts RJJ, Rowe RCC. Characterisation of the surface energetics of milled dl-propranolol hydrochloride using inverse gas chromatography and molecular modelling. *Int J Pharm*. 1998;174(1-2):179–186. https://doi.org/10.1016/S0378-5173(98)00247-6.
167. Höckerfelt MH, Nyström C, Alderborn G. Dry mixing transformed micro-particles of a drug from a highly crystalline to a highly amorphous state. *Pharm Dev Technol*. 2009;14(3):233–239. https://doi.org/10.1080/10837450802585252.
168. Kaneniwa N, Ikekawa A, Hashimoto K. Influence of operational variables on ball-milling of sulfadimethoxine and white alundum. *Chem Pharm Bull*. 1973;21(3):676–681. https://doi.org/10.1248/cpb.21.676.
169. Hüttenrauch R, Fricke S, Zielke P. Mechanical activation of pharmaceutical systems. *Pharm Res*. 1985;2(6):302–306. https://doi.org/10.1023/A:1016397719020.
170. Chamarthy SP, Pinal R. The nature of crystal disorder in milled pharmaceutical materials. *Colloids Surfaces A Physicochem Eng Asp*. 2008;331(1-2):68–75. https://doi.org/10.1016/j.colsurfa.2008.06.040.
171. Burnett DJ, Khoo J, Naderi M, Heng JYY, Wang GD, Thielmann F. Effect of processing route on the surface properties of amorphous indomethacin measured by inverse gas chromatography. *AAPS PharmSciTech*. 2012;13(4):1511–1517. https://doi.org/10.1208/s12249-012-9881-5.
172. Luisi BS, Medek A, Liu Z, Mudunuri P, Moulton B. Milling-induced disorder of pharmaceuticals: one-phase or two-phase system? *J Pharm Sci*. 2012;101(4):1475–1485. https://doi.org/10.1002/jps.
173. Feng T, Pinal R, Carvajal MT. Process induced disorder in crystalline materials: differentiating defective crystals from the amorphous form of griseofulvin. *J Pharm Sci*. 2008;97(8):3207. https://doi.org/10.1002/jps.
174. Trasi NS, Boerrigter SXM, Byrn SR. Investigation of the milling-induced thermal behavior of crystalline and amorphous griseofulvin. *Pharm Res*. 2010;27:1377–1389. https://doi.org/10.1007/s11095-010-0129-3.
175. Otte A, Zhang Y, Carvajal MT, Pinal R. Milling induces disorder in crystalline griseofulvin and order in its amorphous counterpart. *CrystEngComm*. 2012;14(7):2560–2570. https://doi.org/10.1039/c2ce06365d.
176. Ito T, Byrn S, Chen X, Carvajal MT. Thermal insight of mechanically activated bile acid powders. *Int J Pharm*. 2011;420(1):68–75. https://doi.org/10.1016/j.ijpharm.2011.08.022.
177. Trasi NS, Byrn SR. Mechanically induced amorphization of drugs: a study of the thermal behavior of cryomilled compounds. *AAPS PharmSciTech*. 2012;13(3):772–784. https://doi.org/10.1208/s12249-012-9801-8.
178. Andrew Otte MTC. Assessment of milling-induced disorder of two pharmaceutical compounds. *J Pharm Sci*. 2011;100:1793–1804. https://doi.org/10.1002/jps.22415.
179. Nguyen Thi Y, Rademann K, Emmerling F. Direct evidence of polyamorphism in paracetamol. *CrystEngComm*. 2015;17(47):9029–9036. https://doi.org/10.1039/C5CE01583A.
180. Skotnicki M, Apperley DC, Aguilar JA, Milanowski B, Pyda M, Hodgkinson P. Characterization of two distinct amorphous forms of valsartan by solid-state NMR. *Mol Pharm*. 2016;13(1):211–222. https://doi.org/10.1021/acs.molpharmaceut.5b00646.
181. Grisedale LC, Belton PS, Jamieson MJ, Barker SA, Craig DQMM. An investigation into water interactions with amorphous and milled salbutamol sulphate: The development of predictive models for uptake and recrystallization. *Int J Pharm*. 2012;422(1-2):220–228. https://doi.org/10.1016/j.ijpharm.2011.10.055.
182. Purohit HS, Trasi NS, Sun DD, et al. Investigating the impact of drug crystallinity in amorphous tacrolimus capsules on pharmacokinetics and bioequivalence using discriminatory in vitro dissolution testing and physiologically based pharmacokinetic modeling and simulation. *J Pharm Sci*. 2018;107(5):1330–1341. https://doi.org/10.1016/j.xphs.2017.12.024.
183. Van den Brande N, Van Assche G, Van Mele B. Isothermal crystallization of PC 61 BM in thin layers far below the glass transition temperature. *Cryst Growth Des*. 2015;15(11):5614–5623. https://doi.org/10.1021/acs.cgd.5b01331.
184. Sun Y, Xi H, Chen S, Ediger MD, Yu L. Crystallization near glass transition: transition from diffusion-controlled to diffusionless crystal growth studied with seven polymorphs. *J Phys Chem B*. 2008;112(18):5594–5601. https://doi.org/10.1021/jp7120577.
185. Mehta M, Ragoonanan V, Mckenna GB, Suryanarayanan R. Correlation between molecular mobility and physical stability in pharmaceutical glasses. Published online 2016. https://doi.org/10.1021/acs.molpharmaceut.5b00853.
186. Newman A, Zografi G. What are the important factors that influence API crystallization in miscible amorphous API-excipient mixtures during long-term storage in the glassy state? *Mol Pharm*. 2022;19(2):378–391. https://doi.org/10.1021/acs.molpharmaceut.1c00519.
187. Yu L. Surface mobility of molecular glasses and its importance in physical stability. *Adv Drug Deliv Rev*. 2016;100:3–9. https://doi.org/10.1016/j.addr.2016.01.005.
188. Tsukushi I, Yamamuro O, Matsuo T. Solid state amorphization of organic molecular crystals using a vibrating mill. *Solid State Commun*. 1995;94(12):1013–1018. https://doi.org/10.1016/0038-1098(95)00161-1.
189. Ward GH, Schultz RK. Process-induced crystallinity changes in albuterol sulfate and its effect on powder physical stability. *Pharm Res*. 1995;12(5):773–779. https://doi.org/10.1023/A:1016232230638.
190. Thakral NK, Mohapatra S, Stephenson GA, Suryanarayanan R. Compression-induced crystallization of amorphous indomethacin in tablets: characterization of spatial heterogeneity by two-dimensional X-ray diffractometry. *Mol Pharm*. 2015;12(1):253–263. https://doi.org/10.1021/mp5005788.
191. Bhugra C, Shmeis R, Pikal MJ. Role of mechanical stress in crystallization and relaxation behavior of amorphous indomethacin. *J Pharm Sci*. 2008;97(10):4446–4458. https://doi.org/10.1002/jps.21291.
192. Powell CT, Xi H, Sun Y, et al. Fast crystal growth in o -terphenyl glasses: a possible role for fracture and surface mobility. *J Phys Chem B*. 2015;119(31):10124–10130. https://doi.org/10.1021/acs.jpcb.5b05389.
193. MacFhionnghaile P, Hu Y, Gniado K, Curran S, McArdle P, Erxleben A. Effects of ball-milling and cryomilling on sulfamerazine polymorphs: a quantitative study. *J Pharm Sci*. 2014;103(6):1766–1778. https://doi.org/10.1002/jps.23978.
194. Willart J-F, Durand M, Briggner L-E, Marx A, Danède F, Descamps M. Solid-state amorphization of linaprazan by mechanical milling and evidence of polymorphism. *J Pharm Sci*. 2013;102(7):2214–2220. https://doi.org/10.1002/jps.23573.
195. Brodka-Pfeiffer K, Häusler H, Graß P, Langguth P. Conditioning following powder micronization: influence on particle growth of salbutamol sulfate. *Drug Dev Ind Pharm*. 2003;29(10):1077–1084. https://doi.org/10.1081/DDC-120025865.
196. Qi S, Weuts I, De Cort S, et al. An investigation into the crystallisation behaviour of an amorphous cryomilled pharmaceutical material above and below the glass transition temperature. *J Pharm Sci*. 2010;99(1):196–208. https://doi.org/10.1002/jps.21811.
197. Depasquale R, Lee SL, Saluja B, Shur J, Price R. The influence of secondary processing on the structural relaxation dynamics of fluticasone propionate. *AAPS PharmSciTech*. 2015;16(3):589–600. https://doi.org/10.1208/s12249-014-0222-8.
198. Lim RTY, Hoong AYJ, Ng WK, Tan RBH. Anomalous size evolution of partially amorphized pharmaceutical particles during post-milling storage. *Powder Technol*. 2015;286:1–8. https://doi.org/10.1016/j.powtec.2015.08.002.
199. Feng T, Stanciu L, Carvajal M. Making sense of milling: the role of water on the micro-structural relaxation-like of cryo-milled griseofulvin. *Water*. 2012;4:18–36. https://doi.org/10.14294/WATER.2012.3.
200. Zografi G. States of water associated with solids. *Drug Dev Ind Pharm*. 1988;14(14):1905–1926. https://doi.org/10.3109/03639048809151997.
201. Kiang Y-H, Nagapudi K, Liu J, Staples RJ, Jona J. Crystal structure study and investigation of solid-state cyclization for AMG 222, a channel hydrate. *Int J Pharm*. 2013;441(1-2):299–306. https://doi.org/10.1016/j.ijpharm.2012.11.029.
202. Ressler C. Solid-state dehydrogenation of L-1,4-cyclohexadiene-1-alanine hydrate to L-phenylalanine. *J Org Chem*. 1972;37(19):2933–2936. https://doi.org/10.1021/jo00984a003.
203. Clay RJR, Knevel AAM, Byrnx SR, Byrn S. The desolvation and oxidation of crystals of dialuric acid monohydrate. *J Pharm*. 1982;71(11):1289–1291. https://doi.org/10.1002/jps.2600711127.
204. Guerrieri P, JARRING K, TAYLOR LS. Impact of counterion on the chemical stability of crystalline salts of procaine. *J Pharm Sci*. 2010;99(9):3719–3730. https://doi.org/10.1002/jps.22009.
205. Hsieh YL, Yu W, Xiang Y, et al. Impact of sertraline salt form on the oxidative stability in powder blends. *Int J Pharm*. 2014;461(1-2):322–330. https://doi.org/10.1016/j.ijpharm.2013.11.054.
206. Duggirala NK, Perry ML, Almarsson Ö, Zaworotko MJ. Pharmaceutical cocrystals: along the path to improved medicines. *Chem Commun*. 2016;52(4):640–655. https://doi.org/10.1039/C5CC08216A.
207. Badawy S, Hussain M, Zhao F, Ye Q, Huang Y, Palaniswamy V. Degradation pathways of a corticotropin-releasing factor antagonist in solution and solid states. *J Pharm Sci*. 2009;98(8):2636–2647. https://doi.org/10.1002/jps.21637.
208. Farag Badawy SI. Effect of salt form on chemical stability of an ester prodrug of a glycoprotein IIb/IIIa receptor antagonist in solid dosage forms. *Int J Pharm*. 2001;223(1-2):81–87. https://doi.org/10.1016/S0378-5173(01)00726-8.
209. Sheth AR, Lubach JW, Munson EJ, Muller FX, Grant DJW. Mechanochromism of piroxicam accompanied by intermolecular proton transfer probed by spectroscopic methods and solid-phase changes. *J Am Chem Soc*. 2005;127(18):6641–6651. https://doi.org/10.1021/ja045823t.

210. Šagud I, Zanolla D, Perissutti B, Passerini N, Škorić I. Identification of degradation products of praziquantel during the mechanochemical activation. *J Pharm Biomed Anal*. 2018;159:291–295. https://doi.org/10.1016/j.jpba.2018.07.002.
211. Perissutti Beatrice, Passerini N, Trastullo R, et al. An explorative analysis of process and formulation variables affecting comilling in a vibrational mill: the case of praziquantel. *Int J Pharm*. 2017;533(2):402–412. https://doi.org/10.1016/j.ijpharm.2017.05.053.
212. Adrjanowicz K, Kaminski K, Grzybowska K, et al. Effect of cryogrinding on chemical stability of the sparingly water-soluble drug furosemide. *Pharm Res*. 2011;28(12):3220–3236. https://doi.org/10.1007/s11095-011-0496-4.
213. Qiu Z, Stowell JG, Morris KR, Byrn SR, Pinal R. Kinetic study of the Maillard reaction between metoclopramide hydrochloride and lactose. *Int J Pharm*. 2005;303(1-2):20–30. https://doi.org/10.1016/j.ijpharm.2005.06.016.
214. Modhave D, Saraf I, Karn A, Paudel A. Understanding concomitant physical and chemical transformations of simvastatin during dry ball milling. *AAPS PharmSciTech*. 2020;21(5):152. https://doi.org/10.1208/s12249-020-01687-z.
215. Makoto O, Nobuyoshi K. Effect of grinding on the crystallinity and chemical stability in the solid state of cephalothin sodium. *Int J Pharm*. 1990;62(1):65–73. https://doi.org/10.1016/0378-5173(90)90031-X.
216. Satoshi K, Akira M, Shigetaka K, Yukiyoshi M. Effect of grinding on the solid-state stability of cefixime trihydrate. *Int J Pharm*. 1989;56(2):125–134. https://doi.org/10.1016/0378-5173(89)90005-7.
217. Correia NT, Moura Ramos JJ, Descamps M, Collins G. Molecular mobility and fragility indomethacin: a thermally stimulated depolarization current study. *Pharm Res*. 2001;18(12):1767–1774. https://doi.org/10.1023/A:1013339017070.
218. Kawakami K, Harada T, Yoshihashi Y, Yonemochi E, Terada K, Moriyama H. Correlation between glass-forming ability and fragility of pharmaceutical compounds. *J Phys Chem B*. 2015;119(14):4873–4880. https://doi.org/10.1021/jp509646z.
219. Pas T, Smeets B, Ramon H, et al. Mechanodegradation of polymers: a limiting factor of mechanochemical activation in the production of amorphous solid dispersions by cryomilling. *Mol Pharm*. 2020. https://doi.org/10.1021/acs.molpharmaceut.0c00376. Published online.
220. Sailaja U, Thayyil MS, Kumar NSK, Govindaraj G. Molecular dynamics of amorphous pharmaceutical fenofibrate studied by broadband dielectric spectroscopy. *J Pharm Anal*. 2016;6(3):165–170. https://doi.org/10.1016/j.jpha.2014.09.003.
221. Szab E, Haraszti A, Petra Z, et al. Evaluation of different thermoanalytical methods for the analysis of the stability of naproxen-loaded amorphous solid dispersions. Published online 2022.
222. Schenck L, Neri C, Jia X, et al. A co-processed API approach for a shear sensitive compound affording improved chemical stability and streamlined drug product processing. *J Pharm Sci*. 2021;110(9):3238–3245. https://doi.org/10.1016/j.xphs.2021.05.013.
223. Polizzi MA, Singhal D, Colvin J. Mechanoradical-induced degradation in a pharmaceutical blend during high-shear processing. *Pharm Dev Technol*. 2008;13(6):457–462. https://doi.org/10.1080/10837450802328869.
224. Ueyama E, Suzuki N, Kano K. Mechanistic study of the oxidative degradation of the triazole antifungal agent CS-758 in an amorphous form. *J Pharm Sci*. 2013;102(1):104–113. https://doi.org/10.1002/jps.
225. Munjal M, ElSohly MA, Repka MA. Polymeric systems for amorphous Δ9-tetrahydrocannabinol produced by a hot-melt method. part ii: effect of oxidation mechanisms and chemical interactions on stability. *J Pharm Sci*. 2006;95(11):2473–2485. https://doi.org/10.1002/jps.20711.
226. Kanaujia P, Poovizhi P, Ng WK, Tan RBH. Preparation, characterization and prevention of auto-oxidation of amorphous sirolimus by encapsulation in polymeric films using hot melt extrusion. *Curr Drug Deliv*. 2019;16(7):663–671. https://doi.org/10.2174/1567201816666190416123939.
227. Kotha RR, Zhang K, Yehl P, Kumar A. Oxidative degradation in pharmaceuticals: mechanism and stabilization of a spray-dried amorphous drug – a case study. *J Pharm Biomed Anal*. 2022;220(February): 114962. https://doi.org/10.1016/j.jpba.2022.114962.
228. Fujita M, Himi S, Handa T. Effects of compression and grinding on chemical stability of a benzodiazepine receptor agonist. *Chem Pharm Bull*. 2010;58(1):51–55. https://doi.org/10.1248/cpb.58.51.
229. Ikeda Y, Ban J, Ishikawa T, Hashiguchi S, Urayama S, Horibe H. Stability and stabilization studies of TAK-599 (ceftaroline fosamil), a novel N-phosphono type prodrug of anti-methicillin resistant Staphylococcus aureus cephalosporin T-91825. *Chem Pharm Bull*. 2008;56(10):1406–1411. https://doi.org/10.1248/cpb.56.1406.
230. Matsunaga Y, Bando N, Yuasa H, Kanaya Y. Effects of compression pressure on physical and chemical stability of tablets containing an anticancer drug TAT-59. *Chem Pharm Bull*. 1994;42(12):2582–2587. https://doi.org/10.1248/cpb.42.2582.
231. PubChem-Gabapentin. Accessed December 15, 2022. https://pubchem.ncbi.nlm.nih.gov/compound/Gabapentin.
232. Ardiana F, Lestari MLAD, Indrayanto G. Candesartan cilexetil. Profiles of Drug Substances, Excipients and Related Methodology. *Vol 37*. 1st ed. Elsevier Inc.; 2012:79–112. https://doi.org/10.1016/B978-0-12-397220-0.00003-9.
233. Naveršnik K. A simple non-linear kinetic model to evaluate stability of a pressure sensitive drug. *J Pharm Sci*. 2022;111(11):3108–3113. https://doi.org/10.1016/j.xphs.2022.07.010.
234. Zakowiecki D, Cal K, Kaminski K, et al. The improvement of the dissolution rate of ziprasidone free base from solid oral formulations. *AAPS PharmSciTech*. 2015;16(4):922–933. https://doi.org/10.1208/s12249-015-0285-1.
235. PubChem-Ziprasidone. Accessed December 15, 2022. https://pubchem.ncbi.nlm.nih.gov/compound/Ziprasidone.
236. Hong J, Shah JC, Mcgonagle MD. Effect of cyclodextrin derivation and amorphous state of complex on accelerated degradation of ziprasidone. *J Pharm Sci*. 2011;100(7):2703–2716. https://doi.org/10.1002/jps.22498.
237. Butreddy A, Sarabu S, Bandari S, et al. Influence of Plasdone™ S630 ultra—an improved copovidone on the processability and oxidative degradation of quetiapine fumarate amorphous solid dispersions prepared via hot-melt extrusion technique. *AAPS PharmSciTech*. 2021;22(5):1–13. https://doi.org/10.1208/s12249-021-02069-9.
238. Baghel S, Cathcart H, Redington W, O'Reilly NJ. An investigation into the crystallization tendency/kinetics of amorphous active pharmaceutical ingredients: a case study with dipyridamole and cinnarizine. *Eur J Pharm Biopharm*. 2016;104:59–71. https://doi.org/10.1016/j.ejpb.2016.04.017.
239. Peng T, She Y, Zhu C, et al. Influence of polymers on the physical and chemical stability of spray-dried amorphous solid dispersion: dipyridamole degradation induced by enteric polymers. *AAPS PharmSciTech*. 2018;19(6):2620–2628. https://doi.org/10.1208/s12249-018-1082-4.
240. Wu Y, Dali M, Gupta A, Raghavan K. Understanding drug-excipient compatibility: oxidation of compound A in a solid dosage form. *Pharm Dev Technol*. 2009;14(5):556–564. https://doi.org/10.1080/10837450903182140.
241. Alzghoul A, Alhalaweh A, Mahlin D, Bergström CAS. Experimental and computational prediction of glass transition temperature of drugs. *J Chem Inf Model*. 2014;54(12):3396–3403. https://doi.org/10.1021/ci5004834.
242. Kerč J, Srčič S. Thermal analysis of glassy pharmaceuticals. *Thermochim Acta*. 1995;248(94):81–95. https://doi.org/10.1016/0040-6031(94)01949-H.
243. Guerrieri P, Taylor LS. Role of salt and excipient properties on disproportionation in the solid-state. *Pharm Res*. 2009;26(8):2015–2026. https://doi.org/10.1007/s11095-009-9918-y.
244. Hasegawa J, Hanano M, Awazu S. Decomposition of acetylsalicylic acid and its derivataives in solid state. *Chem Pharm Bull*. 1975;23(1968):86–87. https://doi.org/10.1248/cpb.23.86.
245. Eddleston MD. Personal communication. Published online 2015.
246. Michalchuk AAL, Boldyreva EV, Belenguer AM, Emmerling F, Boldyrev VV. Tribochemistry, mechanical alloying, mechanochemistry: what is in a name? *Front Chem*. 2021;9(May):1–29. https://doi.org/10.3389/fchem.2021.685789.
247. Boldyrev V V. Mechanochemistry and mechanical activation of solids. *Russ Chem Rev*. 2006;75(3):177–189. https://doi.org/10.1070/rc2006v075n03abeh001205.
248. Kajdas C. Mechanical activation of chemical process. *Mater Sci Appl*. 2015;06(01):60–67. https://doi.org/10.4236/msa.2015.61008.
249. Beyer MK, Clausen-Schaumann H. Mechanochemistry: the mechanical activation of covalent bonds. *Chem Rev*. 2005;105(8):2921–2948. https://doi.org/10.1021/cr030697h.
250. Krusenbaum A, Grätz S, Tigineh GT, Borchardt L, Kim JG. The mechanochemical synthesis of polymers. *Chem Soc Rev*. 2022;51(7):2873–2905. https://doi.org/10.1039/d1cs01093j.
251. Carta M, Colacino E, Delogu F, Porcheddu A. Kinetics of mechanochemical transformations. *Phys Chem Chem Phys*. 2020;22(26):14489–14502. https://doi.org/10.1039/d0cp01658f.
252. Loh ZH, Samanta AK, Sia Heng PW. Overview of milling techniques for improving the solubility of poorly water-soluble drugs. *Asian J Pharm Sci*. 2014;10(4):255–274. https://doi.org/10.1016/j.ajps.2014.12.006.
253. Martínez LM, Cruz-Angeles J, Vázquez-Dávila M, et al. Mechanical activation by ball milling as a strategy to prepare highly soluble pharmaceutical formulations in the form of co-amorphous, co-crystals, or polymorphs. *Pharmaceutics*. 2022;14(10):2003. https://doi.org/10.3390/pharmaceutics14102003.
254. Shi Q, Moinuddin SM, Cai T. Advances in coamorphous drug delivery systems. *Acta Pharm Sin B*. 2019;9(1):19–35. https://doi.org/10.1016/j.apsb.2018.08.002.
255. Konishi Y, Kadota K, Tozuka Y, Shimosaka A, Shirakawa Y. Amorphization and radical formation of cystine particles by a mechanochemical process analyzed using DEM simulation. *Powder Technol*. 2016;301:220–227. https://doi.org/10.1016/j.powtec.2016.06.010.
256. Minode M, Kadota K, Kawabata D, Yoshida M, Shirakawa Y. Enhancement in dissolution behavior and antioxidant capacity of quercetin with amino acids following radical formation via mechanochemical technique. *Adv Powder Technol*. 2022;33(5): 103582. https://doi.org/10.1016/j.apt.2022.103582.
257. Kuzuya M. Mechanolysis of glucose-based polysaccharides as studied by electron spin resonance. *J Phys Chem B*. 1999;103(38):8051–8059. https://doi.org/10.1021/jp984278d.
258. Sasai Y, Yamauchi Y, Kondo SI, Kuzuya M. Nature of mechanoradical formation of substituted celluloses as studied by electron spin resonance. *Chem Pharm Bull*. 2004;52(3):339–344. https://doi.org/10.1248/cpb.52.339.
259. Iyer J, Saraf I, Ray A, Brunsteiner M, Paudel A. Assessment of diverse solid–state accelerated autoxidation methods for droperidol. *Pharmaceutics*. 2022;14(6):1–14. https://doi.org/10.3390/pharmaceutics14061114.
260. Petzoldt C, Bley O, Byard SJ, et al. An example of how to handle amorphous fractions in API during early pharmaceutical development: SAR114137 - a successful approach. *Eur J Pharm Biopharm*. 2014;86(3):337–350. https://doi.org/10.1016/j.ejpb.2013.09.015.
261. Peterson GI, Ko W, Hwang YJ, Choi TL. Mechanochemical degradation of amorphous polymers with Ball-Mill grinding: influence of the glass transition temperature. *Macromolecules*. 2020;53(18):7795–7802. https://doi.org/10.1021/acs.macromol.0c01510.
262. Iyer J, Barbosa M, Saraf I, Pinto JF, Paudel A. Mechanoactivation as a tool to assess the autoxidation propensity of amorphous drugs. *Mol Pharm*. 2023;20(2):1112–1128. https://doi.org/10.1021/acs.molpharmaceut.2c00841.
263. Moser J, Ashworth IW, Harris L, Hillier MC, Nanda KK, Scrivens G. N-nitrosamine formation in pharmaceutical solid drug products: experimental observations. *J Pharm Sci*. Published online 2023. doi:https://doi.org/10.1016/j.xphs.2023.01.027.

264. Nanda KK, Tignor S, Clancy J, Marota MJ, Allain LR, D'Addio SM. Inhibition of N-nitrosamine formation in drug products: a model study. *J Pharm Sci*. 2021;110(12):3773–3775. https://doi.org/10.1016/j.xphs.2021.08.010.
265. Schlingemann J, Burns MJ, Ponting DJ, et al. The landscape of potential small and drug substance related nitrosamines in pharmaceuticals. *J Pharm Sci*. 2022. https://doi.org/10.1016/j.xphs.2022.11.013. 000.
266. Ponting DJ, Dobo KL, Kenyon MO, Kalgutkar AS. Strategies for assessing acceptable intakes for novel N-nitrosamines derived from active pharmaceutical ingredients. *J Med Chem*. 2022;65(23):15584–15607. https://doi.org/10.1021/acs.jmedchem.2c01498.
267. Pazesh S, Persson AS, Alderborn G. Atypical compaction behaviour of disordered lactose explained by a shift in type of compact fracture pattern. *Int J Pharm X*. 2019;1(September). https://doi.org/10.1016/j.ijpx.2019.100037.
268. Huang C, Klinzing G, Procopio A, et al. Understanding compression-induced amorphization of crystalline posaconazole. *Mol Pharm*. 2019;16(2):825–833. https://doi.org/10.1021/acs.molpharmaceut.8b01122.
269. Moseson DE, Hiew TN, Su Y, Taylor LS. Formulation and processing strategies which underpin susceptibility to matrix crystallization in amorphous solid dispersions. *J Pharm Sci*. 2023;112(1):108–122. https://doi.org/10.1016/j.xphs.2022.03.020.
270. Lee WA, Sewell JH. Influence of cohesive forces on the glass transition temperatures of polymers. *J Appl Polym Sci*. 1968;12:1397–1409.
271. Roberts RJJ, Rowe RCC, York P. The relationship between Young's modulus of elasticity of organic solids and their molecular structure. *Powder Technol*. 1991;65(1-3):139–146. https://doi.org/10.1016/0032-5910(91)80176-J.
272. Zhou G, Zhao T, Wan J, Liu C, Liu W, Wang R. Predict the glass transition temperature and plasticization of β-cyclodextrin/water binary system by molecular dynamics simulation. *Carbohydr Res*. 2015;401:89–95. https://doi.org/10.1016/j.carres.2014.10.026.
273. Gupta J, Nunes C, Jonnalagadda S. A molecular dynamics approach for predicting the glass transition temperature and plasticization effect in amorphous pharmaceuticals. *Mol Pharm*. 2013;10(11):4136–4145. https://doi.org/10.1021/mp400118v.
274. Abdel-Halim H, Traini D, Hibbs D, Gaisford S, Young P. Modelling of molecular phase transitions in pharmaceutical inhalation compounds: an in silico approach. *Eur J Pharm Biopharm*. 2011;78(1):83–89. https://doi.org/10.1016/j.ejpb.2010.12.019.
275. Li D-X, Liu B-L, Liu Y, Chen C. Predict the glass transition temperature of glycerol-water binary cryoprotectant by molecular dynamic simulation. *Cryobiology*. 2008;56(2):114–119. https://doi.org/10.1016/j.cryobiol.2007.11.003.
276. Simperler A, Kornherr A, Chopra R, et al. Glass transition temperature of glucose, sucrose, and trehalose: an experimental and in silico study. *J Phys Chem B*. 2006;110(39):19678–19684. https://doi.org/10.1021/jp063134t.
277. Zheng L, Luo SN, Thompson DL. Molecular dynamics simulations of melting and the glass transition of nitromethane. *J Chem Phys*. 2006;124(15):1–8. https://doi.org/10.1063/1.2174002.
278. Yoshioka S, Aso Y, Kojima S. Prediction of glass transition temperature of freeze-dried formulations by molecular dynamics simulation. *Pharm Res*. 2003;20(6):873–878.
279. Momany F a, Willett JL. Molecular dynamics calculations on amylose fragments. I. Glass transition temperatures of maltodecaose at 1, 5, 10, and 15.8% hydration. *Biopolymers*. 2002;63(2):99–110. https://doi.org/10.1002/bip.10014.
280. Buchholz J, Paul W, Varnik F, Binder K. Cooling rate dependence of the glass transition temperature of polymer melts: molecular dynamics study. *J Chem Phys*. 2002;117(15):7364. https://doi.org/10.1063/1.1508366.
281. Paudel A, Meeus J, Van den Mooter G. Structural characterization of amorphous solid dispersions. *Amorphous Solid Dispersions*. New York, NY: Springer; 2014:421–485. https://doi.org/10.1007/978-1-4939-1598-9_14.
282. Sumie Yoshioka YA. Correlations between molecular mobility and chemical stability during storage of amorphous pharmaceuticals. *J Pharm Sci*. 2007;96:960–981. https://doi.org/10.1002/jps.
283. Oliver WC, Pharr GM. An improved technique for determining hardness and elastic modulus using load and displacement sensing indentation experiments. *J Mater Res*. 2011;7(06):1564–1583. https://doi.org/10.1557/JMR.1992.1564.
284. Rowe RC, Roberts RJ. Simulation of crack propagation in porous compacted specimens of aspirin. *J Mater Sci*. 1993;28(12):3385–3390. https://doi.org/10.1007/BF00354262.
285. Roberts RJ, Rowe RC, York P. The relationship between indentation hardness of organic-solids and their molecular-structure. *J Mater Sci*. 1994;29(9):2289–2296. https://doi.org/10.1007/Bf00363416.
286. Roberts RJ, Rowe RC, York P. The relationship between the fracture properties, tensile strength and critical stress intensity factor of organic solids and their molecular structure. *Int J Pharm*. 1995;125(1):157–162. https://doi.org/10.1016/0378-5173(95)00157-E.
287. Roberts RJ, Rowe RC. Influence of polymorphism on the Young's modulus and yield stress of carbmazepine, sulfathiazole and sulfanilamide. *Int J Pharm*. 1996;129(1-2):79–94. https://doi.org/10.1016/0378-5173(95)04253-9.
288. Roberts RJ, Rowe RC. Relationships between the modulus of elasticity and tensile strength for pharmaceutical drugs and excipients. *J Pharm Pharmacol*. 1999;51(9):975–977. https://doi.org/10.1211/0022357991773438.
289. Roberts RJ, Payne RS, Rowe RC. Mechanical property predictions for polymorphs of sulphathiazole and carbamazepine. *Eur J Pharm Sci*. 2000;9(3):277–283. https://doi.org/10.1016/S0928-0987(99)00065-2.
290. Payne RS, Roberts RJ, Rowe RC, McPartlin M, Bashal A. The mechanical properties of two forms of primidone predicted from their crystal structures. *Int J Pharm*. 1996;145(1-2):165–173. https://doi.org/10.1016/S0378-5173(96)04760-6.
291. Gupta J, Nunes C, Vyas S, Jonnalagadda S. Prediction of solubility parameters and miscibility of pharmaceutical compounds by molecular dynamics simulations. *J Phys Chem B*. 2011;115(9):2014–2023. https://doi.org/10.1021/jp108540n.
292. Gilman JJ. *Chemistry and Physics of Mechanical Hardness*. John Wiley & Sons; 2009.
293. Qiao XG, Starink MJ, Gao N. The influence of indenter tip rounding on the indentation size effect. *Acta Mater*. 2010;58(10):3690–3700. https://doi.org/10.1016/j.actamat.2010.03.004.
294. Wang MH, Yang RY, Yu a. B.. DEM investigation of energy distribution and particle breakage in tumbling ball mills. *Powder Technol*. 2012;223:83–91. https://doi.org/10.1016/j.powtec.2011.07.024.
295. Ketterhagen WR, am Ende MT, Hancock BC. Process modeling in the pharmaceutical industry using the discrete element method. *J Pharm Sci*. 2009;98(2):442–470. https://doi.org/10.1002/jps.21466.
296. Cottrell AH. *Dislocations and Plastic Flow in Crystals*. Oxford Univ. Press; 1953.
297. Reddy CM, Rama Krishna G, Ghosh S. Mechanical properties of molecular crystals—applications to crystal engineering. *CrystEngComm*. 2010;12(8):2296. https://doi.org/10.1039/c003466e.
298. Kubavat H a, Shur J, Ruecroft G, Hipkiss D, Price R. Investigation into the influence of primary crystallization conditions on the mechanical properties and secondary processing behaviour of fluticasone propionate for carrier based dry powder inhaler formulations. *Pharm Res*. 2012;29(4):994–1006. https://doi.org/10.1007/s11095-011-0640-1.
299. Lei L, Koslowski M. Mesoscale modeling of dislocations in molecular crystals. *Philos Mag*. 2011;91(6):865–878. https://doi.org/10.1080/14786435.2010.533135.
300. Zeng Y, Alzate-Vargas L, Li C, et al. Mechanically induced amorphization of small molecule organic crystals. *Model Simul Mater Sci Eng*. 2019;27(7): 074005. https://doi.org/10.1088/1361-651X/ab234a.
301. Munday LB, Solares SD, Chung PW. Generalized stacking fault energy surfaces in the molecular crystal αRDX. *Philos Mag*. 2012;92(24):3036–3050. https://doi.org/10.1080/14786435.2012.685191.
302. Wolstenholme WE. Correlation of physical and polymer chain properties. *Polym Eng Sci*. 1968;8(2):142–150. https://doi.org/10.1002/pen.760080210.
303. Batzer H, Kreibich UT. Zusammenhänge zwischen Glasübergang, thermodynamischen und mechanischen Größen als Möglichkeit zur Voraussage über Materialeigenschaften aus der chemischen Struktur. *Angew Makromol Chemie*. 1982;105(1):113–130. https://doi.org/10.1002/apmc.1982.051050113.
304. Caleman C, van Maaren PJ, Hong M, Hub JS, Costa LT, Van Der Spoel D. Force field benchmark of organic liquids: density, enthalpy of vaporization, heat capacities, surface tension, isothermal compressibility, volumetric expansion. *J Chem Theory Comput*. 2011;8(1):61–74. https://doi.org/10.1021/ct200731v.
305. Zhang J, Tuguldur B, van der Spoel D. Force field benchmark of organic liquids. 2. Gibbs energy of solvation. *J Chem Inf Model*. 2015;55(6):1192–1201. https://doi.org/10.1021/acs.jcim.5b00106.
306. Nordström FL, Rasmuson ÅC. Prediction of solubility curves and melting properties of organic and pharmaceutical compounds. *Eur J Pharm Sci*. 2009;36(2-3):330–344. https://doi.org/10.1016/j.ejps.2008.10.009.
307. Ran Y, Yalkowsky SH. Prediction of drug solubility by the general solubility equation (GSE). *J Chem Inf Comput Sci*. 2001;41(2):354–357. https://doi.org/10.1021/ci000338c.
308. Salahinejad M, Le TC, Winkler DA. Aqueous solubility prediction: do crystal lattice interactions help? *Mol Pharm*. 2013;10(7):2757–2766. https://doi.org/10.1021/mp4001958.
309. Jouyban A, Soltanpour S, Soltani S, Chan HK, Acree WE. Solubility prediction of drugs in water-cosolvent mixtures using Abraham solvation parameters. *J Pharm Pharm Sci*. 2007;10(3):263–277.
310. Palmer DS, McDonagh JL, Mitchell JBO, van Mourik T, Fedorov M V. First-principles calculation of the intrinsic aqueous solubility of crystalline druglike molecules. *J Chem Theory Comput*. 2012;8(9):3322–3337. https://doi.org/10.1021/ct300345m.
311. Paluch AS, Cryan DD, Maginn EJ. Predicting the solubility of the sparingly soluble solids 1,2,4,5-tetramethylbenzene, phenanthrene, and fluorene in various organic solvents by molecular simulation. *J Chem Eng Data*. 2011;56(4):1587–1595. https://doi.org/10.1021/je101251n.
312. Sheth AR, Zhou D, Muller FX, Grant DJW. Dehydration kinetics of piroxicam monohydrate and relationship to lattice energy and structure. *J Pharm Sci*. 2004;93(12):3013–3026. https://doi.org/10.1002/jps.20191.
313. Hess B, Peter C, Ozal T, van der Vegt NF. Fast-growth thermodynamic integration: calculating excess chemical potentials of additive molecules in polymer microstructures. *Macromolecules*. 2008;41(6):2283–2289. https://doi.org/10.1021/ma702070n.
314. Ozal Ta, Peter C, Hess B, van der Vegt NFA. Modeling solubilities of additives in polymer microstructures: single-step perturbation method based on a soft-cavity reference state. *Macromolecules*. 2008;41(13):5055–5061. https://doi.org/10.1021/ma702329q.
315. Hess B, van der Vegt N. Predictive modeling of phenol chemical potentials in molten bisphenol A-polycarbonate over a broad temperature range. *Macromolecules*. 2008;41:7281–7283.
316. Westergren J, Lindfors L, Höglund T, Lüder K, Nordholm S, Kjellander R. In silico prediction of drug solubility: 1. Free energy of hydration. *J Phys Chem B*. 2007;111(7):1872–1882. https://doi.org/10.1021/jp064220w.
317. Lüder K, Lindfors L, Westergren J, Nordholm S, Kjellander R. In silico prediction of drug solubility: 2. Free energy of solvation in pure melts. *J Phys Chem B*. 2007;111(7):1883–1892. https://doi.org/10.1021/jp0642239.
318. Lüder K, Lindfors L, Westergren J, Nordholm S, Kjellander R. In silico prediction of drug solubility. 3. Free energy of solvation in pure amorphous matter. *J Phys Chem B*. 2007;111(25):7303–7311. https://doi.org/10.1021/jp071687d.

319. Lüder K, Lindfors L. In silico prediction of drug solubility: 4. Will simple potentials suffice? *J Comput Chem*. 2009;30(12):1859–1871. https://doi.org/10.1002/jcc.
320. Vasileiadis M. Calculation of the free energy of crystalline solids. 2013;(November).
321. Aragones JL, Noya EG, Valeriani C, Vega C. Free energy calculations for molecular solids using GROMACS. *J Chem Phys*. 2013;139(3): 034104. https://doi.org/10.1063/1.4812362.
322. Lin Y, Cogdill RP, Wildfong PLD. Informatic calibration of a materials properties database for predictive assessment of mechanically activated disordering potential for small molecule organic solids. *J Pharm Sci*. 2009;98(8):2696–2708. https://doi.org/10.1002/jps.
323. Zoltán Juhász A. Aspects of mechanochemical activation in terms of comminution theory. *Colloids Surf A Physicochem Eng Asp*. 1998;141(3):449–462. https://doi.org/10.1016/S0927-7757(98)00245-3.