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Perspective

Crystallinity: A Complex Critical Quality Attribute of Amorphous Solid Dispersions

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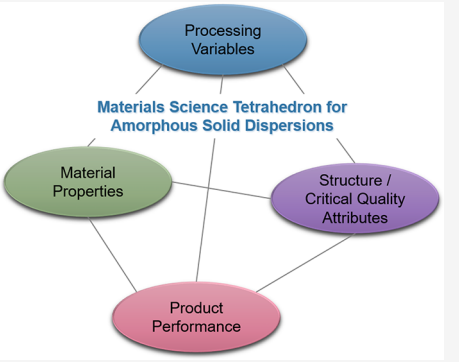
ABSTRACT: Does the performance of an amorphous solid dispersion rely on having 100% amorphous content? What specifications are appropriate for crystalline content within an amorphous solid dispersion (ASD) drug product? In this Perspective, the origin and significance of crystallinity within amorphous solid dispersions will be considered. Crystallinity can be found within an ASD from one of two pathways: (1) incomplete amorphization, or (2) crystal creation (nucleation and crystal growth). While nucleation and crystal growth is the more commonly considered pathway, where crystals originate as a physical stability failure upon accelerated or prolonged storage, manufacturing-based origins of crystallinity are possible as well. Detecting trace levels of crystallinity is a significant analytical challenge, and orthogonal methods should be employed to develop a holistic assessment of sample properties. Probing the impact of crystallinity on release performance which may translate to meaningful clinical significance is inherently challenging, requiring optimization of dissolution test variables to address the complexity of ASD formulations, in terms of drug physicochemical properties (e.g., crystallization tendency), level of crystallinity, crystal reference material selection, and formulation characteristics. The complexity of risk presented by crystallinity to product performance will be illuminated through several case studies, highlighting that a one-size-fits-all approach cannot be used to set specification limits, as the risk of crystallinity can vary widely based on a multitude of factors. Risk assessment considerations surrounding drug physicochemical properties, formulation fundamentals, physical stability, dissolution, and crystal micromeritic properties will be discussed.



KEYWORDS: *amorphous solid dispersion, critical quality attributes, processing, physical stability, dissolution, crystallinity*

1. INTRODUCTION

Amorphous solid dispersions (ASDs) have become a popular strategy for oral delivery of poorly water-soluble compounds.[1,2] As of 2023, more than 30 US FDA-approved products containing an ASD have been commercialized, using spray drying, hot melt extrusion, and other manufacturing technologies for their production.[3] The underlying complexity of amorphous solid dispersions results from the interplay of raw material attributes, formulation, manufacturing processes, and resulting critical quality attributes (CQAs) on product performance and subsequent bioavailability. A major underlying risk of these formulations lies in the propensity of the amorphous drug to crystallize due to thermodynamic instability.[4]

Per ICH Q6A guideline, when a polymorphic form (including the amorphous form) can affect drug product performance, bioavailability, or stability, the solid state form should be specified, monitored, and controlled.[5] Thus, there is widespread interest in setting specifications for crystalline content so as to limit the impact of crystallinity on the dosage form's performance in the clinical setting.[6] However, due to a multitude of factors, the relevance and risk of crystallinity in a formulation and setting specification limits cannot use a one-size-fits-all approach. This perspective will briefly review several of these aspects, in particular to illuminate the origins of crystallinity in ASDs and potential impact on release performance. Several case studies will then serve as the basis to highlight areas of low and high risk of crystallinity within ASD formulations. Considerations surrounding drug physicochemical properties, formulation fundamentals, physical stability,

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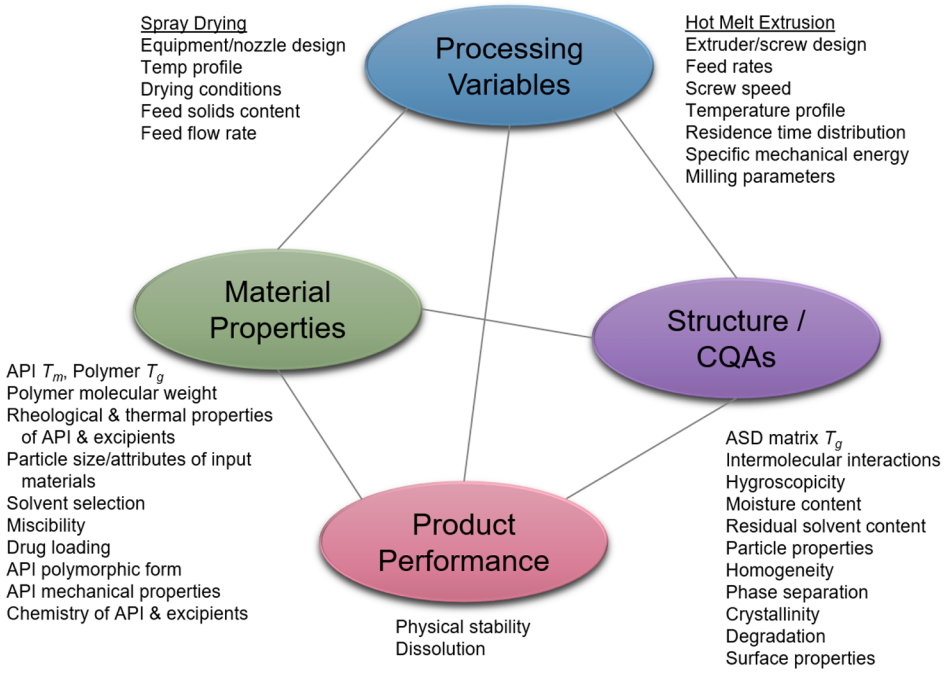

Figure 1. Materials science tetrahedron (MST) as applied to amorphous solid dispersions. The two most popular processing techniques, spray drying and hot melt extrusion, are included to provide examples of key processing variables.

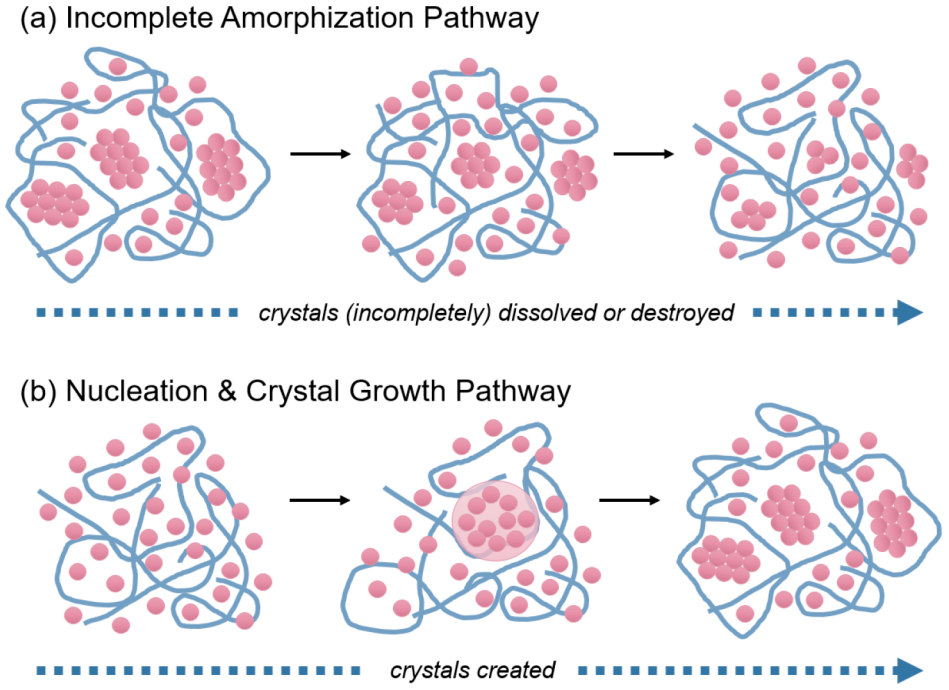

Figure 2. Formation pathways of crystallinity in amorphous solid dispersions: (a) incomplete amorphization, (b) nucleation and crystal growth.

dissolution, and crystal micromeritic properties will be discussed in terms of a risk assessment strategy.

2. MATERIALS SCIENCE TETRAHEDRON FOR AMORPHOUS SOLID DISPERSIONS

The materials science tetrahedron (MST) concept pioneered by Sun for pharmaceutical systems[7] can be applied to the formulation and processing design of ASDs. A nonexhaustive list of material properties, processing variables, structural attributes, and product performance metrics are listed in Figure 1 to describe the pharmaceutical development aspects relevant to ASDs. Material properties are interconnected with processing choices, which combine to impact the structure and CQAs of ASD drug product intermediates, which in turn impact the product performance. In addition, structural attributes such as homogeneity and crystallinity can change over time upon storage. Developing an understanding of the structure−property relationship with respect to crystallinity is among the primary goals of this Perspective.

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Aside from the well-known attributes of physical, chemical, and microbiological purity that are expected of a drug product, several CQAs play a significant role in the performance of ASDs (Figure 1). First, the amorphous drug must be fully transformed from the crystalline material. Any crystallinity in the system, either remaining from the manufacturing process or generated upon storage, may contribute to loss of solubility advantage and further development of crystallization during storage or upon dissolution.[8−11] Next, the ASD intermediate must be homogeneous. Lack of homogeneity, due to poor miscibility, high drug loading, poor mixing, or phase separation may accelerate crystallization.[12−14] Lastly, for thermal-based processing methods, the drug and/or polymer may undergo chemical degradation.[15−17]

The crystallinity aspect is the main focus of the remainder of this Perspective, although MST aspects of material properties, ASD structure, and processing contributions will be discussed. Crystallinity in ASDs may directly contribute to changes in bioavailability.[18] This may happen through three mechanisms. First, crystallinity may result in lost solubility advantage. If the drug is not in its amorphous form, it cannot contribute to the solubility advantage. Second, crystals present may initiate additional crystallization, causing reduced dissolution rate and extent, as well as desupersaturation. Lastly, crystals may grow during storage, further reducing solubility advantage and hindering release performance.

3. FORMATION PATHWAYS OF CRYSTALLINITY IN ASDS

Crystallinity may be found in an ASD from one of two pathways: incomplete amorphization during processing (Figure 2a) or crystal creation (Figure 2b). The incomplete amorphization pathway (Figure 2a) may occur when the crystalline-to-amorphous phase transformation is based on crystal dissolution or size reduction mechanisms. The more commonly considered pathway is that of crystal creation: nucleation and crystal growth (Figure 2b). Most typically, nucleation and crystal growth occur during long storage durations, or under conditions used for accelerated stability testing.[19] However, crystals may be also created during manufacturing depending on the processing conditions employed.

3.1. Manufacturing Methods. ASD preparation methods can be broadly classified as solvent-based or thermal-based processes.[20] Solvent-based ASD manufacturing processes typically consist of three major steps: (1) dissolving the drug and polymer in a volatile solvent, (2) removing the bulk of the solvent to produce solids, and (3) secondary drying to further remove any residual solvent.[21] Solvent-based processes used to produce ASDs include spray drying, coprecipitation, rotary evaporation, vacuum drying, freeze-drying, and the use of supercritical fluids.[21,22] Solvent-based processes are more common because they are applicable to a wide range of compounds and are material-sparing in early phase development.[22,23]

Thermal-based ASD manufacturing methods consist of two major steps: (1) melting or dissolution of drug within the polymer at elevated temperature and (2) rapid cooling of the molten material so it solidifies into a one-phase system.[21,24] Thermal-based methods include hot melt extrusion (HME) and KinetiSol dispersing technology.[21] For thermally stable systems, HME offers several advantages over solvent-based processing: it is solvent-free, inexpensive, continuous, high-throughput, and easily scalable and requires only a small facility footprint, enabling batch size flexibility and fast production.[25,26]

Mechanochemical activation forms a third category of ASD manufacturing methods.[27] While this encompasses all kinds of high-energy milling, cryomilling is the most common in the literature.[27−29] At present, there are no commercialized ASD products which use this method.

3.2. Incomplete Amorphization Pathway. The incomplete amorphization pathway (Figure 2a) is most relevant to manufacturing processes such as hot melt extrusion (HME), Kinetisol dispersing, microwave-irradiation, or milling to create amorphous forms.[29−35] In such processes, thermal and/or mechanical input is provided, which enable the crystalline drug to dissolve, crystalline particles to be fractured, or the crystal lattice to be otherwise disrupted. For some molecules, milling may induce amorphization through reduction of crystallite size and through propagation of crystalline defects.[29,35−38] With thermal-based processing, amorphization may take place by solubilizing the drug in the molten polymer while providing sufficient mixing energy to expedite the dissolution process.[32,39−41] As this type of processing is inherently kinetic, the amount of processing time is key to complete the crystalline-to-amorphous transformation. Residual crystals may remain if insufficient thermodynamics (temperature) or mixing kinetics (mechanical input, residence time) is provided.

This failure mode would also be relevant to solvent-based processing. The bulk crystalline drug must fully dissolve in the solvent, prior to processing. If the drug has not completely dissolved upon processing, crystallinity will remain in the final ASD particles.

3.2.1. Thermodynamics of ASD Formation during Thermal-Based Processing. For thermal-based processes, such as HME, Kinetisol, or microwave-irradiation, the minimum temperature threshold for successfully dissolving all crystalline drug (solute) into the molten polymer (solvent) is the formulation critical temperature (T_c), sometimes referred to as the solubility temperature (T_s).[30] The kinetics of the dissolution process is typically considered with respect to the concentration gradient of the equilibrium solubility of the crystalline drug in the molten polymer minus the concentration at time, t, ($C_s - C$) defined by the Noyes-Whitney (eq 1) and Stokes−Einstein equations (eq 2)

$$\frac{dC}{dt} = \frac{DA}{hV}(C_s - C) \tag{1}$$

$$D = \frac{k_B T}{6\pi\eta r} \tag{2}$$

where dC/dt is the differential change in solute concentration in solution with time, D is the diffusion coefficient, A is the surface area available for dissolution, h represents the mass transfer boundary layer thickness at the solid−liquid interface, and V is the volume of the liquid phase. Terms impacting the diffusion coefficient, D, include the Boltzmann constant k_B, temperature, T, viscosity, η, and radius of the diffusing species, r. The solubility of the drug in the polymer refers to the ability of the crystalline form of the drug to be solubilized in a polymer.[42] Thus, for a fixed composition, the temperature where all of the crystalline drug can be solubilized can be determined, which should occur at a temperature lower than the drug melting point, for a miscible drug−polymer system.

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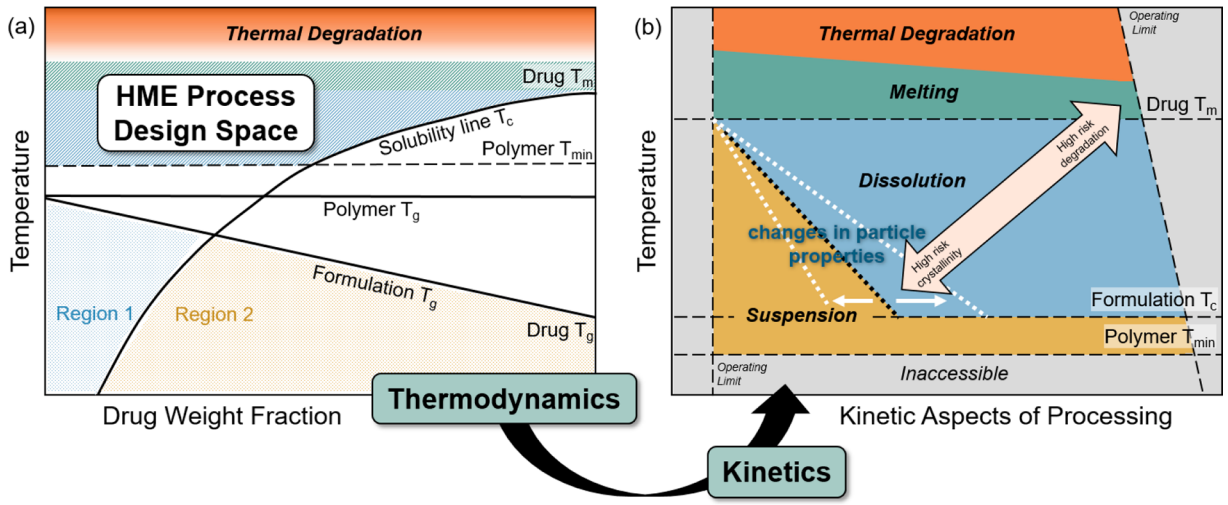

Figure 3. Temperature−composition phase diagrams describing the thermodynamics and kinetics of drug−polymer phase behavior and representing the hot melt extrusion process. (a) Temperature−composition phase diagram as related to the hot melt extrusion process. ASDs can be formed in the melting (above the drug's T_m) or dissolution processing regime (bounded by the drug's melting temperature and formulation critical temperature T_c located on the solubility line). Two regions are highlighted below the formulation T_g line: Region 1 (to the left of the solubility line) represents compositions and temperatures of thermodynamic and kinetic stability, and region 2 (to the right of the solubility line) represents compositions and temperatures of a thermodynamic metastability and kinetic stability. (b) Process operating design space diagram, delineating three processing regimes (melting, dissolution, and suspensions) by temperature and kinetic considerations. The black dotted line represents the time corresponding to the complete crystalline-to-amorphous transition at a given temperature. With changes in particle-level properties, this transition could be shifted earlier or later as represented by the yellow dotted lines, increasing risks for processing challenges or residual crystallinity. Higher temperatures and greater process kinetics (e.g., long residence time, high specific mechanical energy) correspond to a greater risk for thermal degradation of drug and/or polymer, while lower temperatures and reduced process kinetics correspond to a greater risk of residual crystallinity. Figure adapted and reprinted with permission from refs 30 and 41. Copyright 2018 Elsevier and 2021 American Chemical Society.

In a miscible drug−polymer system, solubility determinations by multiple methods are considered to be thermodynamically equivalent.[43] For example, in the melting point depression method by differential scanning calorimetry (DSC), the solubility equilibrium is approached by heating a fixed composition to determine the temperature at which dissolution is complete (melting point offset temperature). In contrast, during processing, complete solubility is achieved by solute dissolution into the molten polymer from an under-saturated state under isothermal conditions.

Solubility is a thermodynamic parameter and can be theoretically described through the Flory−Huggins framework of melting point depression.[42,44−48] Moseson and Taylor describe the theoretical concepts behind the application of this theory to HME process design.[30] A miscible drug−polymer system is one in which the (supercooled) liquid form of the drug homogeneously mixes with the polymer across all compositions.[14] Miscible drug−polymer systems exhibit melting point depression because the chemical potential of the drug in the drug−polymer system is reduced relative to that of the pure drug due to a favorable entropy of mixing and, for some systems, an exothermic mixing enthalpy, as shown in the temperature−composition phase diagram in Figure 3a. This relationship is described by eq 3

$$\frac{1}{T_c} - \frac{1}{T_m} = -\frac{R}{\Delta H}\left[\ln \phi + \left(1 - \frac{1}{m}\right)(1 - \phi) + \chi(1 - \phi)^2\right] \quad (3)$$

where T_m is the melting temperature of the pure drug (in Kelvin), T_c is the depressed melting point of the drug−polymer system (in Kelvin), R is the gas constant, ΔH is the enthalpy of fusion of the drug, ϕ is the volume fraction of the drug, m is the ratio of the polymer segment to drug molecular volume, and χ is the Flory−Huggins interaction parameter. A negative or small positive value of χ indicates a miscible system. Limitations of this approach and further discussion of the interaction parameter can be found in the literature.[49−52]

Temperature−composition phase diagrams can be readily constructed by thermal analysis methods such as the melting point depression DSC method or recrystallization method.[30,53−55] Besides Flory−Huggins theory, other approaches are commonly used to determine the solubility temperature and to build phase diagrams, such as PC-SAFT and empirical models.[56−58] Rheology has also recently been shown to identify the attributes of crystal dissolution, as an alternative means of determining T_c.[59,60] Phase diagrams are also useful for identifying compositions which have thermodynamic and/or kinetic stability, based on considering the storage temperature of the system and the location of the solubility line and glass transition temperature line. In region 1 (Figure 3a), below the glass transition temperature curve and above (or to the left of) the solubility curve, a composition has both thermodynamic and kinetic stability. In region 2 (Figure 3a), below the glass transition temperature curve and below (or to the right of) the solubility curve, compositions have some degree of kinetic stability.

3.2.2. Kinetics of ASD Formation during Thermal-Based Processing. As interpreted from the Noyes−Whitney (eq 1) and Stokes−Einstein equations (eq 2), amorphization through a dissolution-based mechanism is inherently kinetic. While solubility is a thermodynamic requirement, additional material structural and property variables intersect with processing

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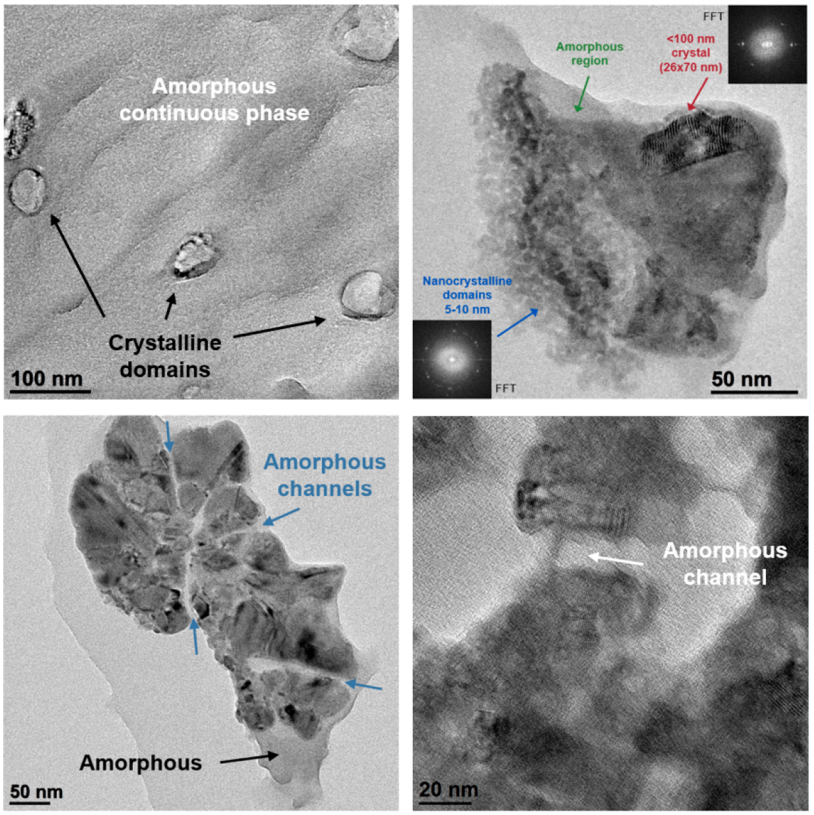

Figure 4. TEM images of residual crystallinity in indomethacin/PVPVA ASDs. Figure adapted and reprinted with permission from refs 8, 31, and 62. Copyright 2018 American Chemical Society, 2019 American Chemical Society, and 2020 Elsevier.

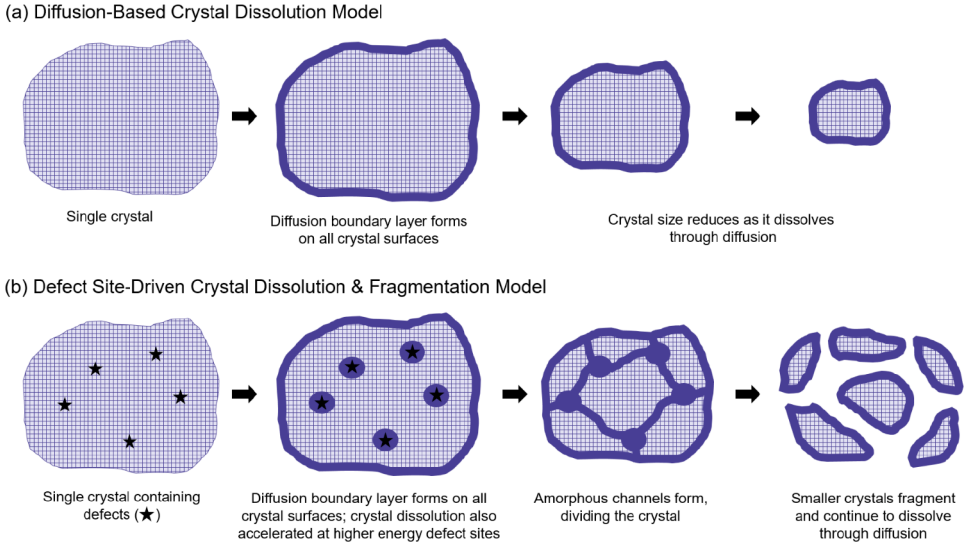

Figure 5. Models of crystal dissolution into polymer melts: (a) diffusion-based crystal dissolution and (b) defect-site driven crystal dissolution and fragmentation. Figure reprinted with permission from ref 31. Copyright 2019 American Chemical Society.

variables to achieve complete dissolution.[41,61] Kinetics of dissolution are accelerated by high surface area, high diffusion coefficients, high temperatures, and intense mixing kinetics through operating parameters and equipment design. Examination of residual crystals, i.e., those incompletely dissolved or destroyed during thermal processing, using transmission electron microscopy (Figure 4) suggests dissolution mechanisms beyond diffusion.[31,62] Under thermal exposure in the absence of mixing, accelerated dissolution kinetics were observed due to crystal defects, which served to increase available surface area for dissolution, via a fragmentation mechanism (Figure 5).[31] In a processing environment, this same phenomenon was observed experimentally and confirmed with population balance modeling of the hot melt extrusion process using input materials with various particle attributes (e.g., particle size, defect density), demonstrating the relevance of the mechanism to the formation of ASDs.[41] In the HME process, fragmentation could result both from

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accelerated dissolution at defect sites, but also through mechanical breakage at these same sites, where the crystal is weaker. The body of evidence thus far suggests that using crystals of greater defect density can accelerate amorphization kinetics for ASD formation.[31,41,62]

3.3. Crystal Creation Pathway. The more commonly considered pathway is that of crystal creation: nucleation and crystal growth (Figure 2b). An amorphous solid or supersaturated solution will ultimately crystallize to the stable form. This conversion will happen over a time scale depending on the crystallization tendency of the compound, as well as thermodynamic driving forces and kinetic factors. Depending on kinetics and other process parameters, nucleation or growth can compete for the consumption of supersaturation in the amorphous solid.[63] Upon storage of an ASD, crystals nucleate and grow in the ASD intermediate or drug product. The common rule-of-thumb to achieve a stability period of years is that a storage condition must be 50 °C below the sample's T_g.[64] However, there are several reported examples of ASDs having achieved long-term physical stability of years at much less stringent stability conditions.[65,66] Several review articles are available which cover the topic in depth.[19,67,68]

Many physical stability risk factors have been identified in the literature, which include the drug's crystallization tendency,[69−71] polymer selection and intermolecular interactions,[72−74] the overall molecular mobility of the system,[64] the use of a high drug loading which the polymer cannot stabilize,[13,14,75] and water-induced plasticization and/or phase separation.[76,77] Therefore, selection of appropriate storage conditions and packaging is of considerable importance for an ASD formulation during its shelf life and once out of its primary packaging and dispensed to patients. A risk-based approach was recently outlined by Liu and co-workers.[78]

3.3.1. Crystallization Considerations Based on Theoretical Aspects. 3.3.1.1. Nucleation. The formation of crystals begins with nucleation. Nucleation may take place in the absence of crystalline matter (primary nucleation, higher activation energy barrier) or in systems where crystals are present (secondary nucleation, lower activation energy barrier). Classical nucleation theory (CNT), although originally derived for condensation of a vapor into a liquid, is the most widely used theory to describe the nucleation process of crystals from supersaturated solutions.[79] The formation of a stable nucleus occurs when individual molecules orient themselves in a lattice structure to form a critical nucleus of sufficient size to resist dissolution. Below the critical size, the nuclei formed are unstable and can redissolve.

The nucleation rate, J, is the number of nuclei formed per unit time per unit volume, which can be expressed by eq 4

$$J = A \exp\left[\frac{16\pi\gamma^3\nu^2}{3(k_B T)^3(\ln S)^2}\right] \tag{4}$$

where A is a constant, γ is the interfacial tension, υ is the molecular volume, k_B is the Boltzmann constant, T is the temperature, and S is the supersaturation. Supersaturation, a measure of the excess chemical potential relative to the reference state (the crystalline solid), can be expressed by eq 5

$$\ln S = \frac{\mu - \mu^*}{RT} = \ln\frac{a}{a^*} \quad \ln\frac{\gamma c}{\gamma^* c^*} \tag{5}$$

where μ is the solute chemical potential in the supersaturated solution, c is solute concentration, a is solute activity, γ is the solute activity coefficient, and * is the property at saturation (i.e., for a solute in a solution in equilibrium with the crystal). For dilute aqueous solutions without solubilizing components, it may be reasonable to assume that γ/γ^* is 1, leading to expression of the supersaturation ratio, S, in terms of the relative concentrations (eq 6).

$$S = \frac{c}{c^*} \tag{6}$$

These equations provide insight into the role of temperature and supersaturation on nucleation rate, in that higher temperatures and supersaturation will increase nucleation rates. Due to the stochastic nature of the nucleation process, faster agitation rates (in solution) will promote nucleation. Molecular interactions between the drug and additives may interfere with or promote the self-assembly process.[80]

Because nucleation requires an activation energy barrier to be overcome, the extent of supersaturation is a critical parameter in determining if crystallization will be observed. It is well-known that there often exists a metastable zone, where nucleation is thermodynamically favored because the solution is supersaturated, but crystallization is not seen over the observation time scale. Thus, the extent of supersaturation rather than the existence of supersaturation per se is an important consideration. Supersaturation does not always indicate that a solution will crystallize over a relevant time frame, and solutions with low extents of supersaturation can persist for long periods of time. Furthermore, additives such as polymers may change the metastable zone width;[81] polymers that inhibit nucleation allow higher supersaturation to persist for longer periods of time.[82]

3.3.1.2. Crystal Growth. After the formation of stable nuclei, the crystal growth rate process begins. Growth depends on many external and internal factors. External factors such as temperature, supersaturation, solvent, and presence of impurities or additives will affect the type of interactions at the liquid−solid interface. Internal factors such as the three-dimensional crystal structure and crystal defects will be determined by the nature and strength of the intermolecular interactions between the solution species and crystal surface.[63,83] The different growth rates of each crystal face govern the resulting morphology of the crystal.[83,84]

Crystal growth can be described as a diffusion−reaction model, where a diffusion process transports molecules from the bulk liquid to crystal surface and the solute molecules arrange at the crystal surface where they integrate into the crystal lattice. The overall growth rate per unit area, R_G, combines the diffusion-controlled and reaction-controlled growth rates into eq 7

$$R_G = K_G(C_x - C_{eq})^g \tag{7}$$

where K_G is the overall crystal growth coefficient, $C_x - C_{eq}$ describes the driving force for crystal growth, and g is the order of the crystal growth process.[63] Studies have shown that polymers can reduce crystal growth rates, and the underlying mechanism has been attributed to adsorption of the polymer onto the crystal surface which interferes with the ability of the solute molecule to integrate into the crystal lattice.[8,85,86] As crystal growth proceeds, supersaturation is reduced because the excess solution concentration decreases as molecules transfer from the solution phase to the growing crystals. As the supersaturation decreases, the growth rate decreases. When growth inhibitors are present, growth may be arrested even

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though supersaturation still persists in the solution.[87,88] This is an important concept, because it means that even though crystallization has occurred, when polymers are also present in solution, the concentration may not return to the equilibrium crystalline solubility over a relevant time frame.

3.3.1.3. Melt Crystallization. The general principles discussed above apply to solution-mediated crystallization but also take place in supercooled liquids, i.e., melt crystallization. In addition, it should be highlighted that, for crystallization from supercooled liquids and glasses, molecular mobility is often the rate-limiting step in crystallization. In other words, although the thermodynamic driving force is favorable to nucleation and crystal growth, the hindered molecular mobility in a deeply supercooled liquid or glass prevents or substantially delays molecular self-organization. The reader is referred to several reviews on crystallization of pharmaceutical amorphous glasses and miscible amorphous-excipient systems.[19,89−92]

3.3.2. Nucleation and Crystal Growth Due to Processing. Nucleation and crystal growth may take place as a result of manufacturing processes. In solvent-based processing, the solvent and polymer system must adequately solubilize/stabilize the drug in the amorphous form upon solvent evaporation. In a cosolvent system, if solvent evaporation rates are dissimilar, drug may be susceptible to recrystallization (or phase separation) due to insufficient solubility in the more slowly evaporating solvent, combined with a high mobility.[22,93] Moisture is an additional risk factor for phase separation and crystallization, if present in the solvent system or if uncontrolled relative humidity (RH) conditions are found in the manufacturing environment.[94,95] For solvent-based processing, the secondary drying step to remove residual solvent could take place hours later. During this time, the overall system mobility is higher due to the residual solvent, which could be a risk factor for crystallization. In thermal processing, the cooling rate must be sufficient to maintain the amorphous form of the drug through temperature zones where nucleation and crystal growth are favored and mobility is high.[75] Crystallization may also take place following thermal or solvent-based processing if the drug loading is too high for stabilization by the polymer.[13,75] These concepts can be described by a ternary phase diagram representing the drying process (Figure 6), where the thermodynamic or kinetic stability may or may not be achieved based on the spray drying conditions selected.[96] An excellent series of papers by Sadowski and co-workers further expand on this design space to address many additional factors including solvent selection, multisolvent systems, miscibility gaps during drying, liquid−liquid phase separation in the supersaturated spray feed during drying, and crystallization.[93,96−100]

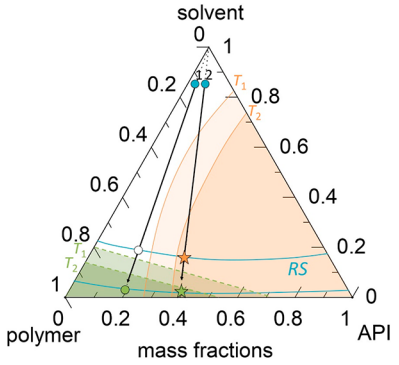

Figure 6. Schematic drying process in a ternary system consisting of API, polymer, and solvent. The API solubility at different drying temperatures T_1 and T_2 ($T_2 > T_1$) are indicated by orange lines, where the orange region represents where the API is supersaturated. Blue lines indicate the residual-solvent (RS) contents represented by achieving different extent of drying completion. Glass transitions at different system temperatures are shown as green dashed lines, and green regions represent the system being below the glass transition temperature. The drying process is illustrated for two different initial feeds (with API loads equal to 0.2 and 0.4 in the solvent-free ASD, blue circles 1 and 2) by black arrows resulting in a thermodynamically stable ASD above glass transition (white circle), a thermodynamically and kinetically stable ASD (green circle), a thermodynamically unstable and kinetically metastable ASD (orange star), or a thermodynamically unstable and kinetically stabilized ASD below glass transition (green star). Figure reprinted from ref 96 per open access terms associated with Creative Commons CC-BY license.

4. CRYSTALLINITY DETECTION METHODS AND IN VITRO PERFORMANCE TESTING

4.1. Solid-State Detection Methods. Detection of crystallinity in ASDs is a significant analytical challenge. Orthogonal analytical tools should be employed to develop a holistic assessment of the sample properties, with an understanding of the limitations which stem from the properties of the instrument, method, or sample. The need to detect low levels of crystallinity is significantly hindered by dilution of the ASD powder into a matrix of excipients within a drug product. An additional complexity is the unsuitable nature of many of these characterization tools in a quality control (QC) manufacturing environment but which may find usefulness during product development.

X-ray powder diffraction is the most common tool for crystallinity detection[101] but has relatively poor sensitivity to detect low levels of crystalline content, limited by mass fraction and dilution, crystal quality, and method parameters.[9,30,101−104] Solid-state nuclear magnetic resonance spectroscopy (ssNMR) is a powerful technique to distinguish small fractions of crystalline material in a primarily amorphous sample, although is not commonly available as a quality control tool.[105] For example, using ^{19}F ssNMR methods, 0.04% crystallinity was quantified in an ASD tablet containing a fluorinated drug.[106] It should be noted that this result may not be generalizable to all drugs or drug products, depending on fluorine content (or lack thereof) and instrument parameters. Differential scanning calorimetry (DSC) can effectively demonstrate that a single glass transition (T_g) is formed for the ASD system, although it may yet be inhomogeneous on a smaller length scale, which may lead to physical instability.[12,107] DSC is relatively ineffective at identifying crystallinity in miscible drug−polymer systems, because the dynamic heating process can induce crystal dissolution, and detection is further limited by mass fraction and domain size.[9,30,43,102] Other techniques have been used to detect crystallinity, such as terahertz spectroscopy,[108] mid-infrared spectroscopy (MIR),[109,110] near-infrared spectroscopy (NIR),[111,112] and Raman spectroscopy.[113]

Several microscopy techniques are also capable of differentiating amorphous and crystalline content. Polarized light microscopy (PLM) is highly sensitive to detect the presence of crystallinity, even in an X-ray amorphous sample,[75] but resolution is limited by the diffraction limitation and thus it may not detect very small crystals. Crystals in hot melt extruded ASDs have been regularly identified to be smaller

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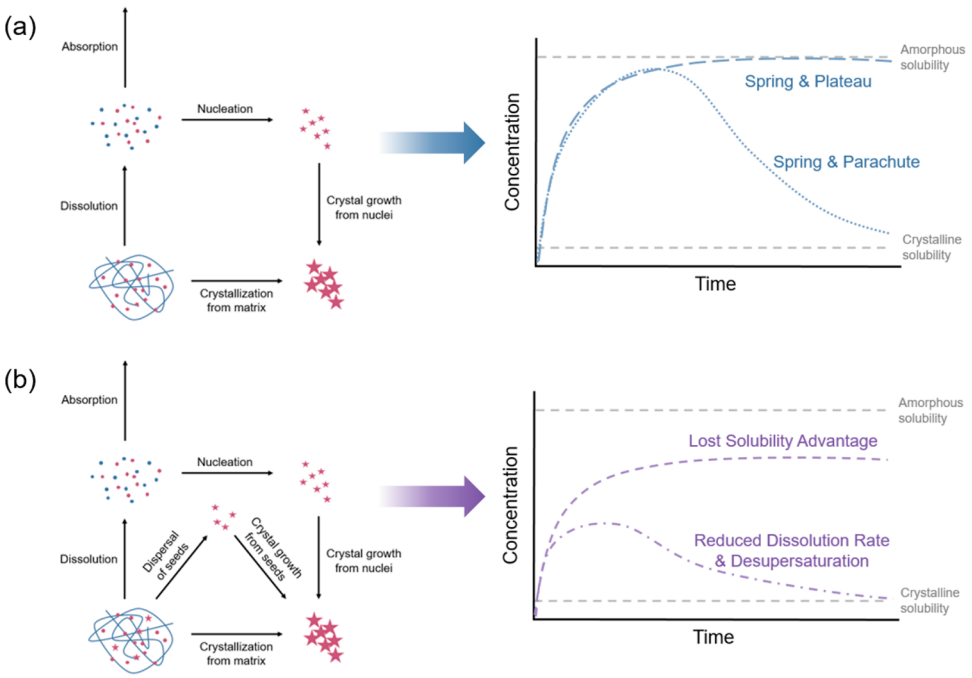

Figure 7. Pathways of dissolution and crystallization and resulting idealized dissolution profiles of amorphous solid dispersion (a) without crystallinity and (b) containing crystallinity. Figure adapted and reprinted with permission from ref 8. Copyright 2020 Elsevier.

than 1 μm[8,9,62,114] and as small as 5−10 nm.[62] Transmission electron microscopy (TEM) is highly sensitive but low throughput to identify crystals in amorphous systems through electron diffraction.[62,114] Scanning electron microscopy (SEM) can be used to detect trace crystallinity based on their distinctive shape but is only useful for detecting surface crystals.[115,116] Second harmonic generation is highly sensitive to noncentrosymmetric systems, enabling quantification of trace crystallinity in the parts per billion range.[117−119] X-ray micro computed tomography (microCT) is useful to identify low levels of crystallinity (<1%), but resolution is limited to crystals ∼10 μm or greater.[120]

4.2. Release Testing. In vitro release testing has also been observed to be more sensitive to the presence of crystals or other phase behavior changes in amorphous formulations than most other analytical techniques.[121−125] However, typical experimental variability of ±5% indicates that detection of <10% crystallinity might not be possible in a QC environment.[124] This suggests that release testing may be an appropriate challenge test by which to validate solid-state methods which can detect the necessary level of crystallinity which may be considered significant for that specific formulation. However, optimizing release test variables to address the complexity of ASD formulations, in terms of drug physicochemical properties (e.g., crystallization tendency), level of crystallinity, crystal reference material selection, and formulation characteristics is a tremendous challenge.[124] A recent publication by the IQ Consortium Dissolution Working Group reviewed challenges of dissolution testing to detect crystallinity in amorphous solid dispersions and presented case studies.[126]

Even when crystallinity is detected, does it matter to the performance of the product? What level of scrutiny is sufficient, enabling appropriate specifications to be established? The ICH Q8(R2) guideline states that "scientific understanding to support the establishment of the design space, specifications, and manufacturing controls" should be provided.[127] Certainly, a well-designed in vivo study would provide the ideal metric to answer to this question; however, in some scenarios, such as with medications designed for oncology populations, such testing may have ethics concerns. Well-designed dissolution studies to detect drug release can illuminate this question. The goal of a release test for supersaturating systems is to provide an in vitro quality control tool with sufficient discriminating power to link product changes (e.g., interbatch variability, manufacturing process, formulation) to clinical performance.[128,129] With complex formulations such as amorphous solid dispersions, traditional sink conditions have little relevance to the biopharmaceutical performance.[80] Nonsink conditions enable evaluation of both release and crystallization kinetics of supersaturating systems and are thus essential for assessing the product performance.[80,130−132] Further, noncompendial testing methods including an absorptive compartment can be used to link formulation changes and release profiles with a more in vivo relevant platform.[133−136]

Sink and nonsink conditions can be defined by the dimensionless sink index (SI),[80,137,138] where the following equations represent sink index with respect to crystalline solubility (eq 8) and amorphous solubility (eq 9):

$$\mathrm{SI}_{\mathrm{cr}} = \frac{C_{cr}}{\mathrm{dose}/V} \tag{8}$$

$$\mathrm{SI}_{\mathrm{am}} = \frac{C_{\mathrm{am}}}{\mathrm{dose}/V} \tag{9}$$

where C_{cr} and C_{am} represent the crystalline and amorphous solubility respectively, *dose* is the amount of drug added to the dissolution experiment, and V is the media volume. Several studies have begun to illuminate the predictive quality of a dissolution test based on sink index, representing the driving force for dissolution and crystallization, for detecting or

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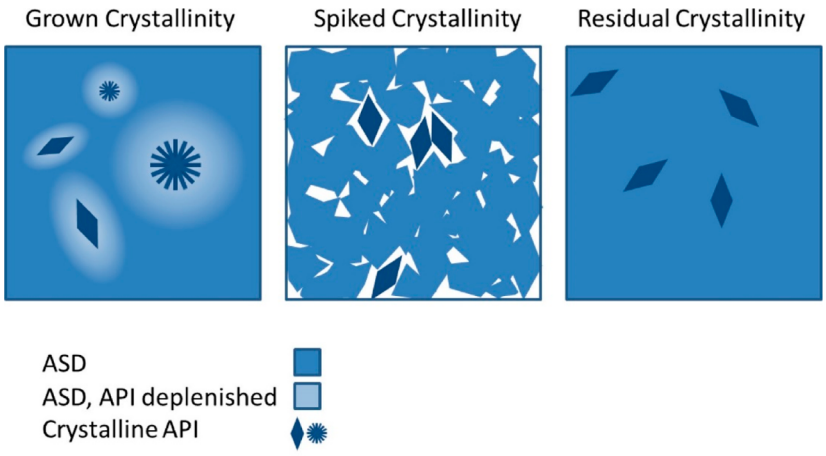

Figure 8. Schematic description of three types of crystallinity found in ASDs and used for performance testing risk assessment: grown crystallinity, spiked, and residual crystallinity. Although quantities of crystals on a mass basis are equivalent in each case, differences in detectability or dissolution performance impact may arise for different analytical methods. Figure reprinted with permission from ref 6. Copyright 2022 Elsevier.

evaluating the impact of crystallinity on the dissolution performance of an ASD.[9,139,140] It should be noted that amorphous solubility is defined as the concentration at which a liquid−liquid phase separation event may be observed,[126,141] and this value may change depending on the composition of the amorphous drug−polymer system and media additives.[142−146]

Pathways of dissolution and crystallization resulting from the idealized ASD dissolution profiles at $SI_{cr} < 1$ and $SI_{am} = 1$ dose conditions are shown in Figure 7. In this scenario (Figure 7a), all amorphous material can theoretically dissolve to create a supersaturated solution, given sufficient driving force for dissolution and an absence of crystallization (the "spring and plateau" profile) and be absorbed. If crystallization occurs, desupersaturation will be observed (the "spring and parachute" profile). In systems containing crystallinity (Figure 7b), crystal seeds now can influence the resulting dissolution profiles, and two corresponding profiles can be anticipated.[8,80] First, the extent of supersaturation that can be achieved is proportional to the level of amorphous content, in essence a lost solubility advantage. Any crystalline content is essentially inert, as it has no driving force for dissolution, and crystals do not grow. In the second scenario, reduced dissolution rate and desupersaturation are observed due to crystal growth occurring immediately upon dissolution. It is readily apparent that the first scenario is preferable, and crystallinity would represent a relatively low-risk to product performance. The reduction in area under the dissolution curve in the second scenario would translate to a significant reduction in bioavailability.

The scenario of $SI_{am} < 1$ dose conditions represents an even more likely biorelevant scenario for amorphous solid dispersions, where fluid volumes are low and doses are high. Achieving concentrations in excess of the amorphous solubility has been shown to result in the formation of colloidal, drug-rich aggregates, i.e., the occurence of liquid−liquid phase separation (LLPS). These in turn have been shown to result in increased bioavailability due to a reservoir effect,[147−149] where recent studies suggest that an increased number of colloidal species help to maintain a concentration closer to the amorphous solubility at the membrane surface, thereby improving flux.[150−152] For this favorable process to occur, crystallization must be prevented. The presence of crystals in a formulation may reduce the achievable supersaturation through crystal growth mechanisms.

Another approach that has been investigated to detect crystallinity within a dissolution test relies on differences in dissolution rate associated with each solid-state form.[125] There are several concerns with this approach. First, extensive control over the particle surface area distribution is required in order to eliminate this source of variability. Next, the applicability of such a method is limited to the ASD drug product intermediate only, as the excipient matrix of a drug product will impact release rates. Other sources of batch-to-batch variability may be found within the drug product which may also impact the release rate.[140,153] This approach is also limited to a subset of ASDs in which the release rate is governed only by the amorphous form and not impacted by the polymer carrier where congruent release of drug and polymer are observed.[154] Lastly, as most amorphous compounds have release rate advantages of 2−20× over their crystalline counterparts,[141] sufficient discriminating ability may not be found for many compounds.

4.3. Reference Materials. When investigating the impact of crystals on an amorphous formulation in dissolution performance testing, the source of those crystals should be scrutinized. Crystals can be of three basic origins, as described earlier: (1) crystals grown within the ASD, (2) spiked/seeded crystals, or (3) residual from the manufacturing process (Figure 8). The properties of these crystals are potentially quite different in particle size/surface area, crystal habit, polymorphic form, and matrix environment, and their resulting contributions to product performance can also be expected to vary. The key property of crystal seeds is how they drive crystal growth, which is directly related to surface area as well as other properties, but notably not related to their mass amount. Thus, bulk crystalline material is not well-suited to mimic intrinsic crystals that may be found in an amorphous solid dispersion resulting from a nucleation and growth or a crystal dissolution pathway (Figure 2). These differences in reference materials were highlighted in a recent industry white paper.[6]

Grown crystals are useful to represent the impact of stability performance failures. These crystals may be small or large, depending on the extent of crystallization or the conditions under which they were grown, and could be of multiple polymorphic forms. Residual crystals have a manufacturing

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failure origin. In the case of a hot melt extrusion process failure, they are most likely to be the thermodynamically stable form and may exist as nanometer-scale crystals or as relatively few but large crystals.[41,62] Alternately, if the crystals have nucleated (as in a spray drying process failure), they could be of multiple polymorphic forms. Generally, regardless of origin, residual crystals are likely to be at the nanometer-scale (<1 μm) and likely to have high surface area and defect density.[8,62] Both grown and residual crystals will have intimate contact with the polymeric matrix, which may slow or inhibit crystallization. Grown crystals may have higher polymer concentration in the immediate vicinity of nucleated crystal, where the API has been depleted due to incorporation into the nucleated crystals.[155] Nucleation events need not be detectable by common methods in order to have significant product performance impact.[156,157]

Spiked (or seeded) crystals represent a departure from most of those expected properties. Spiked crystals would be those added from a source of bulk drug crystals, so they would be of defined polymorphic form and particle size distribution. Notably, because these crystals are quite likely to be comparably large (>10 μm) and were grown under controlled conditions, they have low surface area and defect density compared to either other source of intrinsic crystals. Lastly, spiked crystals do not have intimate contact with the matrix environment to initiate interactions. These crystals would be generally expected to grow much more slowly and impact the performance of the ASD to a lesser extent.[158] It is worth noting that spiked crystals enable the use of different polymorphic forms to assess their impact on dissolution and precipitation properties.[159]

A related caution is the consideration of crystallinity on a weight % basis. The same 10% crystallinity from spiked crystal represents far lower surface area and lack of intimate interactions than that from grown or residual crystals of smaller size. Hence, establishing acceptable limits based on spiked crystals is particularly challenging, as these measures likely underpredict the impact of grown or residual crystals. Thus, use of dissolution tests as a direct surrogate for solid-state quantification is particularly challenging.[10,124]

5. CASE STUDIES

Now that the framework for understanding the origin and significance of crystallinity in ASDs has been established, reviewing examples from the literature will enable us to look at limitations of crystallinity detection methods, design of performance tests, and outcomes for different scenarios. The following case studies were selected to cover a range of model compounds and manufacturing methods and to illuminate different crystallinity formation pathways.

5.1. Case Study 1: Indomethacin/PVPVA HME ASDs.

Indomethacin/PVPVA was used as a model drug−polymer system to investigate the correlation of temperature−composition phase diagrams and thermodynamic solubility on crystallinity of ASDs produced by HME.[30] A formulation critical temperature of 131 °C was found for the 50% DL, indicating that all crystalline drug could be solubilized in the molten polymer at that temperature (Figure 9a). Using temperatures at or above the formulation critical temperature (T_c), a fully amorphous extrudate could be prepared, given sufficient residence time. At temperatures below the T_c, residual crystallinity, as detected by XRPD, remained regardless of temperature or residence time (Figure 9b). The

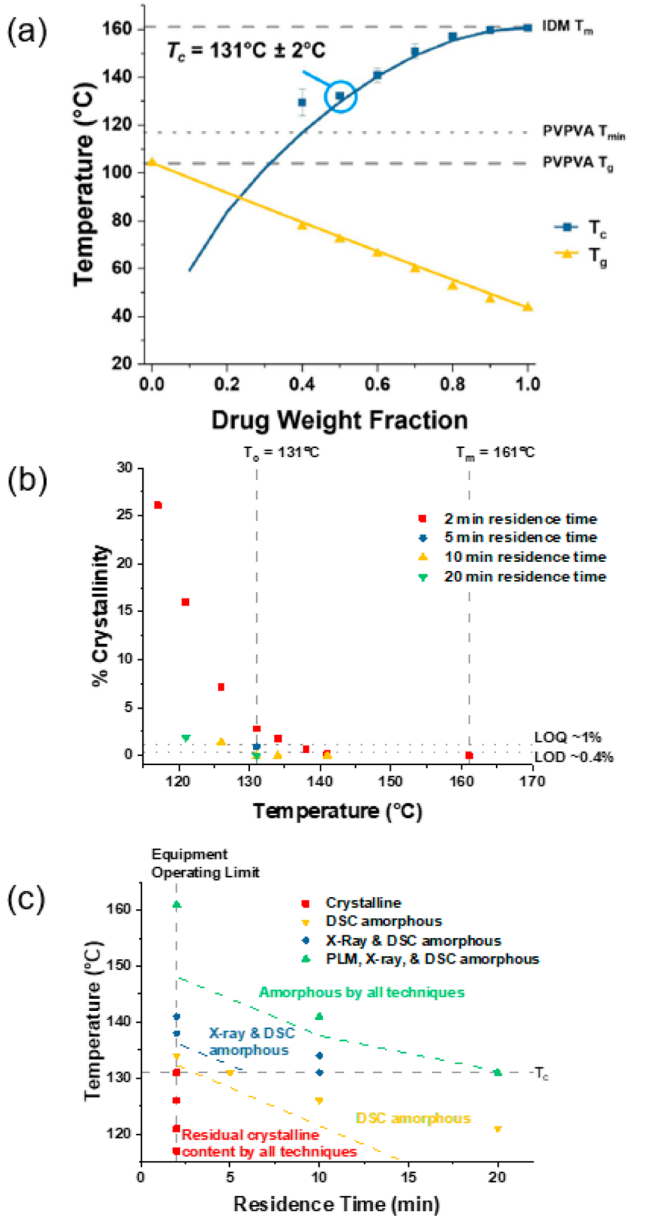

Figure 9. (a) Indomethacin/PVPVA temperature−composition phase diagram. (b) Percent (%) crystallinity vs processing temperature for ASD samples produced by HME. (c) Process operating design space (temperature vs residence time) demonstrating differential sensitivity among crystallinity detection methods. Figure adapted and reprinted with permission from ref 30. Copyright 2018 Elsevier.

process operating design space (processing temperature vs residence time) enabled a sensitivity comparison of several crystallinity detection methods (Figure 9c). PLM, although nonquantitative, was found to be more sensitive than XRPD, and both were more sensitive than DSC to crystallinity in some formulations. In a formulation prepared at the T_c and for the longest residence time used, which was found to be amorphous by PLM, XRPD, and DSC, crystals as small as 5−10 nm were observed by TEM.[62]

Nonsink dissolution profiles of indomethacin/PVPVA ASDs containing 0−25% residual crystallinity demonstrated a loss in achievable supersaturation (Figure 10a).[8] Dissolution profiles of physical mixtures of a fully amorphous ASD and spiked crystals to represent 0−40% crystallinity demonstrated a

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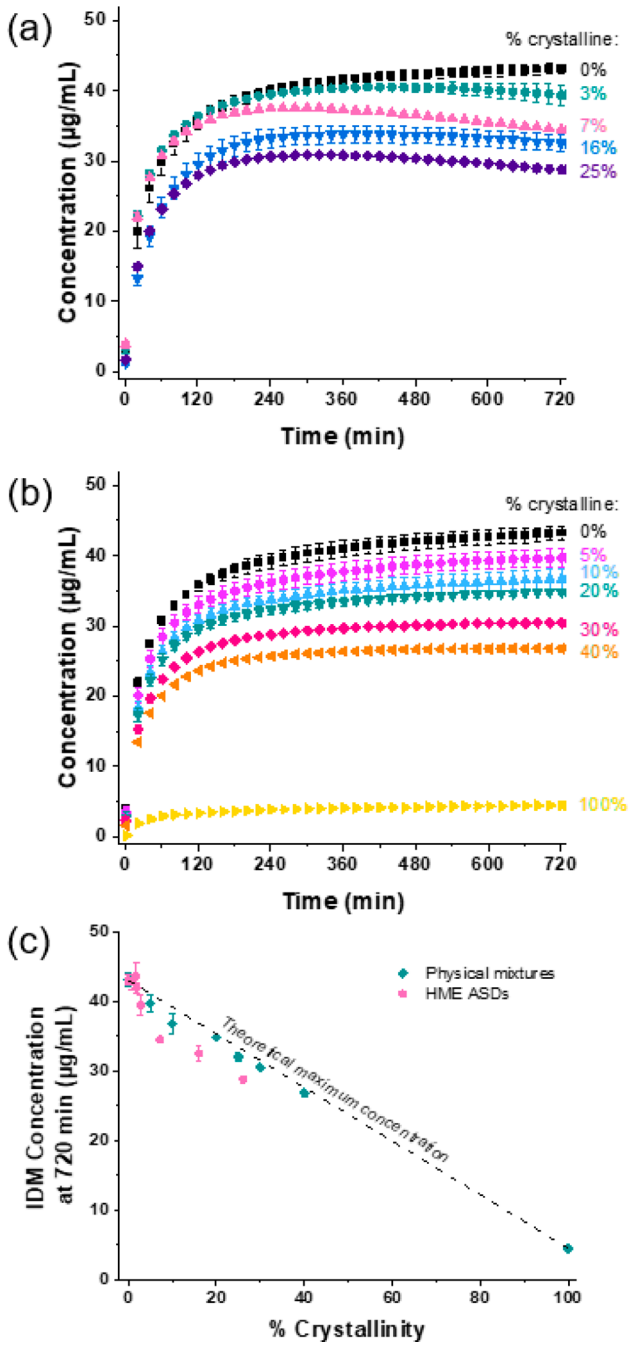

Figure 10. Dissolution profiles of (a) indomethacin/PVPVA ASDs prepared by HME containing 0−25% residual crystallinity and (b) indomethacin/PVPVA physical mixtures (PM) of ASD prepared by solvent evaporation (SE) and crystalline drug to yield a crystalline content of 0−40%. (c) Comparison of theoretical maximum concentration based on crystalline content and achieved dissolution concentration from HME ASD or SE ASE/PM samples. Figure adapted and reprinted with permission from ref 8. Copyright 2020 Elsevier.

similar loss in achievable supersaturation (Figure 10b). For both types of preparations, the loss fell along the theoretical maximum concentration which corresponds to the level of amorphous content in the preparation (Figure 10c). This indicates that the crystal seeds present in the mixture do not grow, and dissolution rates are not affected. Adsorption of the polymer onto the crystal surfaces was shown to prevent/slow crystal growth. The HME ASDs had slightly lower achievable concentration, which was hypothesized to be due to the greater surface area and surface energy of the residual crystals in comparison to the bulk crystals used in the physical mixtures or systematic underestimation of crystalline content in HME ASDs by the XRPD quantification technique.

5.2. Case Study 2: Bicalutamide/PVPVA HME ASDs. Similar to the indomethacin/PVPVA system, melting point depression was also observed for bicalutamide/PVPVA ASDs, where a formulation critical temperature of 145 °C was determined.[9,41] HME ASDs were prepared using processing conditions which enabled a fully amorphous ASD to be prepared, as well as three samples with crystallinity up to 30%. One crystalline sample was considered to have less than 1% crystallinity, whereby the level was not detectable by XRD but could be observed by TEM.[9]

The nonsink dissolution profile of the fully amorphous bicalutamide/PVPVA ASDs indicated matrix crystallization (Figure 11a), as complete drug release was not achieved and desupersaturation was not observed (which would be due to solution-mediated crystallization). Time lapse imaging by polarized light microscopy showed nucleation at the solid−liquid interfaces, confirming the matrix crystallization pathway (Figure 11b). The metastable polymorph was formed through this crystallization pathway (Figure 11c). For samples containing crystallinity, distinctly lower supersaturation was achieved, because of rapid crystal growth of the stable polymorph within the amorphous solid (Figure 11a,b,d). The dose conditions were modulated within the study, and matrix crystallization was observed to occur in samples containing crystallinity even under sink conditions, highlighting the detrimental impact of even <1% crystallinity within this drug−polymer system.[9] Follow-up studies regarding the matrix crystallization pathway of bicalutamide/PVPVA ASDs indicated that risk factors for matrix crystallization included high drug loading above the system's limit of congruency (LoC) and processing which mechanically activated the sample.[160]

5.3. Case Study 3: Comparison of Spray Drying and HME To Prepare Naproxen/PVP ASDs. A study by Haser et al. investigated the formation and physical stability of 30% and 60% drug-loaded naproxen/PVP ASDs through two manufacturing methods: spray drying and hot melt extrusion.[75] Fully amorphous ASDs could be prepared at 30% drug loading, and no crystallization was observed after 8 weeks storage at 40 °C (Figure 12). Crystallinity was detected in the 60% drug loading ASDs directly after manufacture by both spray drying (6%) and hot melt extrusion (0.4%), indicating that the drug loading was beyond what the polymer could stabilize, and that the mobility of the drug during the solvent drying process was greater than that in the melt during cooling or that the thermodynamic driving force for crystallization was higher during spray drying. Upon stability storage, the level of crystallinity increased in both samples, from 6% to 22% in the spray dried sample and 0.4% to 3% in the hot melt extruded sample.

5.4. Case Study 4: Kinetisol Processing Condition Selection To Balance Degradation and Crystallinity. In Kinetisol processing to form ASDs, increased high shear mixing may result in greater degradant levels but lower crystallinity. For a shear sensitive drug, a balance may be sought to find processing conditions where acceptable thresholds of both CQAs could be achieved. In a study by

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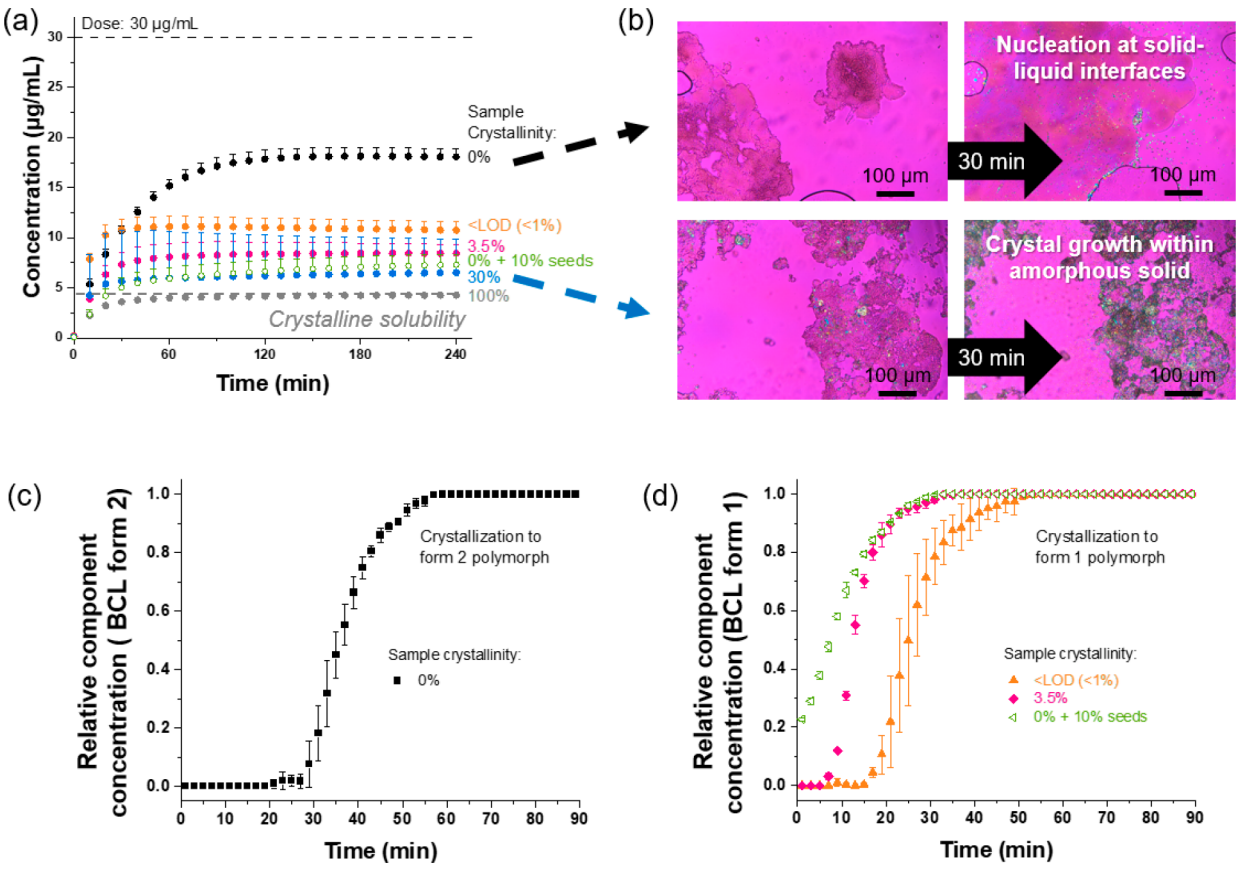

Figure 11. (a) Dissolution profiles of bicalutamide/PVPVA ASDs prepared by HME containing 0−30% residual crystallinity. (b) Polarized light microscopy images of ASD particles undergoing matrix crystallization over 30 min. (c, d) Crystallization kinetics of ASD without (c) and with (d) crystalline content, which crystallize to the metastable polymorph (form 2) or stable polymorph (form 1). Figure adapted and reprinted with permission from ref 9. Copyright 2021 Springer Nature.

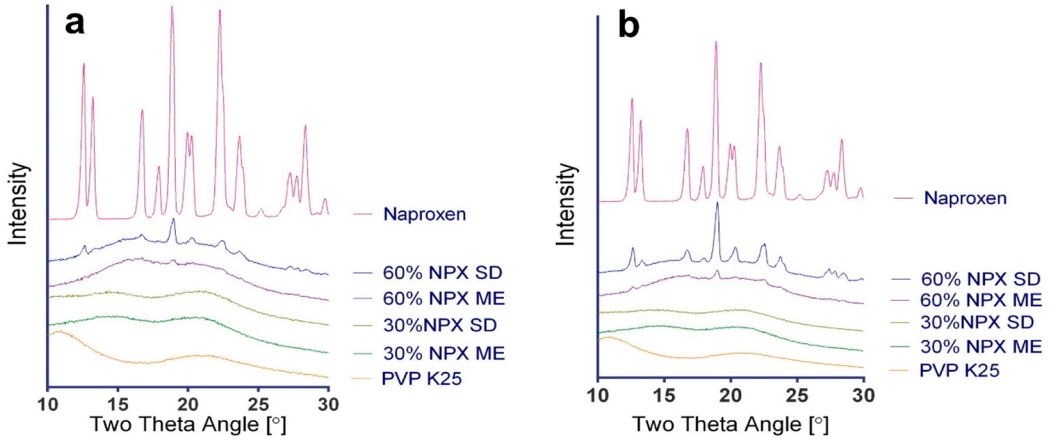

Figure 12. XRPD patterns of naproxen(NPX)/PVP ASDs prepared by spray drying (SD) and hot melt extrusion (ME): (a) initial measurements and (b) following 8 weeks storage at 40 °C. Figure reprinted with permission from ref 75. Copyright 2017 Elsevier.

Davis et al., a shear-labile drug (LY3009120) was processed by Kinetisol under various processing conditions to obtain samples of increasing degradation levels (0.7%, 2.0%, 3.1%) but decreasing crystallinity levels (2.3%, 0.9%, 0.1%).[11] Stability was conducted at 25 °C/60% RH for 4 months, and no increase in degradant products or crystallinity was noted. ^{19}F ssNMR spectroscopy was used for crystallinity quantification, as DSC and XRPD were found to lack the sensitivity required. Nonsink pH shift dissolution testing indicated desupersaturation in the sample containing 2.3% crystallinity but not in samples of lower crystallinity levels. This indicated a threshold where a balance between crystallinity and degradant levels might be found, where suitable product performance objectives could be achieved.

5.5. Case Study 5: Comparison of Spiked and Recrystallized API in Dissolution Testing. A study by Theil et al. investigated the impact of spiked vs recrystallized API in an amorphous formulation.[10] To generate samples with precise levels of recrystallized API, transmission Raman spectroscopy in combination with chemometrics was used to

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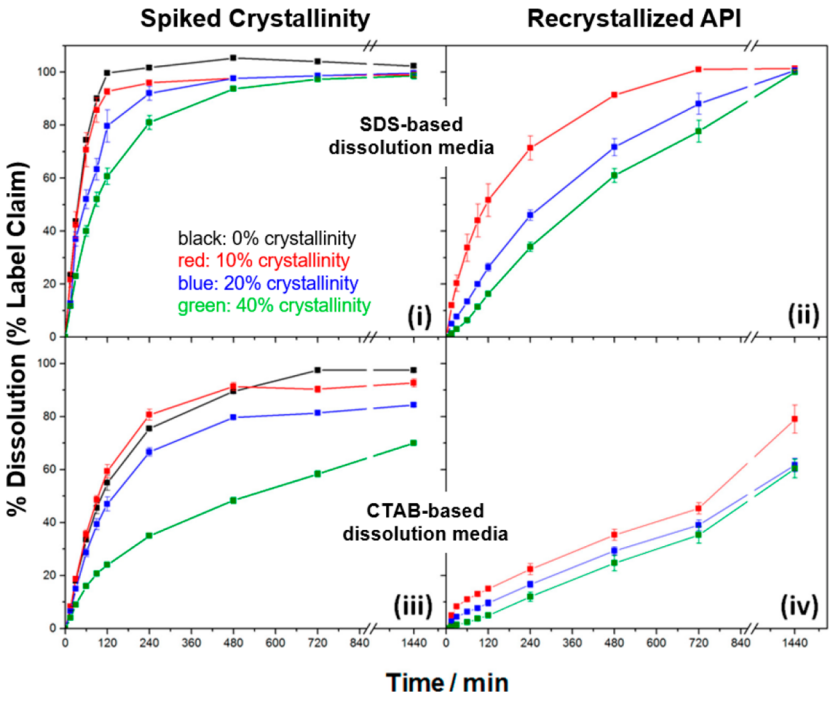

Figure 13. Dissolution profiles of fenofibrate ASD tablets containing 0−40% crystalline API, spiked (i, iii) or recrystallized (ii, iv). Two dissolution methods were used (i, ii: SDS-based dissolution media) and (iii, iv) CTAB-based, which alter the sensitivity of detecting crystals in the formulation. Figure reprinted with permission from ref 10. Copyright 2018 American Chemical Society.

monitor and quantify the level of crystallinity in a tablet exposed to accelerated storage conditions. Two dissolution methods were used, both representing sink conditions but with different media additives, stirring speeds, and media temperatures. Depending on the method used and source of crystallinity, dissolution profiles of samples containing 0−40% crystallinity were nearly indistinguishable or remarkably different (Figure 13). This indicates that development of sensitive dissolution methods to detect crystallinity and determine its potential impact on release is critical to an appropriate risk assessment. In particular, spiked crystals poorly represent the impact of crystals developed within the formulation (either from storage or manufacturing), as has been shown in other studies where crystals of different properties or origin have been used.[8,18,87,140]

5.6. Case Study 6: Tacrolimus ASD Formulations. Dissolution testing of commercial tacrolimus capsules, both fresh and containing different amounts of crystalline drug, were conducted with different dissolution volumes, which modulates the driving force for dissolution and crystallization.[139] The brand, Prograf, was found to be not susceptible to crystallization, while one generic formulation crystallized readily.[161] By exposing the generic formulation to elevated temperature/humidity, tacrolimus could be completely crystallized. Physical mixtures of fresh and crystallized tacrolimus formulation were prepared to yield samples of varying levels of crystallinity. By modulating the sink index through constant dose and varying dissolution volume,[80] the impact of crystallinity could be investigated. At the highest sink index (largest dissolution volume per dose), ASDs containing up to 20% crystallinity showed no marked decrease in achievable supersaturation (Figure 14a). In contrast, at the lowest sink index (lowest dissolution volume per dose), all samples containing crystallinity showed loss in achievable supersaturation as well as desupersaturation due to greater thermodynamic driving force for crystallization (Figure 14b). Interestingly, at both dissolution conditions, the 100% crystallized ASD could achieve concentrations above the crystalline solubility (Figure 14a,b). In a follow up in vivo study in beagle dogs, the 100% crystallized sample similarly outperformed the control crystalline suspension in both AUC and C_{max} (Figure 14c).[18] This observation could result from a few possible reasons: (1) the product cannot be fully crystallized in the matrix, and this cannot be detected due to analytical limitations, (2) the resultant crystals formed in the matrix are highly defective, or (3) the crystals formed are very small which provides for rapid redissolution which somewhat mitigates the conversion to the crystalline state. These general observations highlight the importance of using a representative crystalline material when undertaking risk assessment of amorphous formulations.

5.7. Case Study 7: Physical Stability of Miscible and Immiscible ASDs. Ivanisevic has demonstrated that physical stability under ambient conditions is directly related to the miscibility of the formulated matrix.[13] Broadly, miscible systems were observed to be stable and resistant to crystallization. Systems classified as immiscible, or phase-separated, developed crystals within 1−2 months. All samples were prepared by the solvent evaporation method and were stored under ambient conditions for the duration of stability monitoring. Two examples will be highlighted here.

Nifedipine/PVP (30−70% drug loading) systems were classified as miscible by structure-based, thermal, and spectroscopic techniques.[162] Interestingly, the 70% drug loading sample had some residual crystallinity detected immediately after preparation, which then developed for the first 6 months of stability monitoring and then did not crystallize further (Figure 15a). The total amount of crystallinity was estimated to be less than 10%. Ivanisevic hypothesized that the crystallinity observed was the amount of

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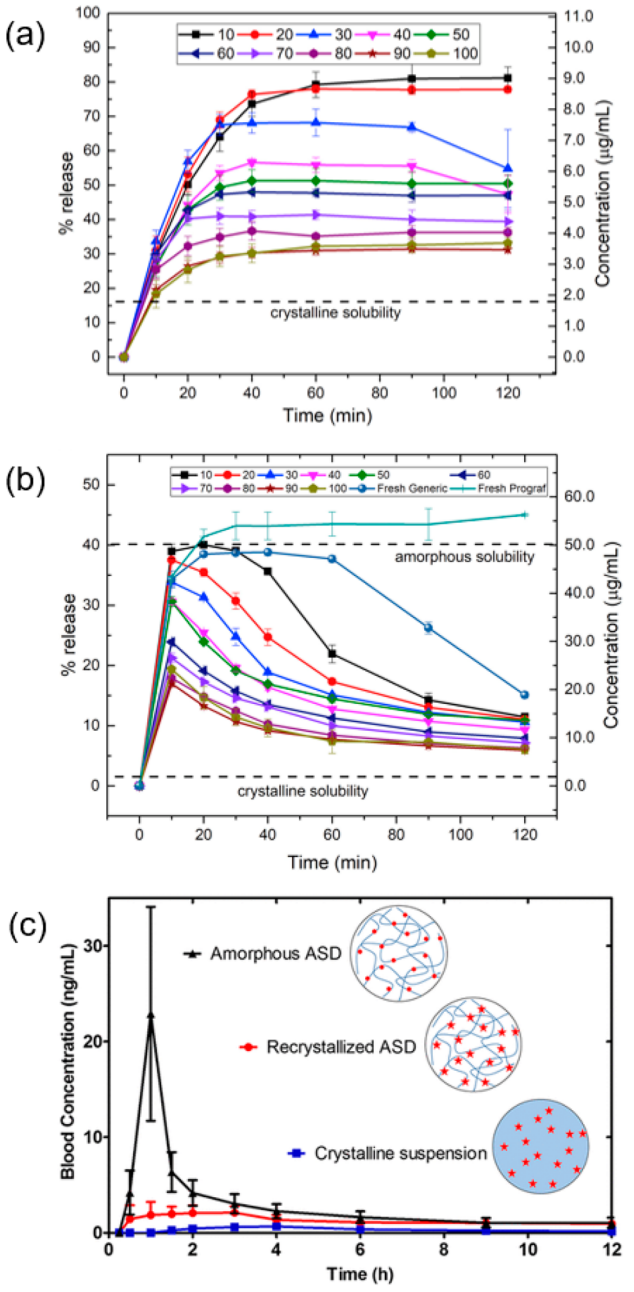

Figure 14. Dissolution profiles of a 5 mg dose of tacrolimus from brand (Prograf) and generic ASDs formulations containing varying levels of crystallinity in (a) 450 mL and (b) 40 mL of dissolution media. (c) Blood concentration vs time of tacrolimus amorphous and crystalline samples. Figure adapted and reprinted from refs 18 and 139. Copyright 2018 Elsevier and 2019 American Chemical Society.

drug not stabilized by the polymer, and that the remainder of the amorphous matrix remained miscible and stable, despite the presence of some crystallinity.[13]

Two formulations of ketoconazole/PVP (30% and 70% drug loading) were observed to be miscible and immiscible/phase-separated. While the 30% drug loading sample did not crystallize within approximately 1 year of monitoring, the 70% drug loading sample crystallized after approximately 2 months, whereby crystallinity extent progressed over the duration of the study (Figure 15b).[13]

While storage conditions with respect to the formulation's properties, such as T_g, were certainly important to the author's

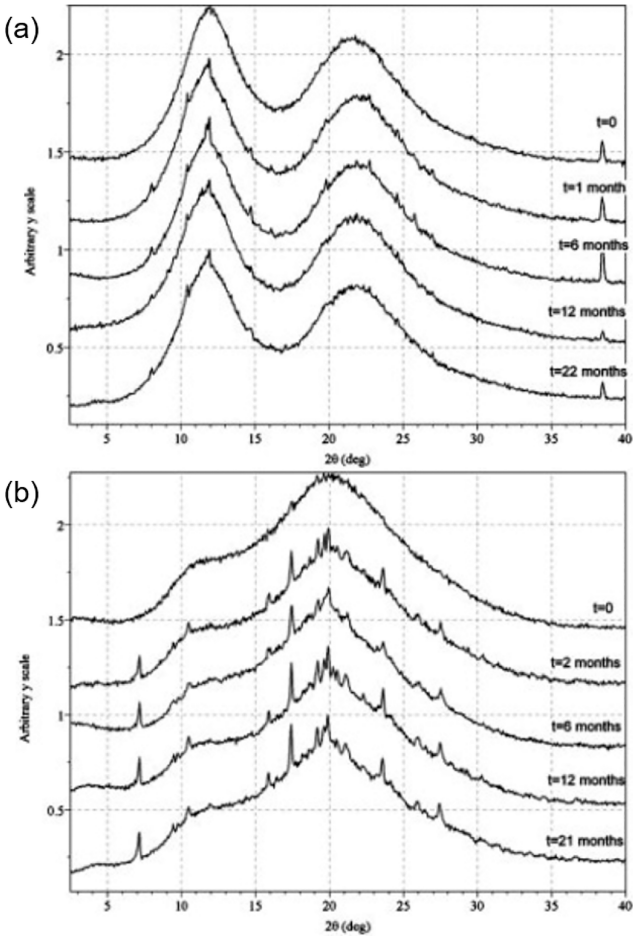

Figure 15. XRPD patterns of ASD samples initially classified as (a) miscible (nifedipine/PVP 70% drug loading) and (b) immiscible (ketoconazole/PVP 70% drug loading) over time. Crystallization initiated in the ketoconazole sample after approximately 2 months and progressed for the remainder of the study. Some crystals were observed in the nifedipine sample initially after solvent-based manufacturing, which grew slightly for the first 6 months and then ceased growing with the total estimated crystalline content less than 10%. Figure adapted and reprinted from ref 13. Copyright 2010 Elsevier.

findings, the study highlights that the properties of the surrounding matrix dominate the ability of any crystalline material, either nucleated during storage or from the manufacturing process, to grow. In this case, the failure mode consisted of the drug loading being too high for the polymer to stabilize.

6. ASSESSMENT OF CRITICAL QUALITY ATTRIBUTES

6.1. Risk Assessment. Through the case studies, several high and low risk aspects of the drug properties, ASD formulation, and crystallization mechanisms were highlighted. These as well as other considerations found in Figure 16 will be discussed, for the purposes of assessing the risk of crystallinity in amorphous formulations. The pyramid structure of risk assessment categories intends to suggest scientific rationale, rather than a sequence, workflow, or decision tree.

6.1.1. Drug Physicochemical Properties. Amorphous formulations take advantage of the thermodynamic solubility advantage found by selecting the amorphous form of a drug. The drug may have several polymorphic forms as well. A first

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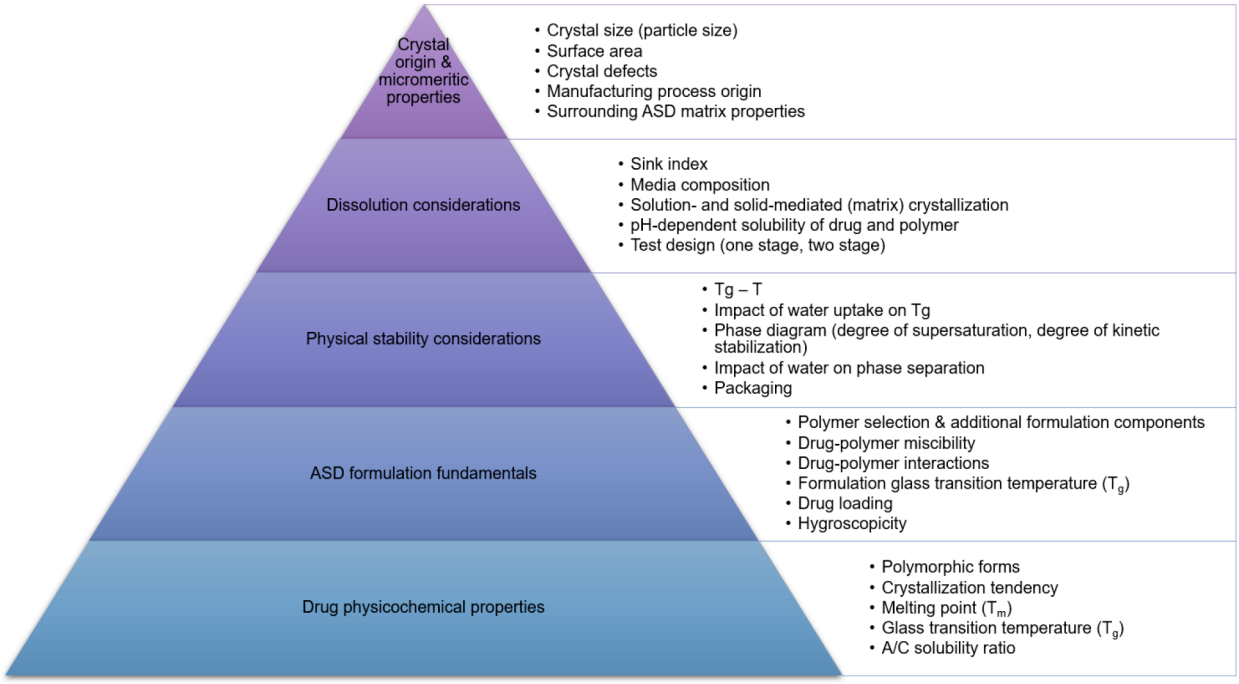

Figure 16. Categories for assessment of risk of crystallinity within amorphous solid dispersion formulations.

consideration regarding risk of crystallinity in an amorphous form is whether or not a crystalline form of the drug molecule exists. For example, ledipasvir and clopidogrel have no known crystalline forms. The existence of polymorphic forms may be advantageous for drugs undergoing crystallization following dosing of an ASD formulation. For example, if crystallization typically occurs from solution to the metastable polymorph, the transient higher solubility of this form enables some level of supersaturation to be maintained with respect to the equilibrium solubility of the thermodynamically stable form until the final polymorphic transformation occurs. However, as was observed in the bicalutamide case study, if crystals of the stable polymorph are found in the formulation, the natural crystallization pathway of the amorphous solid to the metastable form no longer occurs, removing the solubility advantage of the metastable form.[9] In that case, crystallinity (stable polymorph) in the formulation was highly detrimental.

The crystallization tendency of a drug is another risk factor for an amorphous formulation. Classification systems have been developed to categorize drug molecules.[69,163−165] Frequently, crystallization tendency is estimated by applying a cooling/reheating cycle to the melt.[163] Parameters such as molecular mobility and configurational entropy (heat capacity change at T_g) have been used to estimate and predict amorphous stability.[165−167] Certainly, molecular mobility may be modified within an amorphous solid dispersion formulation through incorporation of a high T_g polymer and by "locking in" configuration through drug−polymer interactions. However, these features do not guarantee stability, as phase separation and crystallization may yet occur due to other underlying risk factors or matrix changes due to storage conditions and water uptake.[19] Newman and Zografi have also emphasized that other factors beyond molecular mobility contributed to crystallization of a glass, such as the method used to produce the glass, heterogeneous nucleation due to processing conditions, secondary Johari−Goldstein relaxations, nondiffusional crystal growth in the glass, and surface crystallization.[89]

6.1.2. ASD Formulation Considerations. While this Perspective cannot provide an extensive overview of best practices for formulating ASDs, several main points will be highlighted with the focus on risk factors for crystallization failure within the formulation (i.e., physical stability failure) and within the in vitro/in vivo dissolution environment.

The selection of a polymer contributes to ASD performance both from a stability and dissolution perspective. Reduced risk of physical stability failure will be found with a miscible, high T_g polymer with low hygroscopicity, at lower drug loadings (this is both a thermodynamic and kinetic effect), and in the presence of drug−polymer interactions that reduce crystallization kinetics.[19,67,74,90] Under these circumstances, even in the presence of crystal seeds (i.e., residual crystals from a manufacturing failure), slow crystal growth rates could be expected, as the surrounding matrix has limited crystallization propensity.

In a dissolution environment, the polymer can facilitate dissolution, as well as prolong supersaturation. However, strong drug−polymer interactions in the ASD matrix may impede release performance if they persist in the presence of water.[74,168] Crystal seeds can be detrimental to release performance, by facilitating solution-mediated or solid-mediated (matrix) crystallization. Depending on the propensity for crystal growth, the impact of these seeds can vary widely. Polymer adsorption onto crystal seeds can poison crystal growth.[8] Supersaturation conditions will modulate the thermodynamic driving force for crystallization.[8,9] The matrix crystallization pathway is also reduced by modulation of drug loading.[160]

The impact of additional formulation components has similar considerations. Surfactant inclusion is expected to negatively impact physical stability by T_g reduction.[169,170] Surfactants can also induce a wide variety of phase separation morphologies,[171−173] which can be expected to influence crystallization behavior. Surfactants can facilitate dissolution, but also induce solution phase crystallization.[116,173−180]

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6.1.3. Stability Storage Conditions. Most ASD compositions are likely to be within the thermodynamically metastable and kinetically stable zone (Figure 3a, region 2) at ambient storage conditions, and many studies have investigated aspects of kinetic stabilization.[19,56,65,66,181] The temperature−composition phase diagram found in Figure 3a is for a water-free system, which does not reflect the practical environmental considerations. Importantly, water forms a third component of the ASD matrix, and changes to relative humidity can shift the phase behavior and stability of the composition through changes to the glass transition temperature and degree of supersaturation, as well as possible phase separation/crystallization. Figure 17 highlights these changes in the phase diagram comprising the model system of naproxen and several polymers with increasing relative humidity. First, we can examine the figure with respect to thermodynamic solubility by comparing the placement of the composition (orange stars) with respect to the solubility line at the same temperature (solid lines). By transitioning from dry conditions (a) to typical and high levels (b, c) of humidity exposure at ambient temperature, the 40% drug loading composition becomes more thermodynamically unstable, as the solubility line for each polymer system shifts to lower compositions. The 20% drug loading composition, while initially thermodynamically stable for the PVP (blue) and PVPVA (gray) systems, becomes thermodynamically metastable at 75% relative humidity conditions. Second, we can examine Figure 17 with respect to kinetic stability by comparing the placement of the composition (orange stars) with respect to the glass transition lines (dotted lines). Both 20% and 40% compositions initially are kinetically stabilized with $T_g - T$ of ranging from 10 to 100 °C dry conditions (compare to the rule of thumb for kinetic stability:[182] $T_g - T > 50$ °C). Due to water uptake at 60% RH, the kinetic stability reduces to −5 to 25 °C, depending on the drug load and polymer system. With water uptake at 75% RH, the glass transition temperatures of the 20% drug loading ASDs with PVP and PVPVA (blue and gray dotted lines) are below ambient conditions and are no longer kinetically stabilized; a similar result is observed for the 40% drug loading ASDs with PVPVA and HPMCAS (gray and black dotted lines). This example highlights the importance of packaging design for humidity production during long-term storage and once dispensed to patients.

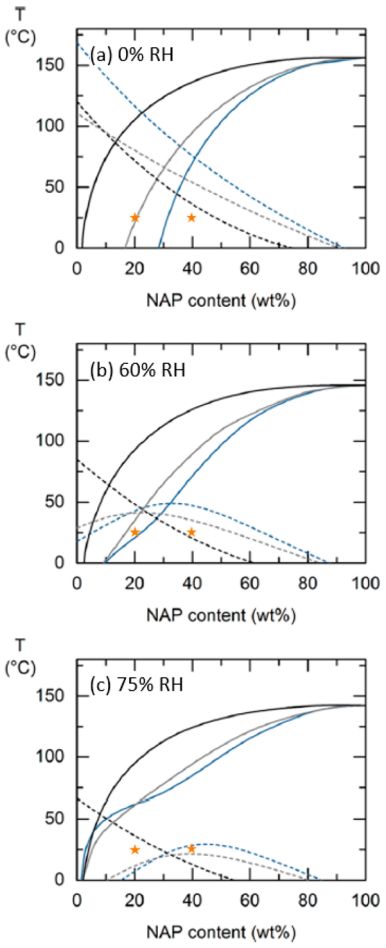

Figure 17. Phase diagrams calculated with PC-SAFT for naproxen (NAP)/polymer ASDs at different storage conditions: (a) 0% RH, (b) 60% RH, and (c) 75% RH. Blue, gray, and black represent the different excipients PVP, PVPVA64, and HPMCAS, respectively. The solid lines represent the calculated solubility lines, while the dashed lines represent the calculated glass-transition temperatures. The *x*-axis refers to the API content in the water-free ASDs. The orange stars mark the 20% and 40% drug loading compositions, to enable ease of reader identification of changes that occur due to relative humidity exposure with respect to thermodynamic and kinetic stability. Figure adapted and reprinted with permission from ref 181. Copyright 2017 American Chemical Society.

Beyond the humidity modulation example shown here, it can also be important to deconvolute the impact that temperature modulation may have on product stability. For any given composition, modulating the storage temperature will impact the mobility of the amorphous phase. This impacts both the extent of kinetic stability ($T_g - T$), as well as the relative supersaturation, both of which influence the crystallization tendency of the system. For some systems with higher crystallization risk, this may suggest that subambient temperatures may be the most appropriate long-term stability storage condition.

For samples containing crystallinity, the degree of kinetic stability and supersaturation are both important to the potential for crystal growth. For a system that is not supersaturated, the amorphous matrix is thermodynamically stable, regardless of the presence of crystals, and the crystals will not grow. For thermodynamically metastable systems, the mobility in the system ($T_g - T$) will impact the crystal growth rate. These types of considerations were seen in the physical stability case study, where crystal growth ceased when the solubility of the amorphous drug within the polymeric matrix was presumably reached (Figure 15a).

6.1.4. Dissolution/Supersaturation Considerations. Risk factors for the presence of crystallinity on dissolution performance have been discussed by Moseson et al.[9] and Purohit et al.[124] Whether or not an in vitro dissolution test can detect the presence of crystallinity or its impact be observed depends on the design of the test method,[80,124,126,140] and a QC test method with sink conditions is unlikely to provide this level of scrutiny. Beyond previously discussed complexities of amorphous drug−polymer systems such as those highlighted throughout the manuscript (crystallization tendency, solution-mediated crystallization, solid-mediated crystallization, supersaturation conditions, crystal properties) and their relation to the impact of crystallinity in an ASD product, it is pertinent to highlight some additional advanced concerns regarding

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dissolution test design, product design considerations, and media parameters.

The use of a one-stage or two-stage dissolution test may be critically important to detect certain failure mechanisms.[183] Nguyen et al. investigated an interesting case study featuring ASDs formulated with various enteric polymers.[184] The pH of the gastric medium influenced the extent of matrix crystallization observed and therefore the final extent of release. At low gastric pH (pH 1.6), where the drug was highly soluble, some leaching was observed in the first stage and a good extent of drug release occurred in the second stage. At intermediate gastric pH (pH 3), where the drug has become less soluble, matrix crystallization could proceed, resulting in incomplete drug release in the second stage. A single stage test in pH 6.5, where the polymer could ionize, demonstrated complete release. In this instance, a pH shift test from pH 3 to pH 6.5 would have improved discriminatory ability to detect the presence of crystallinity in the ASD.

While the influence of the drug's pH-dependent solubility on its release profile is well-known,[185] the pH-dependent solubility of the polymer is also of relevance to rate and extent of drug release. For example, a negative food effect was observed for an ASD formulated with HMPCAS HF.[186] As this polymer does not ionize and dissolve until ≥ pH 6.8, a different extent of release is achieved in dissolution tests where biorelevant media of different pH and composition were tested. These observations together suggest that the pH conditions in the GI tract in the fed state were below the polymer's threshold pH for release, thereby resulting in reduced bioavailability of the drug.

Media composition also influences crystallization kinetics. Nucleation induction time can both increase or decrease in the presence of complex media when compared to its blank buffer.[187] Varied levels of lecithin and bile salts have been shown to alter crystallization behavior.[88,188−190] The diversity of bile salts in vivo compared to the commercially available biorelevant media (sodium taurocholate only) is an additional complicating factor to media design for predictive in vitro dissolution testing.[187,190,191] Such variation in the in vitro test design could lead to consequences for formulation design decisions, for establishing accurate in vitro−in vivo correlations, or for assessing risk of crystallinity in the formulation.

6.1.5. Crystal Origin and Micromeritic Properties. An earlier section of this manuscript described the different properties of reference materials as surrogates for the crystals that may be found within ASDs. The potential for crystalline material to originate based on a manufacturing- or storage-based pathway should be considered by conducting a holistic risk assessment. Samples containing crystallinity could potentially be made by triggering failure mechanisms during manufacture. For a spray drying process, an antisolvent (such as water) could be added to the spray solvent to trigger phase separation and/or crystallization.[93,95] For hot melt extrusion, by using lower processing temperatures, shorter residence times (by modulating feed or screw speeds), or larger input crystals, the process design space could be varied to induce residual crystallinity.[30,41]

Crystal properties are relevant both in the context of detection/quantification of crystalline content, as well as when evaluating crystal growth and the resultant desupersaturation during in vitro testing. Hermans et al. used milled and unmilled API which altered the sensitivity of the dissolution method to detect crystallinity.[140] Moseson et al. observed greater desupersaturation due to crystal growth in ASD samples containing residual crystals compared to those with externally added crystal seeds, which was hypothesized to be due to (1) greater surface area for an equivalent amount of crystal seeds and (2) higher surface energy for residual crystal seeds due to underlying defect structure.[8]

A further consideration is the properties of the surrounding amorphous matrix. Even if residual crystals are present, the matrix itself may have properties that reduce the risk for crystal growth, such as a high glass transition temperature.

6.2. Additional Considerations. *6.2.1. Phase Separation.* In product risk assessments, not only does crystallization need to be considered, but also other types of phase separation, notably demixing to yield polymer-rich and drug-rich domains. While this Perspective has focused on crystallinity, the potential for negative impacts of this type of phase separation cannot be understated. Phase separation is far harder to determine by common solid-state characterization methods, such as PXRD or PLM. Yet, phase separation due to poor miscibility of drug and polymer at high drug loadings or induced by water uptake can occur, significantly impacting the dissolution profile and resultant bioavailability.[192]

6.2.2. ASDs as Drug Products. The design and performance of amorphous solid dispersions are commonly studied in their powder form as drug product intermediates. However, clinically relevant ASDs are drug products, in which the ASD drug product intermediate is subjected to downstream processing and additional excipients are added to form the tablet or capsule. Downstream processing such as milling or compression are high energy unit operations, which can induce demixing or crystallization of the ASD.[160,193−195] High disintegrant levels are commonly required to achieve disintegration times consistent with immediate release tablets,[196,197] while some commercial ASDs such as ritonavir are formulated as erodible tablets.[196,198] Regardless of the disintegration strategy, release performance is linked to the ASD drug loading, ASD polymer type, and tablet formulation.[197,199,200] The dilution of the ASD into an excipient matrix results in additional complexity to detect crystallinity within a drug product. These are just a few high level considerations for assessing the significance of crystallinity within an ASD drug product.

6.3. Specifications. The detection of drug solid-state form changes, in particular from amorphous to crystalline, presents a significant technical challenge to drug product developers. ICH Q6A suggests that surrogate tests, such as dissolution, are typically suitable to monitor product performance, while solid-state methods should be considered a last resort for a test and acceptance criteria.[5] While the purpose of this Perspective is not to offer regulatory guidance, we have presented numerous case studies and scientific fundamentals that support general caution with this approach. The acceptable level of variability within general product quality tests such as content uniformity and dissolution do not enable the specificity to quantify crystallinity or nonambiguously identify the origin of product quality issues. For example, a QC dissolution test is typically designed to detect formulation and manufacturing error, and differences in release rate may occur that are unrelated to crystallinity and may not be clinically relevant.[126,129,140,153,201] Further, the sink conditions typically associated with such a test do not discriminate for the solubility-based driving force differences between a crystalline and amorphous form. Hermans et al. performed a statistical analysis and found that

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it might be achievable to detect 6% crystalline content in the drug product, assuming no additional variability from sources such as: (1) dosage form assay, (2) analytical varability from both the assay and dissolution methods, or (3) other formulation or manufacturing contributions which may modify release rate.[140] It is clear that each of those assumptions does not apply to a GMP batch manufacturing and QC testing environment. The complexity associated with designing a nonsink QC dissolution test that would meet the needs for detecting/quantifying crystallinity with sufficient sensitivity as well as manufacturing-related criteria suggests that this approach should be applied only when justified by a thorough risk assessment. Such a risk assessment would potentially encompass product development studies, formulation modeling approaches such as PC-SAFT, and in vitro and in vivo correlations, which, in concert, evaluate the likelihood of crystallinity formation during manufacturing or storage as well as the potential impact on bioavailability. Further, if solid-state detection methods can be developed with appropriate sensitivity and relevance and subsequently linked to bioperformance, this could be a suggested appropriate alternative approach. In an industrial context, establishing clinically relevant specifications must be done in a risk-based framework, balanced by resources, time, and clinical outcomes.

7. CONCLUSIONS

Crystallinity is a complex critical quality attribute because detection and quantification can be an analytical challenge and because there is no common standard for acceptable levels across all drug−polymer systems. This is because of the inherent complexity that crystalline content brings to the performance of an amorphous solid dispersion. In some drug−polymer systems, crystal growth rates remain low, and low levels of crystallinity have little impact on the achievable supersaturation profile. However, in some systems, even X-ray amorphous systems may undergo rapid crystallization as a result of trace crystallinity, resulting in highly detrimental impact to supersaturation. This Perspective has attempted to comprehensively cover the theoretical background of the origins of crystallinity within ASDs and the potential significance on ASD performance. We highlighted the analytical difficulties in detecting and quantifying crystalline content and reviewed a wide range of case studies where crystallinity detection and significance to dissolution performance or physical stability was assessed. Ultimately, evaluating the risk of crystallinity to an ASD product performance is not straightforward and should be considered for each product using studies designed to identify the formulation's potential failure modes with the goal of generation of in vitro−in vivo correlations.

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Notes

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