KONA Powder and Particle Journal

KONA Powder and Particle Journal No. 42 (2025) 121–133/https://doi.org/10.14356/kona.2025008 Review Paper

Strategies to Overcome Undesired Physicochemical Changes in Particle Engineering for Inhalation †

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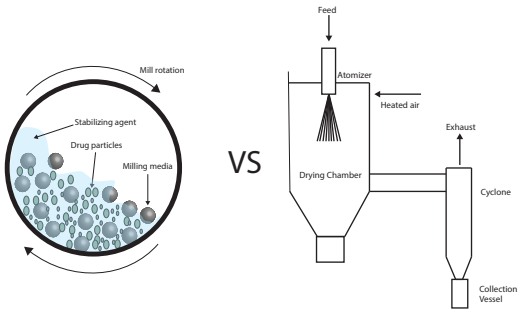
Particle engineering broadly refers to the controlled production of drug particles optimized for size, morphology, and structure. It encompasses both destructive (top-down) and constructive (bottom-up) particle formation processes, of which the most used for commercial dry powder inhaler (DPI) products are milling and spray drying. In both cases, undesirable physicochemical changes may occur because of thermal and mechanical stresses and through interactions with solvents, and can be further potentiated through storage and interaction with atmospheric water. The occurrence and extent of these phenomena are dependent upon the process parameters and the starting material, which necessitates a thorough understanding of these factors to create a stable product with the necessary characteristics for lung deposition. This review covers commonly arising issues in particle engineering and mechanisms of prevention. Topics to be discussed relating to physical changes include (1) the unintended generation of crystalline disorder and amorphous regions in particles; (2) polymorphic transformations; (3) unintended crystallization when amorphization is desired; and (3) triboelectric charging. Topics to be discussed relating to chemical changes include (1) thermal and mechanically activated chemical reactions; and (2) crystalline disorder and chemical reactivity.



Keywords: powder, particle engineering, amorphous, solid-state, spray drying, milling

1. Introduction

The location of inhaled particle deposition within the airways and post-deposition interactions with the lung milieu are influenced by particle properties such as size, density, morphology, hygroscopicity, surface area, and energetics. Particles with desirable properties for inhalation can be generated via particle engineering techniques, which in this article we define as both destructive (top-down) and constructive (bottom-up) particle formation processes. The most used technologies for each respective method are milling and spray drying, both of which have been employed in commercial dry powder inhaler (DPI) drug products. Although these processes can produce particles with the necessary characteristics for inhaled drug delivery, they may also induce undesirable physical and chemical changes in the drugs and excipients due to the inherent stresses and interactions involved during particle formation. These include mechanical stresses, thermal stresses, and interactions with solvents, which can result in surface and bulk changes in the crystalline structure, triboelectric charging, and chemical reactions that may adversely affect aerosol performance and drug efficacy and safety. Moreover, the influence of storage conditions and interactions with atmospheric water can potentiate these effects. Minimization of undesired or unanticipated physicochemical changes during particle engineering requires a thorough understanding of the process, its potential interactions with drug molecules, and subsequent effects on the final process. Careful optimization and control of particle formation processes and rational formulation design must then be employed to minimize and mitigate these undesired changes. By adopting appropriate methods and process parameters, pharmaceutical researchers can produce stable drug particles with the desired characteristics for efficient drug delivery and therapeutic effectiveness.

Destructive or "top-down" particle formation techniques encompass the production of respirable drug particles through the application of mechanical forces that result in particle breakage. Destructive particle engineering approaches include milling and homogenization technologies. In milling, particle breakage is achieved through particle–particle collisions and between the particles and the surrounding equipment. Homogenization also involves impact forces, but particle breakage is also achieved via the application of shear forces, cavitation, and pressure and flow forces. This review will focus on milling as a prototypical destructive particle engineering technique based on its wide use in the manufacturing of respirable powders.

† Received 31 July 2023; Accepted 17 August 2023
J-STAGE Advance published online 6 April 2024
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Constructive or "bottom-up" particle formation processes encompass controlled precipitation approaches for forming particles, such as spray drying, spray freeze drying, thin film freezing, and antisolvent precipitation. In these approaches, the drug and/or excipients are typically dissolved in a solvent and exposed to either a drying medium (spray drying), cryogenic environment (spray freeze drying/thin film freezing), or solvent in which the drug has very little to no solubility (antisolvent precipitation). In the case of spray drying and antisolvent precipitation, this results in rapid precipitation of the drug. Rapid freezing occurs during spray freeze drying and thin film freezing, and the feed solvent is subsequently removed in a secondary lyophilization procedure. Compared to destructive particle engineering techniques, constructive particle engineering techniques can offer more control over particle size, morphology, shape, and surface characteristics but carry unique considerations with regard to thermal stability and interactions between the drug/excipients and solvents. Similar to milling, undesired transformations in the solid-state structure and chemical instability can occur. This review will focus on spray drying as a prototypical constructive particle formation process based on its wide use in the pharmaceutical industry.

This review is structured to provide insight into how the unique stresses occurring in milling and spray drying affect the solid-state properties of the end particles, which in turn affect chemical stability, stickiness, and triboelectric charging, all of which can impact the safety and performance of inhaled drug products. For each process, the impact of the starting material properties on the solid state transformations is discussed. Thus, we intend to provide a guide for formulation scientists to select an appropriate processing approach and adjust process parameters according to the risks associated with a given molecule. Given the unique considerations for the dry state stability of biological products such as proteins, the scope of this review will primarily focus on small molecules.

2. Mitigation of undesired physicochemical changes in milled particles

2.1 Effects of milling process on particle solid state

Particle size reduction in milling occurs through the fracture of particles following collisions with each other, the milling equipment, or the milling media. Fracture mechanisms include impaction (force is applied normal to the particle surface), attrition (force is applied parallel to the particle surface), compression (slow application of force), and shear and cavitation forces when liquid medium is used (Parrott, 1974). The mills used most frequently for orally inhaled drug products are fluid energy mills, in which particle fracture occurs via the application of high-velocity air jets and the generation of turbulence and particle–particle collisions; and ball mills, in which balls or beads are incorporated and cause grinding through collisions with particles (Yokoyama and Inoue, 2007). For either mill, the rates and type of collision impact the end particle size distribution and can result in solid state transformations.

When mechanical stresses are applied to a particle during the milling process, the energy is initially stored as strain energy, and the solid undergoes reversible deformation. Further application of stress beyond the yield point of the solid results in permanent deformation and the initiation of cracking (Brunaugh and Smyth, 2018; Parrott, 1974). For semi-brittle and ductile materials, plastic deformation precedes fracture. The energy balance in particle fracture and the creation of new surfaces can be defined by the first law of thermodynamics (**Eqn. (1)**) (Zeleny and Piret, 1962):

$$W_s = Q_S + \bar{\sigma}_s \Delta A + \Delta D_s \tag{1}$$

where W_s is the work input to the material, Q_S is the heat produced in the material, $\bar{\sigma}_s$ is the average surface energy per unit area of the material, ΔA is the surface area change, and ΔD_s is the deformation energy of the material. Thus, the work required to fracture a particle is dependent upon the surface energy or surface tension of the material. For fracture to occur, the cohesive forces of the molecules on either side of the crack must be overcome. For this reason, cracks will initiate and propagate along existing microflaws in the material, as described by Griffith's theory for crack propagation (Griffith and Taylor, 1921). If a crystal were completely perfect, the applied mechanical forces would be distributed uniformly across the structure, resulting in breakage into uniform, individual units. However, all crystalline solids contain defects in their lattice structure, which results in fracture into a few larger particles and many fine particles and contributes to the typical asymmetrical size distribution of milled materials (Parrott, 1974).

It is well established that comminution via milling can result in the unintentional generation of molecular disorder in the crystalline structure or the generation of amorphous regions (De Gusseme et al., 2008; Feng et al., 2008; Ward and Schultz, 1995). The extent of this disorder is dependent upon the amount of energy imputed into the process (pressure employed in the mill, or the efficiency of the mill). This has several consequences for milled drugs, including changes in solubility, increased particle cohesion, deviations in blend uniformity, and reduction in aerosol performance (Shur et al., 2013). Additionally, disordered surfaces will have a thermodynamic tendency for recrystallization, which can lead to the formation of solid bridges between particles and irreversible aggregation (Dunber et al., 1998).

When the mechanical forces generated in milling exceed the intermolecular forces in the crystal lattice structure (e.g., electrostatic interactions, van der Waals forces, and

hydrogen bonding), disruption and disorder of the crystal lattice structure will occur (York, 1983). Crystal fracture is postulated to occur when the lattice dislocations accumulate and attain a critical density (Olusanmi et al., 2011). In addition to fracture, depending on the material properties and the magnitude of the applied forces, small point defects to complete disruption of the lattice order may occur, resulting in the formation of amorphous or partially disordered structures (Iyer et al., 2023). The resulting increase in entropy of the disordered system increases the free energy of the system and produces solids that are in a so-called "mechanically activated" state in which acceleration of chemical and physical reactions can occur (Hüttenrauch et al., 1985). Crystal to amorphous phase transition during milling is hypothesized to occur as a result of mechanical or thermodynamic destabilization (Crowley and Zografi, 2002). Mechanical destabilization theorizes that if mechanical forces and the resulting anharmonicity of phonons in the material violate the Born stability criteria of the crystal lattice, the lattice will collapse to yield an amorphous form (Tse, 1992). Thermodynamic destabilization theorizes that amorphous transformation occurs when the concentration of defects in the crystal lattice induced by the mechanical energy input exceeds a critical limit beyond which the amorphous form has greater thermodynamic stability than the disordered crystal (Fecht, 1992).

Process optimization to control solid-state transformations in milling has primarily focused on the effects of temperature and milling intensity. The breakage propensity of aspirin during milling was found to increase with temperature (Olusanmi et al., 2010), and it is possible that this could be applied to other materials to improve milling efficiency. However, if the goal is to produce amorphous particles, milling should be performed at temperatures well below the glass transition temperature (T_g) of the expected amorphous state (Descamps et al., 2007; Tsukushi et al., 1995). Milling at temperatures above T_g can lead to polymorphic transformation of the disordered material (Descamps et al., 2007). For some high T_g materials (e.g., trehalose), this can be accomplished under ambient conditions; however, materials with lower T_g may benefit from cryogenic milling. An additional benefit of cryogenic milling is that it can be used to make semi-brittle or ductile materials more brittle. At higher temperatures, thermal activation enables greater movement of crystal lattice dislocations by diffusion, thus enhancing plastic flow (Olusanmi et al., 2010). Indomethacin has provided a useful model for examining the effect of milling intensity on solid-state transformations, as it exhibits multiple polymorphs as well as the formation of a glassy state. In a study using amorphous indomethacin, Desprez et al. (Desprez and Descamps, 2006) found that different milling durations and intensities led to the transformation into different crystalline forms, which was hypothesized to be due to successive solid-state transformations as the milling time progressed. Milling at low intensity or short duration at higher intensity promoted direct crystallization of the stable γ crystalline form, wherease milling at high intensity and long duration promoted crystallization of the metastable α phase, either during the milling process itself or upon reheating the glass. These trends followed those observed with temperature effects on the crystallization of amorphous indomethacin, in which the stable γ form crystallizes at lower temperatures (near the T_g), whereas the metastable α form crystallizes at higher temperatures. Material properties (e.g., hardness, morphology) can confound the impact of the type of mill used on the tendency toward crystalline disorder. Chikhalia et al. (2006) found that specifically for the plate morphology of β-succinic acid, ball milling resulted in greater crystalline disorder than jet milling, although the opposite trend occurred for needle-like morphology.

Several patents (Lee, 2012; Vemuri et al., 2003) describe the incorporation of humidified air into the fluid energy milling process to produce a powder with little to no amorphous content. Alternatively, several formulators (Brodka-Pfeiffer et al., 2003; Depasquale et al., 2015; Ward and Schultz, 1995) have used a process of "curing" or "conditioning" of milled powders, in which recrystallization of partially amorphous solids is induced in a controlled manner through storage under high humidity conditions for a specified duration. In humid environments, water molecules adsorb onto the amorphous regions of the particle surfaces and function as plasticizers, thereby reducing the T_g (Price and Young, 2005). Provided that the surrounding environment maintains a temperature above T_g, the increased molecular mobility within the surface amorphous regions will promote accelerated crystallization. Given that it can alleviate unexpected solid-state transformations and changes in quality attributes during storage, the FDA recommends a conditioning step for micronized drug products in their draft guidance for dry powder inhalers (DPIs) (Food and Drug Administration, 2018), although a specific method is not provided and is probably product dependent. The inclusion of humidified air is critical to the conditioning process for milled powders (Brodka-Pfeiffer et al., 2003); dry conditioning of micronized albuterol for 24 h at 70 °C did not result in recrystallization, whereas a relative humidity above 50 % did produce crystallization. This was hypothesized to be due to the expulsion of water from particle surfaces at high, dry temperatures, which would have a deplasticizing effect. Importantly, in this study, it was found that a combination of higher temperature (40 °C) and high humidity increased particle growth during storage relative to a lower temperature (25 °C) storage. This could have been due to increased molecular mobility at higher temperatures, leading to the formation of crystal bridges.

2.2 Impact of starting material on solid state of milled particles

Mechanical properties such as Young's modulus, hardness, and fracture toughness impact fracture strength, deformation behavior, and subsequently particle breakage in milled materials (Brunaugh and Smyth, 2018). Feed material properties have also been correlated with the propensity to crystal disorder during milling. The molar volume of a crystalline solid has been theoretically (Wildfong et al., 2006) and experimentally (Lin et al., 2009) correlated with amorphization because it relates to geometric constraints on crystal dislocation before a critical density is obtained. A higher T_g has also been correlated with increased amorphization by milling (Lin et al., 2009), likely due to stabilization of the amorphous state during processing.

Hydrates and solvates affect solid-state transformations during milling. Crowley and Zografi (2002) examined the differing propensity of two indomethacin solvates (methanol and t-butanol) toward solid-state transformations during grinding. Although indomethacin is generally recognized as a good glass former, amorphization was initially unobserved upon grinding although desolvation of methanol was. This was hypothesized to be due to the plasticization effects of methanol contributing to the rapid recrystallization of a transient amorphous form, which was confirmed through a modified, cryogenic grinding experiment where an amorphous phase containing residual methanol was formed and required additional drying to stabilize. T-butanol, in contrast, resisted desolvation or solid-state transformation. Similar plasticization effects have been observed with the milling of hydrates; while the milling of anhydrous forms of trehalose and glucose results in amorphization, trehalose dihydrate and glucose monohydrate remain crystalline (Willart et al., 2010). Hydrates have also shown greater susceptibility to particle breakage than anhydrates because of alterations in molecular packing (Schneider-Rauber et al., 2021). Therefore, the use of hydrates and solvates can be a useful approach when avoidance of amorphization is desired.

The inclusion of excipients to prevent amorphization during milling has been explored (Balani et al., 2010; Lau et al., 2017). Balani et al. (2010) found that co-milling of salbutamol sulfate with crystalline alpha-lactose monohydrate, adipic acid, or magnesium stearate was effective in reducing the amorphization of the drug, as assessed by X-ray powder diffraction (XRPD), dynamic vapor sorption (DVS), and differential scanning calorimetry (DSC). Based on XRPD patterns obtained after different milling durations, the stabilizing effect of the excipients was hypothesized to be due to the excipient particles acting as seed crystals to induce recrystallization of the amorphous drug. As confirmed by co-milling crystalline lactose with an amorphous sample of salbutamol sulfate resulted in complete recrystallization. The ability of drug seed crystals to induce recrystallization during milling has been reported in other studies (De Gusseme et al., 2008; Otsuka and Kaneniwa, 1986). It is important to note in this study that an excipient in the crystalline state is necessary to induce recrystallization during the milling process; co-milling with amorphous polyvinylpyrrolidone (PVP) had no effect on drug crystallinity.

2.3 Effects of milling on chemical reactivity

The work of generating new surfaces in milling produces heat. Thus, localized temperature increases during milling (Schmalzried, 1995) may contribute to thermal degradation. Cryogenic milling has also been used to reduce the effect of heat generation on micronized compounds (Chamarthy and Pinal, 2008); however, Adrjanowicz et al. (2011) found that compared with room temperature processing, milling under cryogenic conditions resulted in a duration-dependent chemical degradation of furosemide, with an identical degradation product produced as reported for thermal degradation. This is unusual because the rate of thermally activated chemical reactions typically increases with increasing temperature (Adrjanowicz et al., 2011), and it was hypothesized that the reaction instead occurred through a pathway activated by mechanical energy provided through a combination of high-energy collisions and the increased surface area and amorphous content of the milled material (Adrjanowicz et al., 2011). Thus, milling under cryogenic conditions is not necessarily a guarantee against chemical degradation, and the product must still be carefully monitored.

Regions of crystal lattice damage or amorphousness generated during milling can also increase the chemical degradation rate of the product, particularly when exposed to water (Ahlneck and Zografi, 1990; Weers and Miller, 2015). Amorphous solids take up more water than their crystalline form. Because of the disordered state of the solid, it is possible for water to dissolve in the solid, where it acts as a plasticizer and reduces the T_g. As the ambient temperature increases above T_g, the viscoelasticity of the solid decreases and the molecular mobility of both water and the solid increases. This increased mobility increases the chemical decomposition rate for amorphous solids as well as partially damaged crystal lattice structures (Ahlneck and Zografi, 1990; Pikalet al., 1977). To avoid this risk, the duration and energy of the milling process may be reduced to attenuate crystal lattice disorder.

3. Mitigation of undesired physicochemical changes in spray-dried particles

3.1 Effect of spray-drying process on particle solid state

Spray drying is a manufacturing technique suitable for the large-scale production of powders with ideal characteristics for pulmonary delivery. These properties, which are

generally straightforward to design for different scales, include well-defined particle size with a narrow distribution, good flowability, improved bioavailability resulting from higher aqueous solubility, and enhanced stability of biologics achieved through glass stabilization (Alhajj et al., 2021; Baumann et al., 2021). The aerodynamic size of spray-dried particles can be predicted from a mass-balance equation (**Eqn. (2)**) (Vehring R., 2008a):

$$d_a = d_0 \sqrt[3]{\frac{C_F}{\rho^*}} \sqrt[6]{\frac{\rho_p}{\rho^*}} \tag{2}$$

where d_a and d_0 represent the aerodynamic diameter of the particles and the diameter of the initial atomized droplets, respectively, while C_F, ρ_p, and ρ^* denote the total feed concentration, particle density, and unit density (1000 g/mL), respectively. According to this equation, the final particle size distribution is primarily influenced by the size of the atomized droplets and, to a lesser extent, by the total feed concentration of the solutes.

Fig. 1 illustrates a schematic representation of the spray-drying process, which involves atomizing a solution or suspension into a fine spray within a chamber in the presence of a hot gas flow. Evaporation of a droplet involves the transfer of heat from a hot gas via conduction and convection to the droplet surface and the transfer of vapor from the droplet surface into the gas stream via diffusion and convection. The rate of this transfer is dependent upon the properties of both the drying gas (temperature, humidity, transport properties) and the droplet (diameter, temperature, relative velocity) (Ranz, 1952). Droplet evaporation

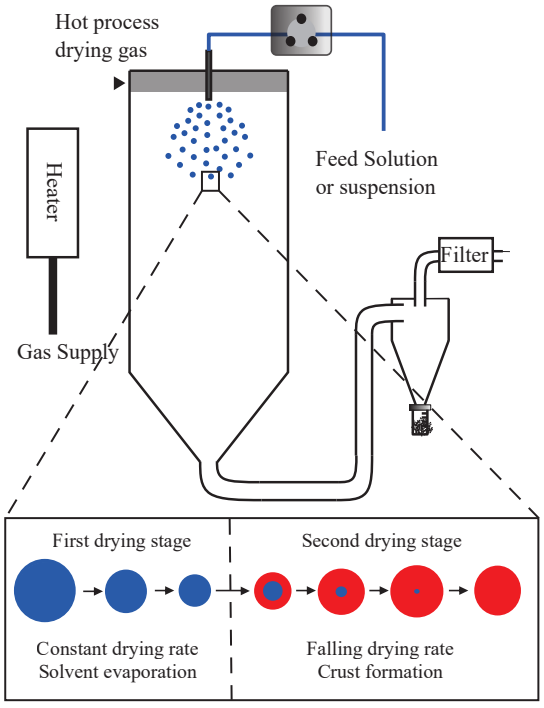

Fig. 1 Schematic of the spray dryer and particle formation in the open mode.

in spray drying is thermodynamically driven by the difference in chemical potential between the solvent in the solidifying droplet and in the carrier gas/vapor phase; thus, the drying rate is proportional to the magnitude of the difference between solvent activity adjacent to the droplet surface and that of the bulk carrier gas (Handscomb et al., 2009a; Singh and Van den Mooter, 2016). This necessitates careful control of humidity during the spray-drying process and efficient solvent removal if operating in a "closed-loop" mode to maintain this differential and if a rapid drying rate is desired. Similarly, the droplet surface must remain saturated with solvent, and the drying rate will begin to decrease once the solvent molecules can no longer diffuse to the surface at a sufficient rate to maintain saturation (Handscomb et al., 2009a). Drying continues until the solvent activity in the solid and vapor phases has reached equilibrium.

The process of solvent removal during spray drying can be broadly classified into two states: 1) a constant drying rate period and 2) a declining drying rate period. During the constant drying rate period, the droplet temperature initially equilibrates to the wet bulb temperature and then begins to increase as the amount of solids at the surface of the droplet increases (Nešić and Vodnik, 1991). Toward the end of this period, the accumulation of solids at the droplet surface causes a reduction in the vapor partial pressure at the surface and a reduced rate of evaporation; the transferred heat is instead used for droplet heating. This marks the start of the declining drying rate period, where the formation of a crust increases the resistance to heat and mass transfer. Depending on the permeability of the crust for vapor diffusion, whether the bulk carrier gas temperature is greater than the solution boiling temperature, and the mechanical properties of the crust, an increase in internal pressure can lead to inflation, cracking, or explosion. Conversely, shrinkage or buckling of the shell may occur because of the capillary pressure of the receding continuous phase (Handscomb et al., 2009b). Thus, manipulation of the drying rate offers some degree of control over particle morphology, as the morphology of the produced particles is strongly dependent on the properties of the formed crust (Handscomb et al., 2009a). Upon bulk solvent removal from the particle core, the drying rate continues to decrease as the residual solvent is evaporated from the pores and micropores until the temperature of the droplet approaches that of the surrounding carrier gas (Nešić and Vodnik, 1991). Once formed, particles are then typically separated from the gas flow using cyclonic separation for further processing (Carrigy and Vehring, 2019; Ordoubadi et al., 2022). The spray-dried powder may be subjected to additional drying processes to further reduce the residual solid content.

Ultimately, whether a spray-dried particle will be amorphous, partially amorphous, or crystalline depends on

whether nucleation and crystal growth can occur before the droplet dries. The time length of this critical period can be decreased through adjustments of process parameters that impact the droplet evaporation rate and surface saturation of the droplet components, which include the inlet temperature, feed flow rate, and feed solid concentration. Given that adjustment of these parameters can have confounding effects on the drying capacity of the spray dryer and the temperatures to which the drying particle is exposed, which can conversely impact molecular mobility, the most efficient mechanism for optimization is probably a multifactorial experimental approach. Mathematical models for particle formation have been extensively presented by Vehring and colleagues (Hoe et al., 2013; Vehring et al., 2007; Vehring, 2008a), an overview of which is presented here. **Eqn. (3)** describes the time it takes for a droplet to dry completely (τ_D):

$$\tau_D = \frac{d_0^2}{\kappa} \tag{3}$$

where d_0 is the initial droplet diameter and κ is the evaporation rate. **Eqn. (4)** describes the time for a component, i, to reach surface saturation:

$$\tau_{sat,i} = \tau_D \left[1 - \left(\frac{c_{0,i} E_i}{c_{sol,i}}\right)^{\frac{2}{3}}\right] \tag{4}$$

where $c_{0,i}$ is the initial concentration of the component i in the droplet, $c_{sol,i}$ is the equilibrium solubility of component i, and E_i describes surface enrichment of component i, that is, the surface concentration of component i in relation to its concentration in the bulk droplet. The time remaining between saturation and complete droplet drying describes the time available for crystallization of component i, referred to as the precipitation time ($\tau_{p,i}$), and is described in **Eqn. (5)**:

$$\tau_{p,i} = \tau_D \left[1 - \left(\frac{c_{0,i}}{\rho_{t,i}} * E_i\right)^{\frac{2}{3}}\right] \tag{5}$$

where $\rho_{t,i}$ is the true density for component i. Depending on whether the component has sufficient time to crystallize before droplet drying is complete, a crystalline, partially amorphous, or amorphous particle will form.

Crystallization kinetics have been modeled in the spray-drying process through several different methods, including those related to the thermodynamic drivers for nucleation and crystal growth kinetics and solid-state transformation that can occur from a transient amorphous to crystalline state as solvent contents change in the drying droplet. For a saturation-based approach to crystallization, each individual droplet can be considered a crystallizer. A thermodynamic drive for nucleation and crystal growth is provided by the difference between the chemical potential of the solute in solution and the crystal form (**Eqn. (6)**) (Dirksen and Ring, 1991):

$$\Delta G = -RT\ln\left(\frac{a}{a^*}\right) = -RT\ln\left(\frac{C}{C_{eq}}\right) \tag{6}$$

where R is the universal gas constant, T is the absolute temperature, and a and a^* are the activities of the solute in supersaturated and saturated conditions, respectively. For an ideal solution, this can be expressed in terms of the ratio of the solute concentration (C) to the equilibrium solubility (C_{eq}) at a given temperature and pressure. Evaporation of solvent during the spray-drying process increases C and the degree of supersaturation, thus increasing the thermodynamic drive for crystallization. The rate of nucleation can be described using an Arrhenius equation (**Eqn. (7)**) according to Classical Nucleation Theory (Thakur et al., 2022):

$$J = A\exp\left(-\frac{\Delta G^*}{k_B T}\right) \tag{7}$$

where A is a constant that depends on the stochastic process of attachment and detachment of the solute from the surface of the nucleus, k_B is Boltzmann's constant, ΔG^* is the change in free energy required for critical cluster formation, and T is the nucleation temperature. The frequency of molecular transport (v) to the nucleus–liquid interface is related to the bulk viscosity (η) using the Stokes–Einstein equation (**Eqn. (8)**) (Rodríguez-Hornedo and Murphy, 1999):

$$v = \frac{kT}{3\pi a_o^3 \eta(T)} \tag{8}$$

where a_o is the mean effective diameter of the diffusing species. Further crystal growth can be controlled by volume diffusion, i.e., it is rate-limited by the diffusion of the solute from the bulk solution to the crystal surface, or it can be controlled by surface integration, i.e., incorporation of the molecule into the crystal lattice is the rate-limiting step (Rodríguez-Hornedo and Murphy, 1999). Ultimately, crystallization is limited by the extent of molecular rearrangement in the liquid adjacent to the interface (Turnbull, 1969). If this molecular rearrangement is slowed and if the clusters cannot assemble into crystals during the timeframe of droplet drying (e.g., through an increase in viscosity), then an amorphous solid will be formed. Unintended polymorph transformations can also occur in bottom-up particle engineering techniques such as spray drying. Ostwald's Rule of Stages states that crystallization from a solution typically occurs in a manner in which the least thermodynamically stable polymorph is formed first, followed by subsequent transitions into more stable forms (Nývlt, 1995). However, the rapid drying times that occur during spray drying may not enable full conversion to the most stable polymorph and can instead result in a metastable

crystalline form or a mixture of polymorphs (Vehring, 2008b). The polymorph in the final product can be influenced by both the process parameters and feed formulation. The length of the drying time has been used as a mechanism of controlling the crystalline state produced, as well as the variation in droplet size (Lee et al., 2011). Lee et al. (2011) found that variation in mannitol polymorphs occurred as a function of droplet size, which was theorized to be due to the slower drying of larger droplets, as the retention of moisture facilitates crystallization to the stable polymorph. Inclusion of excipients in the spray dryer feed solution can control polymorph transition because excipient molecules will adsorb onto crystal surfaces and affect the direction of crystal growth (Kitamura, 2009). Likewise, incorporation of a co-solvent in the feed solution can be used as a mechanism to control the polymorphism, as this will alter the nucleation and crystallization rate (Kitamura, 2009; Lee et al., 2011; Roelands et al., 2006).

Spray drying is unique in that it involves concurrent evaporation and particle formation processes. Using single droplet drying data of lactose solution, Woo et al. determined that before the formation of a solid crust in the drying droplet, a saturation-based analysis similar to that provided above can be used to predict the extent of crystallization; however, upon the formation of the crust, crystallization is more aptly modeled using solid-state approaches (Woo et al., 2012). Solid-phase crystallization in semi-dried or dried particles during the spray-drying process can be modeled using the Williams–Landel–Ferry (WLF) equation, which describes viscosity (v) and thus molecular relaxation as a function of temperature difference from T_g (**Eqn. (9)**) (Williams et al., 1955):

$$\log\left(\frac{v_{\text{ref}}}{v_{\text{max}}}\right)=\frac{-C_1\left(T-T_g\right)}{C_2+T-T_g} \tag{9}$$

where C_1 and C_2 are material-dependent constants. The T_g during the various time steps in the drying process can be estimated using the Gordon–Taylor equation (**Eqn. (10)**) (Gordon and Taylor, 1952):

$$T_g=\frac{w_1T_{g,1}+kw_2T_{g,2}}{w_1+kw_2} \tag{10}$$

The WLF equation can be integrated against the drying time to describe the driving force for crystallization based on changes in molecular mobility, where a larger value indicates that the particle has experienced more crystallization (Woo et al., 2012). Process drying efficiency and trends toward recrystallization of drying particles have been predicted using characteristic drying curves, in which a relative drying rate (the actual drying rate of the solids relative to the unhindered drying rate) is calculated as a function of the characteristic moisture content over the drying process as process parameters are adjusted (Chiou et al., 2007).

Ultimately, whether a spray-dried particle will be amorphous, partially amorphous, or crystalline depends on whether nucleation and crystal growth can occur before the droplet dries. The time length of this critical period can be decreased through adjustments of process parameters that impact the droplet evaporation rate and surface saturation of the droplet components, which include the inlet temperature, feed flow rate, and feed solid concentration. Given that adjustment of these parameters can have confounding effects on the drying capacity of the spray dryer and the temperatures to which the drying particle is exposed (e.g., the outlet temperature), which can conversely impact molecular mobility, the most efficient mechanism for optimization is probably a multifactorial experimental approach.

The inlet temperature, feed flow rate, and solid content are directly related to the heat and mass transfer efficiency in spray drying. Increasing the inlet temperature will increase the evaporation rate because the heat transfer to the droplet surface increases the average kinetic energy of the solvent molecules, enabling them to break free into the vapor phase. As such, the surface saturation rate will also increase and can produce particles with smaller crystals and lower overall crystalline content (Baldelli et al., 2016). More efficient solvent removal can also reduce its plasticization effects and increase the T_g of the solids, although the residual solvent content cannot be reduced below zero. Increasing the temperature to increase drying efficiency must be balanced against the potential for drug degradation at higher outlet/dry bulb temperatures. Furthermore, if an amorphous product is desired, increasing the inlet temperature may also increase the temperature of the drying particle above T_g, thereby increasing molecular mobility and increasing the rate of recrystallization according to the WLF equation. Using experimental and modeling approaches based on the WLF equation, Langrish (2008) found that the rate of crystallization was greatly enhanced when the particle temperature was more than 30 K higher than the T_g of the material. Spray drying above the T_g has also been associated with a significant reduction in production yield because of particles sticking to the walls of the cyclone (Camino-Sánchez et al., 2020).

If an amorphous end product is the goal, the outlet temperature should be maintained below T_g. In the case of molecules with low T_g, this may necessitate the incorporation of anti-plasticizing excipients to increase the T_g of the mixture or the use of highly volatile solvents such as dichloromethane. Conversely, maximizing the positive temperature differential between the particle and its T_g can be an efficient mechanism to induce crystallization. Increasing the feed flow rate results in a decrease in the outlet temperature and decreases the drying efficiency as more mass is added to the system and evaporative cooling occurs. This can produce an increase in residual solvent content in the

dried particles, which can cause plasticization and impact storage stability. While increasing solids content will decrease the time to surface saturation and precipitation, this can also impede solvent removal depending on the permeability of the crust formed during droplet drying.

3.2 Effect of starting material on solid state of spray-dried particles

The formation of amorphous or crystalline particles depends not only on the operating conditions and process variables employed in spray drying but also on the materials that are being fed to the spray drier. Whether a material forms a glass or an ordered crystalline structure depends on the efficiency and timescale of molecular packing as it relates to phase transition into the solid state. Various structural features that affect the packing efficiency of molecules have been identified through experimental and statistical approaches. Identifying these features and understanding their impact on the thermodynamic drive and kinetics of crystallization can provide early guidance on the need for stabilizing excipients or adjustment of spray drying parameters, depending on the desired product outcomes. Generally, the presence of benzene rings in a molecule is associated with a planar structure and increased opportunities for non-specific van der Waals interactions between the aromatic rings, which promote a tightly packed, energetically favorable crystal structure (Mahlin et al., 2011; Yu et al., 2000). A higher molecular weight is associated with increased glass-forming ability, although this may be confounded by the typically higher complexity of these molecules and increased configurational entropy (Yu et al., 2000). Drugs with a molecular weight greater than 300 g/mol exhibit good glass-forming ability using different processing technologies, including spray drying, which may provide a quick screening tool for the tendency to crystalize (Mahlin and Bergström, 2013). Other molecular features that support glass formation during spray drying include a highly branched structure or asymmetry (Mahlin et al., 2011). Molecules with more rotatable bonds exhibit slower crystallization kinetics because of the decreased probability that a molecule conformer will be in the proper orientation to undergo nucleation or be incorporated into the growing lattice structure (Baird et al., 2010; Yu et al., 2000). Increased electronegativity in a molecule also increases the tendency toward amorphization upon spray drying (Mahlin et al., 2011), as it promotes hydrogen bonding between molecules, which has previously been linked with the generation of molecular aggregates that pack poorly and limit the rate of molecular reorganization into the crystalline state (Wang et al., 2009).

For drugs that are poor glass formers, excipients can be incorporated into the feed to stabilize the amorphous state, e.g., through the formation of an amorphous solid dispersion (ASD) in which a matrix-like structure is formed that hinders the molecular mobility of any molecules incorporated into it. Even in the case of drugs that readily form amorphs, an ASD development approach can be a useful strategy to overcome the thermodynamic instabilities of the amorphous form and raise the T_g to a level sufficient for storage stability, e.g., greater than ~50 K of the anticipated storage temperature (Hancock et al., 1995). In the context of spray-drying ASDs for administration via dry powder inhalers, it is important to check that the excipients display properties to ensure that they are well tolerated in humans and are amenable to scale-up production. These properties include an established safety profile, biocompatibility, no displayed toxicity, and polymer processability, e.g., sufficient solubility in solvents for spray drying. Sugar-based excipients and polymers such as HPMC, HPMCAS, and PVPs are generally considered to be biologically inert, are generally recognized as safe, and are present in commercial products (Anane-Adjei et al., 2022). This review will provide a brief discussion on the use of polymers as glass-stabilizing excipients as a case example based on their wide use in the stabilization of amorphous small molecules, although saccharides such as trehalose are commonly used for the stabilization of biological spray-dried products.

The specific polymer used in ASDs directly impacts physical stability and dissolution properties; therefore, it is imperative to understand the interactions between the drug and polymer in ASDs. The most common physicochemical property used to predict the compatibility of drugs and polymers is their miscibility, or ability to form a stable single phase. Intermolecular bonds, primarily hydrogen bonds and ionic interactions, between the polymer and the drug impact miscibility. *In silico* models are often used as a preliminary method for determining the miscibility of an ASD, usually by evaluating the surface charge characteristics of both molecular entities. Models such as COSMO-Rank use this method to determine the miscibility of an API with various established polymers, which are then ranked based on the enthalpy of the predicted interaction. Typically, the more negative the calculated enthalpy is between the API and polymer, the higher the ASD ranking (Anane-Adjei et al., 2022). Hydrophobicity also plays an important role in the success of a polymer in forming an ASD because it affects the strength of interactions between the polymer, the drug, and the feed solvent. Ilevbare et al. (2013) found that a moderate level of polymer hydrophobicity was ideal for inhibiting drug crystal growth in supersaturated solutions, as it enabled non-specific interactions and promoted adsorption of the polymer to the surface of the crystalline drugs (Ilevbare et al., 2013). Excessive polymer hygroscopicity, particularly when coupled with weak polymer–drug interactions, can negatively impact the storage stability of ASDs through moisture-induced amorphous–amorphous phase separation (Rumondor and Taylor, 2010). For polymers, an increase in the molecular weight

of the polymer generally results in an increase in T_g, according to the Flory–Fox equation (Fox and Flory, 1950). Thus, one potential mechanism for stabilizing amorphous spray-dried products is to substitute a polymer with a higher molecular weight in the solid dispersion. However, it must also be considered that increasing the molecular weight will increase droplet viscosity during drying and impede solvent transport from the bulk to the surface (Wu et al., 2011). This can increase the amount of residual solvent and result in plasticization.

Feed solvent selection can impact drug solubility and saturation, thermodynamic drive for crystallization and polymer behavior. The solubility of feed components in the feed solvent can impact crystallinity, as it affects the supersaturation ratio. Harjunen et al. (2002) determined the effects of the ethanol-to-water ratio in the feed solution on the crystallinity of spray-dried lactose. Crystallinity was evaluated by isothermal microcalorimetry and differential scanning calorimetry. The solubility of lactose in water at room temperature is 0.21 mg/mL, whereas it is practically insoluble in ethanol. The authors found that the crystallinity of spray-dried lactose varies from 0% to 100% depending upon the composition of the feed, where an increase in the proportion of ethanol in the feed produced a corresponding decrease in the amorphous content of the spray-dried products. The lactose spray dried from pure ethanol was 100 % crystalline, whereas the lactose spray dried from pure water was 100 % amorphous. Li et al. (2020) examined the phase behavior of ritonavir–copovidone spray-dried dispersions from methanol and methanol–water mixtures. The prepared ASDs were characterized using differential scanning calorimetry (DSC), fluorescence spectroscopy, X-ray photoelectron spectroscopy (XPS), and surface-normalized dissolution rate (SNDR) measurements. Their results indicate that the addition of water to the solvent system could lead to phase separation during the spray-drying process, and even slight modifications in the composition of the solvent mixture resulted in notable alterations in the phase behavior of the ASDs during drying. These findings are relevant because the addition of water to organic solvents is often used to increase the solubility of drugs or polymers in feed and because the use of hygroscopic solvents, such as methanol or acetone, in spray drying can pick up atmospheric moisture, leading to heterogeneity or phase separation of spray-dried ASD particles.

3.3 Effect of spray drying on chemical reactivity

Thermal degradation can be an issue in spray drying of thermolabile compounds, particularly proteins and peptides or biodegradable polymers (Cheow et al., 2011). Although largely beyond the scope of this review, for macromolecular biologics, degradation mechanisms that require the most attention during the formulation development of spray-dried powders are denaturation and aggregation (Mensink et al., 2017). Denaturation of proteins is the unfolding and disruption of their tertiary and secondary structures, which generally occurs due to external stresses, with thermal, interfacial, and dehydration-related stresses being significant during drying processes (Haque and Adhikari, 2015). Protein aggregation is a series of structural changes involving protein–protein interactions that can lead to the formation of reversible or non-reversible clusters (Wang and Roberts, 2018). The formation of these protein clusters can reduce their therapeutic efficacy and potentially increase their immunogenicity and cause immune response after delivery (Lundahl et al., 2021).

Oxidation and hydrolysis are common factors contributing to the chemical degradation of labile drugs and excipients during spray drying and subsequent storage, and these reactions can be catalyzed by the high temperatures present during processing. Although many of these chemical degradation studies have been conducted on food products, the results are likely applicable to certain excipient classes relevant to inhaled drug products, e.g., phospholipids. For example, high (>180 °C) inlet temperatures during spray drying were found to result in increased lipid oxidation in spray-dried egg powder (Javed et al., 2018). Antioxidants have been included in a spray-dried HPMCAS-based ASD to prevent oxidation during storage (Kotha et al., 2022) and could provide similar protective benefits during processing. Sodium caseinate–lactose powders containing an increased percentage of hydrolyzed sodium caseinate exhibited increased powder sticking during processing, increased particle breakage/friability, and a lower T_g and higher percentage lactose crystallinity upon storage, indicating increased moisture sorption behavior (Mounsey et al., 2012). Thus, the chemical reactions such as hydrolysis may have impacts on the physical properties of powders as well as product safety.

4. Triboelectric charging of engineered particles

Because organic compounds typically consist of insulating material (Karner et al., 2014), engineered particles may accumulate electrostatic charges (triboelectrification) during processing as particles move against the solid surfaces of equipment and each other (Kwok and Chan, 2013; Rasenack and Müller, 2004). The extent of triboelectrification depends on ambient relative humidity, temperature, surface impurities, surface roughness, area of contact, and other physicochemical factors (Karner et al., 2014; Kwok and Chan, 2013). Attractive forces produced during particle charging can lead to particle agglomeration and adhesion to equipment surfaces. This may result in alterations in particle size or blocking of powder flow pathways through equipment (Kwok and Chan, 2013). In contrast, if repulsive forces are produced from particle charging, blend

stability and bulk powder density will be reduced, which may in turn affect dose metering (Bailey, 1993). The material from which equipment is constructed will influence charge (stainless steel versus polymers) (Elajnaf et al., 2006), as well as contamination of equipment surfaces over time, which could lead to variations from batch to batch if equipment is not properly cleaned or if detergent residue is left on equipment (Kwok and Chan, 2013). Furthermore, particle charging can be affected by relative humidity (RH), the magnitude of which is dependent on the hygroscopicity of the material. For particles with low hygroscopicity, RH appears to have a negligible effect; however, for particles with high hygroscopicity, electrostatic charging is inversely related to RH (Kwok and Chan, 2013). This is hypothesized to be due to the reduction in surface contact as water is adsorbed.

In addition to altering the equipment material, avoidance of electrostatic charging can be achieved through the addition of certain excipients, such as fillers or lubricants, to the micronized drug powder (Kwok and Chan, 2013). For example, Zhang et al. (2010) included an anti-electrostatic agent (Poloxamer 188) in an azithromycin formulation for inhalation to reduce the effect of charging. The solid state properties of particles can also influence charging behavior. Wong et al. (2014) found that amorphous salbutamol sulfate exhibited more variability in surface charge compared with the crystalline form, which was hypothesized to be due to the less defined molecular arrangement of the amorphous form. According to molecular modeling, the dominant surface face of crystalline salbutamol sulfate contains electronegative sulfate counter-ions which impact the work function (the minimum energy required to remove an electron from the solid surface).

5. Conclusions

Undesirable physicochemical changes in particles engineered for inhalation can be attributed to unanticipated transformations in the solid state due to processing conditions. By understanding material-dependent propensity toward solid-state transformations and how these may be amplified by unique stresses present in top-down particle engineering approaches (e.g., milling) or bottom-up particle engineering approaches (e.g., spray drying), rational decisions can be made regarding the choice of processing approach, limitations of the process design space, and inclusion of stabilizing excipients. Although much research in this area has focused on empirical approaches toward the mitigation of undesirable physicochemical changes in particle engineering, future research directions may incorporate advanced statistical models and artificial intelligence to guide processing and formulation decisions.

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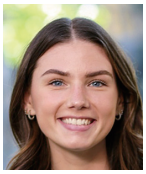

Julia Crowther is a second-year Ph.D. student at the University of Michigan studying Pharmaceutical Sciences. Julia attended the University of Michigan for her undergraduate degree, obtaining a B.S. in Pharmaceutical Sciences with honors. During her undergraduate studies, Julia investigated the impact of lipid composition on atheroprotective properties of HDL-mimetic micelles. Her doctoral research is focused on the role of the gut microbiome in traumatic brain injury.

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