15
Processing-Induced Disorder in Pharmaceutical Materials

Sheng Qi

15.1
Introduction

Q1 Disorder in pharmaceutical materials can be introduced through processing. A good example of unintentionally introduced disorder into the formulation is the generation of a small number of defects at the surface of the tablets during the compression of tableting process [1, 2]. The degree of the disorder can range widely and may be as high as that found in amorphous materials, or it may be relatively low such as is seen in localized defects. The defects can be in the form of point defects, line defects, or plane defects [3]. These defects often can exhibit different levels of effect in terms of altering the physical and mechanical properties of the finished product. If the amount of accumulated defects in the system reaches a critical level, the material can be converted into an amorphous state, and this conversion can impact on the clinical performance of the formulations. The nature and quantity of the disorder are dependent on the intrinsic properties of the material and the particular process used to manipulate the material. A large amount of data has indicated that many of the different processes used for pharmaceuticals may cause disorder of the material. As an example, many recent works have reported the different physical stabilities of amorphous formulations produced by different methods [4–6]. This is likely associated with the different levels of disorder created by different processing methods.

The amorphous state represents the highest level of disorder, which can be recognized through the lack of organized long-range order. Often, during the production of amorphous materials, other disordered states such as different degrees of defects (either different quantity or different type of defects) can be created. The production of amorphous materials can be classified into thermodynamic- and kinetic-based methods, as indicated in Figure 15.1 [3]. Thermodynamic methods are those that follow the equilibrium phase transformation from liquid to the solid state. In these methods, the processed materials are transformed to their liquid state via either melting or dissolving in a solvent. The thermodynamic methods include melt-based methods such as melt-quenching, melt-granulation, hot-melt extrusion (HME), spray-congealing, dry powder coating, thermal

Disordered Pharmaceutical Materials, First Edition. Edited by Marc Descamps.

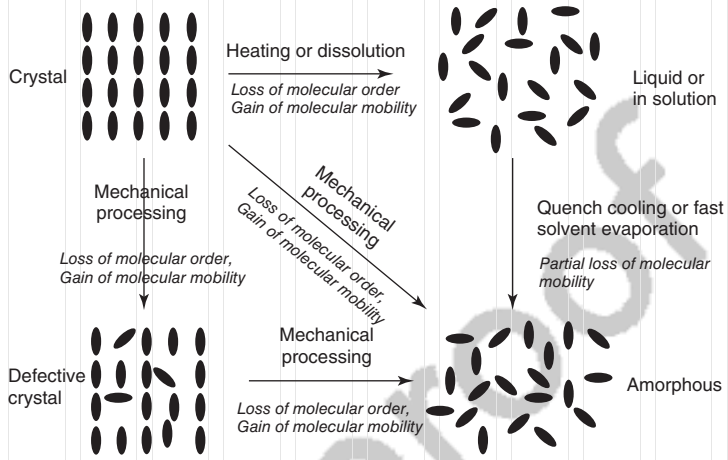

Figure 15.1 Process-induced disorder. (Taken from [3].)

sintering/curing, and solvent-evaporation-based methods such as spray-drying, freeze-drying and electrospinning. Kinetic-based methods rely on the gradual disruption of the molecular arrangement of a crystalline material by progressively creating defects. A typical kinetic-based method is milling. Once the accumulation of the defects reaches a critical level, the material is likely to be converted into an amorphous state. This chapter focuses on the major types of pharmaceutical processing methods that have been widely reported to produce disordered material either intentionally or unintentionally.

15.2 Pharmaceutical Processing

15.2.1 Milling

Milling is common and one of the most frequently used unit operations used by the pharmaceutical industry for reducing the particle size of solids. When milling is applied to crystalline solids, as a result of the mechanical stresses inherent to the milling process, disorder in the crystalline structure of the active pharmaceutical ingredient (API) can be introduced either unintentionally or intentionally. These disorders can take the form of defects in the crystal lattice, polymorphic transformations, complete loss of the crystalline lattice, and conversion to the amorphous state [7–11]. These structural changes may be located only at the surface of the solids, or they may penetrate through the bulk of the material. Depending on the proportion of the material affected, the presence of the disorder can often lead to changes in the physical and chemical properties of the milled solids [11]. The conversion of a crystalline solid to its amorphous state via milling has been

explained by three possible mechanisms: accumulation of crystal defects with a higher free energy level than a certain critical level under kinetically favorable conditions [7, 12]; local overheating during milling, which leads to melting and rapid quenching of the API [7, 8, 11]; and obtaining the amorphous form of the API from the intermediate state formed during polymorphic conversion of the crystalline solid. For instance, the milling of form IV of fananserine could lead to its intermediate amorphous state, which precedes the transformation of the metastable form I polymorphs [11].

The possibility of intentionally generating an amorphous pharmaceutical product through milling or cryo-milling (milling at extremely low temperature) has been reported [7, 11–23]. The amount of disorder induced by milling is governed by many factors including the milling intensity, temperature, additives, and the intrinsic properties of the solid such as glass transition temperature and crystal structure [7, 11–23]. When milling at temperatures below the glass transition of the amorphous API, the increase in Gibbs free energy drives the conversion of the crystalline form to the amorphous form, as illustrated in Figure 15.2 [11]. In these cases (milling at temperatures below the T_g of the API), the milling intensity is crucial in determining the nature of the transformation [11]. Amorphous conversion occurred when the γ-form of crystalline indomethacin was milled with high intensity at room temperature, which is below the T_g of amorphous indomethacin, whereas only polymorphic transformation occurred when milled with lower intensity below T_g [7]. In contrast, regardless of intensity, milling

Color Fig.: **15.2**

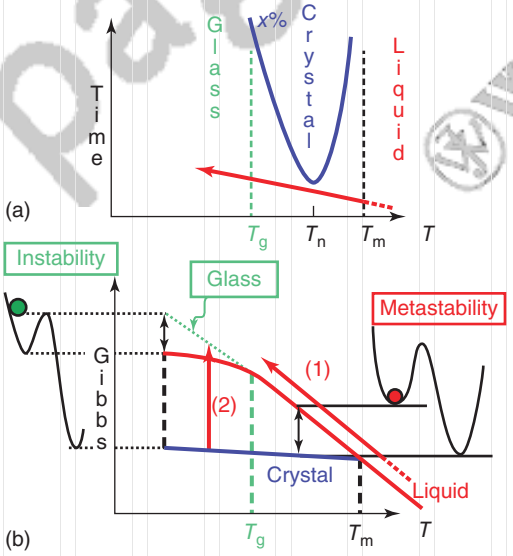

Figure 15.2 (a) Schematic TTT diagram for crystallization in an undercooled melt and conventional vitrification path. (b) Gibbs free enthalpy curve for crystal, liquid (stable and metastable), and glass. Paths 1 and 2 correspond to conventional and solid-state vitrification paths, respectively. (Taken from [11].)

at a temperature above T_g only led to crystalline–crystalline polymorphic transformation [7].

Recently, mechanical milling has also been used to produce solid dispersions and co-amorphous systems [11, 24–29]. However, studies have shown that milling produces less physically stable solid dispersions compared to those prepared by other methods such as spray-drying and melt-quenching [30–32]. Some researchers have attributed this low physical stability to the heterogeneous relaxation of the milled solid dispersions, as indicated by the lower value of the relaxation distribution in comparison to the same systems prepared through spray-drying or melt-quenching [31]. It is also possible that a high proportion of nuclei are present in solid dispersions prepared by milling, which are available to undergo recrystallization on storage. Recently, the formation of co-amorphous materials by milling has been reported. These are complexes of poorly water-soluble drugs in a solid state with other small molecular entities, mainly via intermolecular interaction such as salt formation and hydrogen bonding [29] or interparticle hydrogen bonding [33]. The complexed solids are amorphous in nature. However, the co-amorphous materials produced by milling have been reported to have enhanced physical stability and dissolution rate in comparison to the amorphous APIs alone [26–29]. This has been attributed to the intermolecular interactions between the two drug species at certain stoichiometric ratios, which constrain the molecular mobility of amorphous APIs [26–29].

15.2.2 Thermal Processing Techniques

The basic principles of pharmaceutical thermal processing techniques are partially or completely based on liquefying either the API alone or the API with excipients via heating. Thermal processing techniques are mainly used for controlling or improving the release and the subsequent bioavailability of an API. In many formulations processed by thermal techniques, the disorder states were introduced into the API and the polymeric excipients during the cooling process. The conversion of the crystalline state to a more disordered state, whether completely amorphous or semicrystalline, can facilitate better control of the drug release by altering the properties of the excipients in the formulations. A wide range of thermal processing techniques have been developed or adopted from other industries to pharmaceutical use over the past few decades. Techniques such as melt-mixing, spray-congealing, sintering, melt-granulation, and HME have developed and evolved rapidly for large-scale pharmaceutical production [34]. New emerging thermal processing techniques such as dry powder coating, injection molding, melt-electrospinning, KinetiSol® dispersing, and melt-based 3D printing have been explored for their potential use for scaled-up pharmaceutical manufacturing [34, 35].

15.2.2.1 Simple Melt-Fusion Method

Melt-fusion is the simplest form of thermal processing. It directly liquefies the API and/or excipient, followed by the cooling of mixture into a solid form. If a carrier excipient is involved, mixing during the molten stage is often facilitated by stirring. The common carrier materials are usually lipids and low molecular weight (MW) biopolymers such as fatty acids, triglycerides and self-emulsifying lipids, and low-MW synthetic polymers, such as PEG, GMO, and poloxamers. These materials are mostly crystalline or semicrystalline in nature and have relatively low melting points. The choice of the carrier material plays an important role in controlling or enhancing the dissolution of the API. The molten lipids or polymers can act as the solvent to dissolve the API at temperatures below the melting point of the pure crystalline API. The advantage of using such carrier materials is that they often can facilitate the amorphization of the drug via dissolving the drug in the carrier material during the molten stage.

After cooling, the crystalline state of the excipient material may also be disrupted by the incorporation of the API. In the case of triglycerides, the lipids often solidify as their metastable polymorphs and slowly transform into the stable polymorph on aging [36–38]. This often leads to physical stability concerns regarding the formulation [36–38]. For enhancing the dissolution of poorly soluble APIs, surface-active and self-emulsifying polymers such as Gelucire and poloxamer are often used as carrier materials. Although in some cases the poorly water-soluble APIs are not completely converted into the amorphous state, improvements in the dissolution of the APIs are often still evident [38, 39]. This has been attributed to a number of possible factors including the disorder introduced during the melt cooling (such as the formation of microfine crystals after recrystallization of the drug in the carrier material and partial amorphous conversion) as well as improved solubilization and wetting by the presence of surface-active polymers and lipids [38, 39].

The cooling rate of the melt is one of the most important processing parameters that can affect the degree of disorder. In the case of forming solid dispersions of API in a meltable carrier material, a faster cooling rate has been associated with a lower level of drug recrystallization on aging, rapid reaching of supersaturation state in the dissolution media after dissolution, and enhanced bioavailability of the formulated drug [40, 41]. Melt-quenching is also one of the commonly used methods for converting a crystalline drug to its amorphous state. The melting method can be applied only to compounds that are thermally stable upon melting [42, 43]. For example, piroxicam starts to degrade upon melting, and thus the use of melting methods may not be suitable for this compound [43]. In some cases, it was reported that even the time and temperature allowed for complete melting could affect the physical properties of the generated amorphous system [32, 44]. For example, Van den Brande *et al.* reported a significant degradation of loviride processed using slow cooling [44], but obtained a stable amorphous form by using quench-cooling.

15.2.2.2 Spray-Chilling/Congealing

Spray-chilling is a thermal-based atomization method for producing spherical microparticles containing lipid/polymer excipients and API. The basic principle of spray-chilling is illustrated in Figure 15.3. Droplets of the molten excipients containing either molten API or suspended undissolved API are formed by the atomizers and solidify in the collector [45]. The additional advantage of spray-chilled formulations in comparison to formulations prepared by the melt-fusion method is their small particle size, which leads to a high surface area to volume ratio. This large surface area, at least partially, contributed to the observed improved dissolution of spray-chilled Gelucire–piroxicam microspheres despite that the API was still largely in its crystalline state [39]. During the spray-chilling process, the lipid/polymer excipients are melted and cooled. The cooling process leads to the solidification and recrystallization of the processed materials. This often causes increased disorder of the carrier lipids (recrystallizing to a metastable polymorph) and the API [36–38]. Similar to the melt-fusion method, this can be attributed to the melting and recrystallization process of the formulations.

15.2.2.3 Melt-Granulation

Melt-granulation is a process that involves agglomeration of the API with meltable binders via direct heating or frictional heating during high-shear mixing. The binder material can be premelted and sprayed/dripped into the granulator to form granules, or premixed with the API and then melted during the granulation process [46]. The most popular industrial-scale melt-granulation can be achieved by using fluid-bed melt granulators and high-shear mixers [46]. The granules can be formed through either an immersion-dominated or a coalescence-dominated

Color Fig.: **15.3**

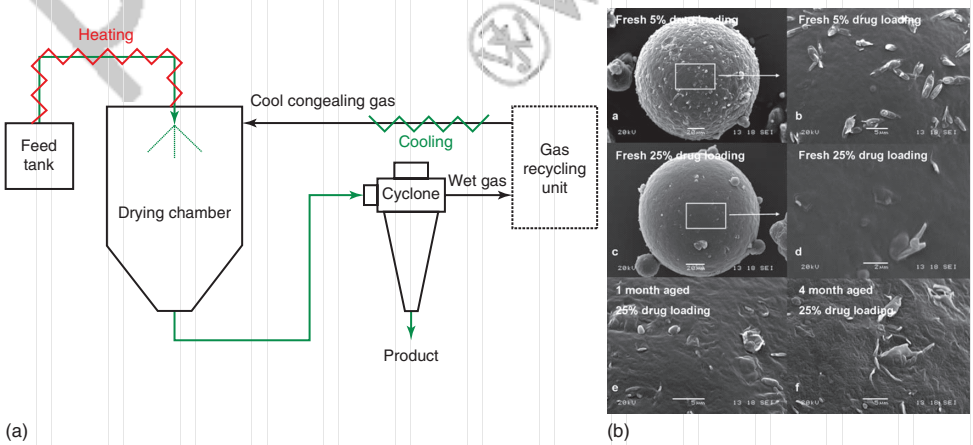

Figure 15.3 (a) Basic operational principle of spray-chilling/congealing (Adapted from *Qi et al.* [39]. Reproduced with permission of Wiley.) and (b) evident drug and lipid excipient instability over aging. (Adapted from Cordeiro *et al.* [45]. Reproduced with permission of Chimica Oggi-Chemistry Today.)

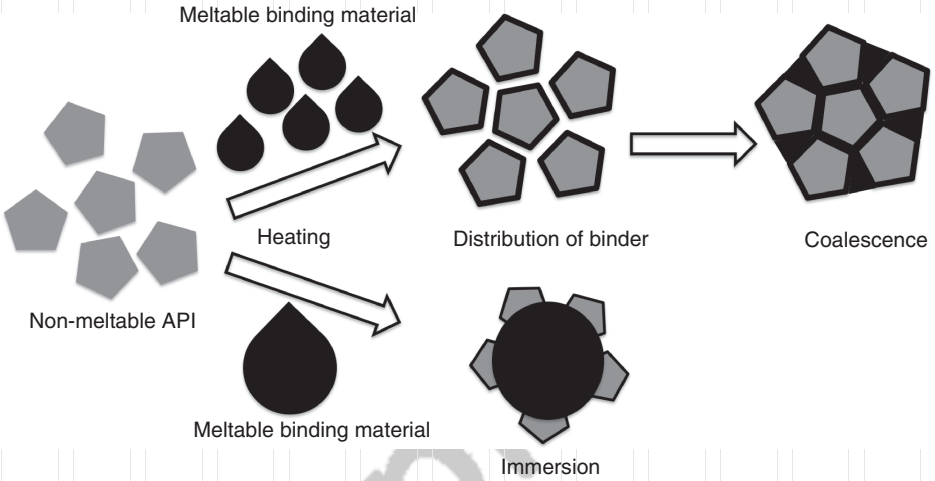

Figure 15.4 Possible mechanisms of granule formation via melt-granulation.

mechanism, as illustrated in Figure 15.4. The mechanism of the formation of granules is highly dependent on the amount of molten binder added and the granulation method used [46].

During the melt-granulation process, the processing temperature is often below the melting point of the API. Thus disorder is mainly introduced into the carrier/binder materials, which experience melting and cooling. The commonly used binder materials for melt-granulation are similar to those used for spray-chilling. These are meltable materials with relatively low melting temperatures (between 50 and 80 °C), such as Compritol 888 ATO, Gelucire, and low-MW PEG. A number of studies have reported the combined use of HME with melt-granulation in order to incorporate polymeric binders with high glass transition temperatures, such as hydroxypropyl methylcellulose (HPMC) and ethylcellulose (EC) into the granules. These polymeric additives have shown good capabilities for modulating the release and disintegration rates of tablets formed by the granules produced by melt-granulation [47, 48].

Q3

15.2.2.4 Thermal Sintering/Curing

Thermal sintering/curing is a less dynamic method in comparison to other thermal processing techniques. It is an additive curing process for preformed pellets, granules, and compressed tablets under elevated temperature [49, 50]. The process can be applied to matrices containing meltable excipients (such as lipids and semicrystalline polymers) or polymers that can be softened during curing [49, 50]. Sintering/curing is often used to modify, in most cases prolong, the drug release behavior of the formulation. It has been reported that the sintering process can cause redistribution of excipients that are thermally responsive [40, 49]. This redistribution of material is believed to be achieved by melting (for meltable excipients) or through increasing the molecular mobility of the excipients in the formulations.

The added advantages of this melting/fusion of excipients in the formulation are reduced porosity (as seen in Figure 15.5) and the subsequent increase in surface hydrophobicity of the formulation attributed to the coating [51]. This decreased porosity and increased surface hydrophobicity can reduce the wettability of the formulation and further contribute to the decrease in the drug release rate [51]. For meltable excipients, the thermal sintering/curing process leads to the recrystallization of the excipient after the curing process is completed. Although scarcely reported in the literature, it is reasonable to predict that lipid-based excipients will go through metastable to stable polymorphic transformation on aging, and the degree of crystallinity of a semicrystallized polymer may be reduced after the sintering process. For polymeric excipients with higher glass transition temperatures, the thermal curing process may introduce an increased degree of cross-linking and structural relaxation is expected after the curing process [49, 51].

15.2.2.5 Dry Powder Coating

Dry powder coating is a process using thermal sintering/curing that converts a dry powder deposited on a surface to a film coating on the surface. This is a solvent-free coating method requiring sufficient adherence of the dry powder to the surface at the first stage of the process. There are a number of dry powder coating techniques based on the adsorption mechanism of the powder layer including liquid-assisted powder deposition, thermal adhesion deposition, and electrostatic deposition [52, 53]. In order to achieve the desired product attributes, novel excipients are often required for these specific manufacturing processes. The success of a dry powder coating process strongly depends on the physical properties of the coating and substrate materials and the interaction between the interfaces formed during the process [52, 53]. Hydrophilic semicrystalline polymers with a low melting point (e.g., polyethylene glycol 3350) are the most frequently used excipients for dry powder coatings. However, other amphiphilic and hydrophobic excipients, such as Pluronic 127 and cetylstearyl alcohol, have also been used. When the processing temperature is above the glass transition temperature of a coating material, the formed film is more "liquid-like" and more susceptible to plastic deformation. As the relationship between the melt viscosity and temperature follows the Arrhenius equation, reduced viscosity can be achieved by using high processing and curing temperatures, which leads to the formation of a higher quality film. A sufficient reduction of the viscosity of the coating material can result in the formation of capillary forces, which facilitate in the adherence of the coating to the solid surface. Under high temperature conditions, surface energy differentials can act as the driving force for the spreading of the semimolten polymer and enhance the coating efficiency [52, 53] (Figure 15.6).

Q4

15.2.2.6 Hot-Melt Extrusion (HME) and Injection Molding

The first use of HME was reported in 1930s for plastic manufacturing as well as in the food industry. It was invented at the end of the eighteenth century by Joseph Brama for the production of lead pipes. This technique was then extensively used in the plastics industry in the middle of the nineteenth century for providing

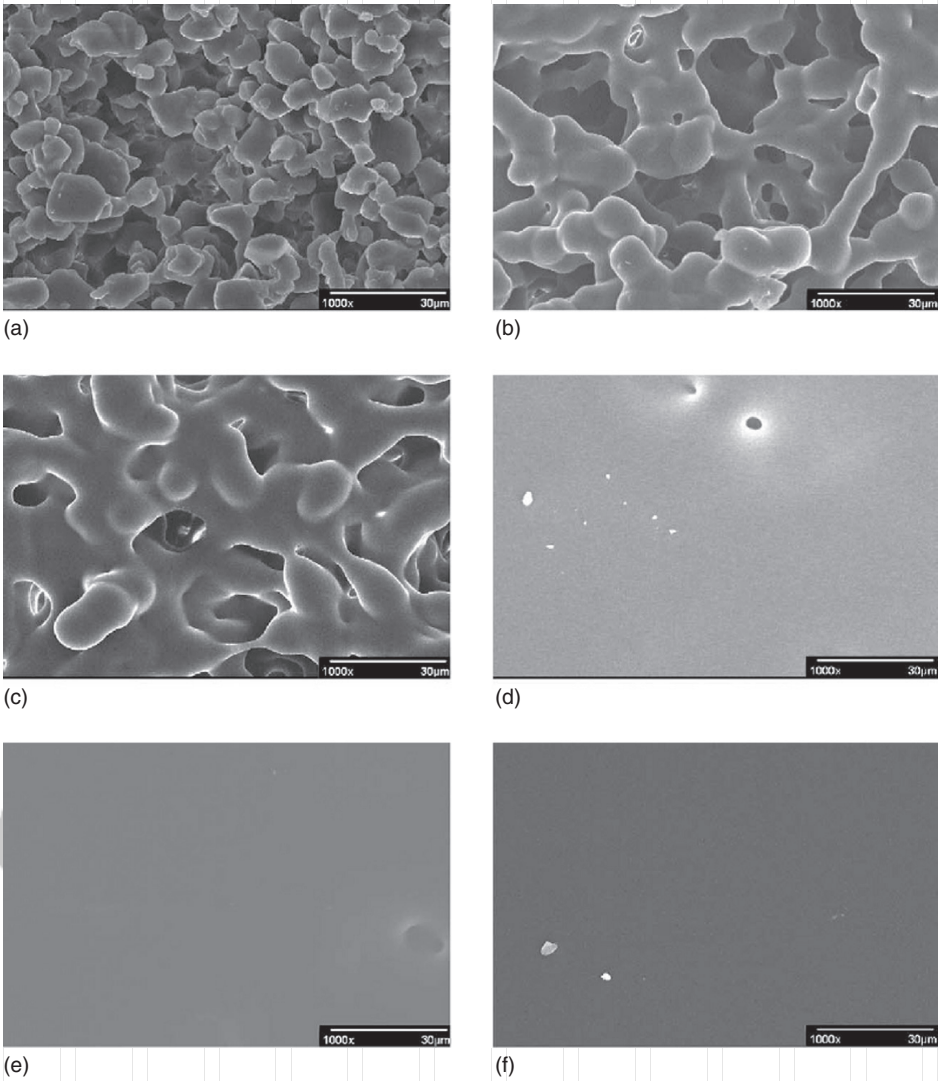

Figure 15.5 SEM images of Eudragit E PO powder films after thermally sintered/cured at 80 °C for (a) 1 h, (b) 2 h, (c) 4 h, (d) 8 h, (e) 12 h, and (f) 24 h. (Adapted from Cerea *et al.* [51]. Reproduced with permission of Elsevier.)

polymeric insulation of wires [54]. More recently, HME has been adopted for producing solid-dispersion-based systems [54, 55]. HME is a single continuous process that involves mixing, melting, homogenizing, and shaping [56]. The ability to process the materials in this way is an obvious requirement associated with HME, and the number of suitable excipients is currently limited. However, the method has the flexibility of being able to use multiple additives such as plasticizers as well as stabilization and solubility/absorption enhancers (such as

Color Fig.: **15.6**

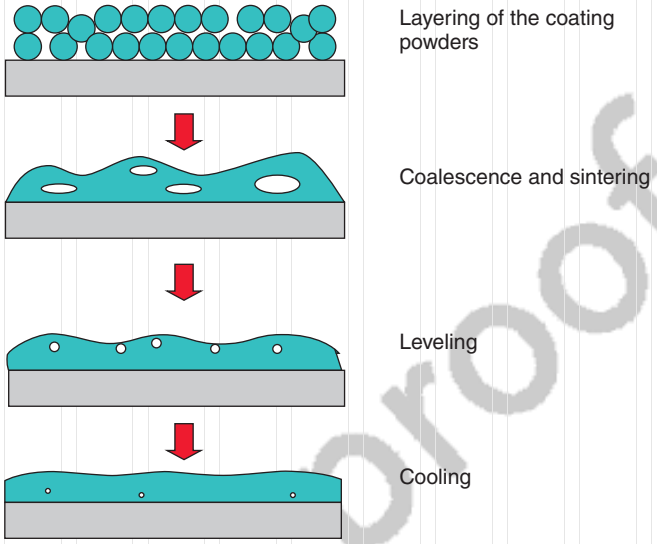

Figure 15.6 Illustration of the essential steps of dry powder coating. (Adapted from Sauer *et al.* [52]. Reproduced with permission of Elsevier.)

surfactants) to optimize the processing behavior and physical performance of the finished dispersions. Amorphous solid dispersions prepared by HME have shown to be able to enhance the dissolution and absorption of poorly soluble drugs, such as indomethacin, itraconazole, felodipine, celecoxib, and ketoprofen (100–106). Other potential applications include targeted and controlled-release dosage forms, multiple unit dosage forms, floating dosage forms, implants, transdermal and transmucosal delivery systems, as well as the formation of nanocomposites for prolonged release [54–56].

The HME process can be divided into three typical zones: the feeding zone, the melting or compression zone, and the metering zone. Each of the zones has a different geometrical screw design that dictates the advance of the process for melting and mixing materials [55]. Because of the elevated operating temperature (at least 30–60 °C above the T_g of the material in order to sufficiently soften the processed materials) and the high level of shear generated by the rotation of the mixing barrels, high levels of disorder can be created during HME. Mixtures of polymers, API, and additives are passed through the feeding system and processed within a closed barrel to allow solubilizing of API in the polymeric matrix. At the end of barrel, high pressure applied within the metering zone forces the molten mass to be extruded through an orifice to produce a product of high density and uniformity [54–56]. Subsequently, the molten material is transported to the downstream equipment for final dosage form manipulation such as melt-pelletization, milling, and tableting.

As with other solid dispersion preparation methods, despite the high number of reported successful case studies in the academic literature, the number of

hot-melt-extruded amorphous solid dispersion products is still very limited. This can be partially attributed to the poor understanding of the material behavior during HME processing and the post processes. Studies on the development of inline analysis of the dispersions during extrusion processing have been tried, showing promising potential for adoption in industrial production [57, 58]. These analytical tools can not only detect in-process degradation and uneven mixing of the drug and excipients but also be used to study the interaction between the drug and polymers in the molten state and under the shearing of the extrusion process. Advanced local and bulk characterization techniques, such as solid-state NMR (SSNMR), atomic force microscopy (AFM), photothermal-microspectroscopy (PT-MS), and thermal transition mapping (TTM), have been used to study hot-melt-extruded solid dispersions on a submicrometer scale in order to gain a better understanding of the disorder in extruded solid dispersions as a result of processing, such as higher level of surface drug recrystallization in comparison to the core of HME extrudates [59–61].

Injection molding is a manufacturing process of shaping thermoplastic or thermoset materials in a closed mold via the application of high temperature and pressure [62]. It is often used in conjunction with HME. It has the advantage over conventional HME in allowing a single-step shape formation of formulations that require precise and/or complex geometries, such as transdermal microneedles or intravaginal rings [63, 64]. Recently, there has been growing interest in using injection molding as a single-step manufacturing process to produce tablet- and capsule-shaped formulations for oral controlled release [65]. The injection molding process introduces additional stress to the hot-melt-extruded samples to allow the material to remelt, which is then forced into the mold under high pressure. However, in most cases, without additional quenching, the cooling process of injection molding is slower in comparison to HME alone. This is because the mold is a large piece of solid metal that has to be preheated to an elevated temperature. Therefore, once the material is injected into the mold, the cooling of the mold to ambient temperate takes much longer than the cooling of the strands of exudates. It is well known that for thermal-melting-based methods, the disorder created during the process is highly dependent on the cooling rate. Therefore injection-molded solid dispersions are expected to be different from HME dispersions in terms of the degree of disorder. However, this has not been extensively studied and requires more work for a better understanding and control of the injection molding process.

15.2.2.7 Other Emerging Thermal Processing Techniques

A range of new thermal processing techniques have been recently developed for manufacturing pharmaceutical formulations. Melt-electrospinning and KinetiSol dispersing (KSD) are two good examples that have shown promising potential in the preparation of solid-dispersion-based formulations. Melt-electrospinning is a modification of the conventional electrospinning technique [35]. This processing technique can produce micro-fibrous structures from polymer melts. The distinct

difference between melt-electrospinning and solution-electrospinning (which will be discussed in a later section in this chapter) is that the electrified molten polymer jet lacks the random dynamic chaotic motion observed in solution-electrospinning. This means that the collection of melt-electrospun fibers can be highly controlled and aligned into predesigned patterns [35]. This has been attributed to the higher viscosity and lack of electrical conductivity of the molten polymer. However, the disadvantage of melt-electrospinning is that the diameters of the produced fibers are within the 5–40 μm range instead of in the nanometer range [35]. Melt-electrospinning has been used to produce amorphous solid dispersions [66], which provided faster dissolution of a poorly soluble model drug in comparison to hot-melt-extruded dispersions. This was attributed to the high surface area of the fibrous formulation. However, the long-term physical stability of the amorphous drug in this form has not been widely studied. As a result of the high surface area, surface instability is expected for this type of formulation on aging (Figure 15.7).

Another good example of an emerging new thermal-based pharmaceutical process is the patented KSD technology. This process uses the frictional heat generated by the shear of sample powder against the paddles rotating at high speed within a cylindrical chamber to melt the API and the excipients to form solid dispersions [67]. In contrast to other thermal processing techniques for producing solid dispersions, the KSD method of elevating the temperature, which leads to the melting of the material, occurs within seconds. This gives this technique the unique advantage of being able to process many thermos-labile APIs that cannot be processed using other thermal methods. The ultrafast temperature elevation accompanied by high shear has also been reported to be able to achieve a higher level of mixing between the drug and polymer in comparison to other thermal processes such as HME [68]. For example, hot-melt-extruded itraconazole and HPMC show phase separation of drug-rich and polymer-rich domains, whereas only a single miscible phase can be detected by differential scanning calorimetry (DSC) in the KSD solid dispersions [68]. Therefore, KSD technology seems to be a good method for intentionally incorporating a high level of disorder into the processed formulations.

15.2.3 Solvent-Evaporation-Based Processing Techniques

Solvent-evaporation-based methods are important processing techniques for both raw materials, such as crystallization of the raw drug, and formulation manufacturing in the pharmaceutical industry. As crystallization is not within the scope of this chapter, we will solely focus on the processing that can potentially induce the formation of the disordered state during the manufacture of formulations. The widely used solvent-evaporation-based processing techniques in pharmaceutical formulation production include spray-drying, freeze-drying, film casting, and film coating. There are new, innovative techniques still at bench-scale development, such as spray-freeze-drying, solution electrospinning,

Color Fig.: **15.7**

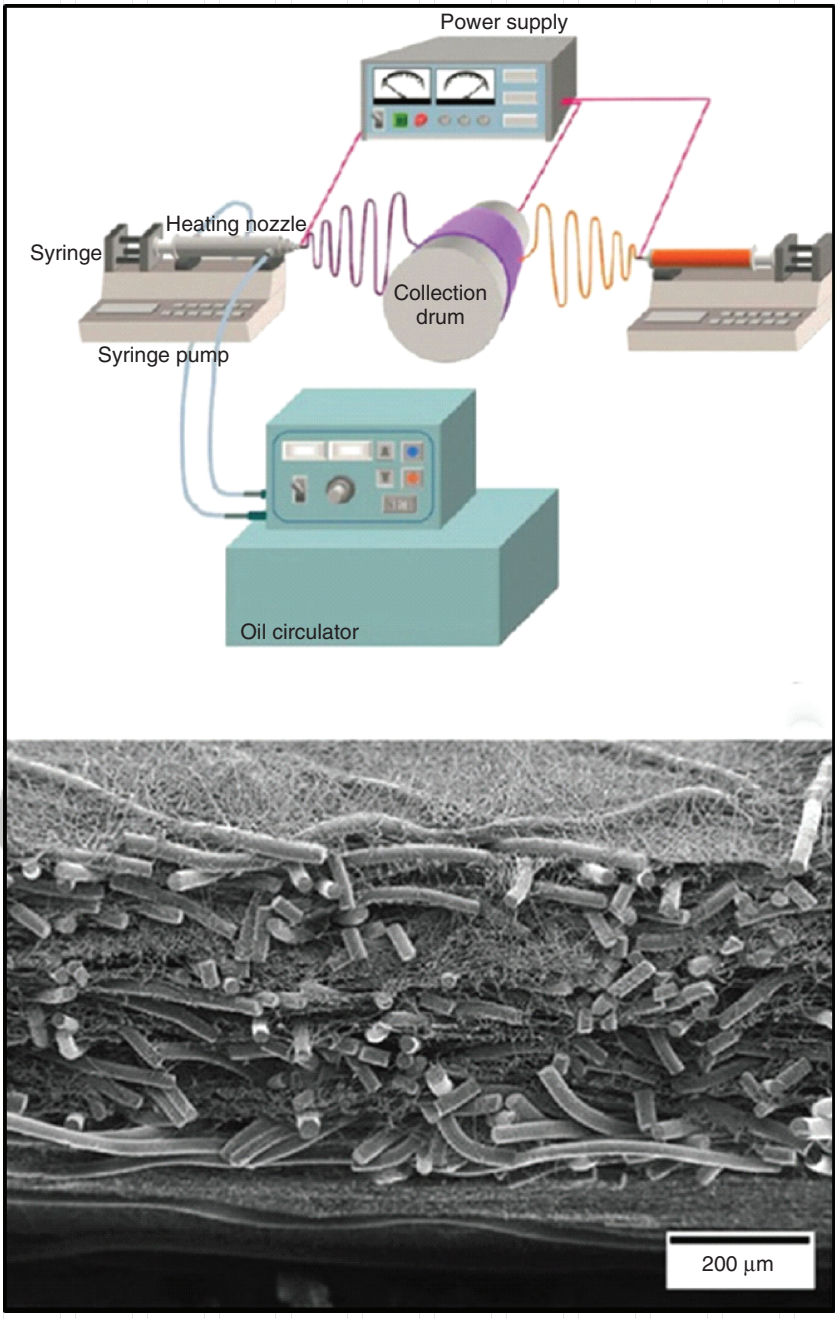

Figure 15.7 Melt-electrospinning setup and the micro and nanofibers produced by melt electrospinning. (Adapted from Brown *et al.* [35]. Reproduced with permission of Wiley.)

and spin coating, which have shown great potential for the preparation of highly sophisticated formulations.

15.2.3.1 Spray-Drying

Spray-drying is a unit operation for transforming liquid solutions or suspensions into solid products by rapidly atomizing the solutions/suspensions and drying them with a hot gas. Modern spray-drying technology can process thermo-liable materials, such as proteins and peptides through careful manipulation of the processing parameters and selection of excipients [69]. It is a well-established technology for the formation of solid microparticles, with applications in the delivery of poorly soluble drugs, proteins, vaccines, and inhalation therapies [69, 70]. The nature of solidifying the formulation via rapid, complete solvent removal leads to an inherent high potential for forming disordered states in the product either intentionally or unintentionally.

A spray-drying process can be divided into the atomization and drying steps. The atomization step produces droplets of the starting solution. The performance of the atomizer directly impacts on the size of the dried particles. There are four main types of industrially used atomizers: rotary atomizers, pressure nozzles, two-fluid nozzles, and ultrasonic atomizers [71]. The droplet size can also be influenced by the feed concentration and solution viscosity of the starting solution. This stage is less likely to contribute to the generation of disorder to the system in comparison to the drying step.

The drying stage is a complex transformation process from droplet to dry particles involving both heat and mass transport in a timescale of milliseconds [72]. During this step, there are rapid and significant changes at the surfaces of the droplets in terms of distribution and movement of the components [70, 72]. For solutions containing polymers and macromolecules, during drying significant surface adsorption of the molecules leads to surface enrichment and saturation followed by shell formation and complete solidification of the hollow particles [70]. However, if the diffusion of the solutes is relatively fast, they remain evenly distributed in the entire droplet. This leads to low surface enrichment and the formation of solid particles instead [70].

Regardless of the geometry of the particles, the formation of disorder during the drying stage is governed by the intrinsic properties of the solutes. For small molecules, whether the solidification process leads to crystallization or the formation of the amorphous form is highly dependent on the glass transition temperature in relation to the drying outlet temperature and the crystallization kinetics of the material. For large molecules with slower diffusion coefficients in solution, the disorder can be concentrated and immobilized at the shell of the particles after drying. Therefore, spray-drying has been used to prepare solid dispersions of small molecular weight drugs with polymeric carriers to intentionally form amorphous state of the drug in order to achieve faster dissolution [69, 70]. The intimate mixing following dissolution in a common solvent with the polymer and rapid drying can have the equivalent effect of fast quenching and "freeze" the drug molecules in a molecular dispersion with the polymeric carrier [69, 72]. For example, the

second-generation non-nucleoside reverse transcriptase inhibitor, etravirine, for treating resistant HIV, was unable to provide efficient bioavailability if formulated into nanocrystals or solid dispersions via HME or film casting, but has proven to be successful when formulated as a spray-dried amorphous dispersion with HPMC [6].

15.2.3.2 Freeze-Drying

Freeze-drying, also known as *lyophilization*, is a well-established process that is traditionally used for used for stabilizing labile substances or processing pharmaceuticals of biological origin such as proteins, serum, vaccines, peptide drugs, and liposomes, often administered parenterally [73]. Recently, the application of freeze-drying has been significantly expanded to include manufacturing orally disintegrating tablets (ODTs) and fast dissolving tablets and films (FDTs), wafers for buccal delivery and wound healing, inhalable powders, and 3D scaffolds [74]. Many of the novel applications of freeze-drying are related to its ability to produce low-density and highly porous material.

The freeze-drying process can be divided into three stages: freezing, primary drying, and secondary drying. In the freezing step, the solvent (typically water) is separated from the solute to form ice crystals. This leads to the solute molecules concentrating as separate micro-islands, and this process is termed *freeze concentration* [73]. This formation of phase-separated, concentrated domains and ice crystals is the first step, which may initiate the formation of disordered phases. Therefore, the widespread opinion is that the primary drying stage should be conducted at temperatures below T_g to ensure the maintenance of the stability of macromolecules in particular [75]. However, some studies have demonstrated that freeze-drying at temperatures well above T_g without the need for vitrification can still preserve the activity of proteins as a result of the slow unfolding kinetics of proteins in relation to the timescale of the freeze-drying process [75].

The primary drying process involves the sublimation of ice under high vacuum with elevated shelf-temperature in order to supply the heat required for ice sublimation. The sublimated ice is then condensed on a cooled plate/coils ($< -50\,^{\circ}C$) in the condenser [73]. The secondary drying phase removes any residual moisture content at a further increased temperature (i.e., $25-60\,^{\circ}C$). Applying a low pressure at elevated temperature further dries any "unfrozen" water in the "freeze concentrate." For labile materials such as proteins, the drying temperatures and their duration are critical for retaining protein activity and post-process stability. These two drying steps are time consuming and can give the system time to further develop any disordered phase formed during the freezing step. However, the literature does not show any discussion on the effect of drying conditions on the stability of the freeze-dried, low-MW compounds.

In order to expand the applications of the freeze-drying process to produce microparticles, in recent years, freeze-drying has been used in conjunction with spray-drying. This combined technology is called spray-freeze-drying. Spray-freeze-drying has been used to prepare solid dispersions for the delivery of poorly soluble APIs [76]. A few studies have reported the ability of using freeze-drying

to stabilize amorphous drugs in a solid dispersion and the superior physical stability and dissolution performance of freeze-dried solid dispersions compared to other solvent-evaporation-based methods [76, 77]. The underlying mechanism of this enhancement is still poorly understood. This may be attributed to the low operating temperatures in comparison to other solvent-based methods. However, the powder obtained from this method often have poor flowability as a result of its low density, which can potentially affect downstream processing for tableting or capsule-filling.

15.2.3.3 Film Coating and Casting

Film coating is one of the most commonly used pharmaceutical processes for coating solid dosage forms such as tablets and pellets for the purpose of taste-masking as well as controlled and targeted drug release [78, 79]. There are two main types of film coating: aqueous film coating and organic solvent film coating. The main components in a coating solution are the coating polymer and plasticizers. The coating liquid is sprayed on to the solid tablets/pellets in a coating pan with continuous (hot) air flow for drying. The process parameters, such as spray rate, atomizing air pressure, inlet air temperature, and the rotation speed of the pan, can significantly affect the quality of the film formed [78, 79]. If the heterogeneity of the coating film is considered to be a degree of disorder, alteration of process parameters and optimization of solution properties such as viscosity, solid content, and interfacial tension at the solid tablet/pellet surface will facilitate the minimization of the disorder created during the process.

Conventional film casting is a more static method compared to film coating, and is considerably different from spray-drying with regard to both film formation and the rate of solvent removal. The drying process of the film casting method can be accomplished with or without elevated temperatures and vacuum. However, the rate of solvent removal in the film casting method is much slower than in the spray-drying and film coating processes. In the cases of using film casting to prepare solid dispersions, the physical structure of the finished solid dispersion can be significantly influenced by the solvent removal rate. Janssens and coworkers compared the solid dispersions of itraconazole prepared by film casting and spray-drying methods [4, 6]. The experimental solubility of the model drug in the casted films was much lower than that measured for the spray-dried dispersions. Although these results were ascribed to the effect of the manufacturing methodology used on the physical structure of the resulting solid dispersion, the mechanism underlying the observed deviation in solubility is still not well understood [4, 6]. It is possible that, during the casting process, the local drug concentration increases with continuous removal of solvents from the film. This may create domains with high drug concentration, which exceeds the saturation solubility of drug in the polymer. These domains may then act as nuclei for drug recrystallization. If the crystallization kinetics of the drug is faster than the solvent removal, a crystalline drug would be expected in the finished film.

Q8

15.2.3.4 Emerging Solvent-Evaporation-Based Processing Technologies

Electrospinning and spin coating are two emerging solvent-based processing technologies that have been recently adopted for pharmaceutical formulation preparation [80–82]. Electrospinning and electrospraying are two electrohydrodynamic techniques that have wide biomedical applications and have just recently been introduced to the pharmaceutical community for the preparation of amorphous solid dispersions [80, 81]. Electrospinning is a process in which a strong electrical potential is applied to a liquid (a solution or molten mixture of the drug and a polymer). At a critical voltage, a charged liquid jet of the sample solution is ejected from the tip of the liquid droplet and travels toward a collector connected to a grounded electrode [82–84]. On the journey to the collector, the solvent evaporates and nano- or microfibers can be formed and collected on the collector, which can be of different geometries. By altering the viscosity of the liquid solution and the processing parameters, electrospinning can be transformed into electrospraying, in which well-separated micro- and nanoparticles can be obtained [80–84]. In comparison to the amorphous solid dispersions formed using other solvent-evaporation-based methods, electrospun fibers can offer even better improvements in the dissolution enhancement of amorphous solid dispersion containing poorly soluble drugs as a result of their unique process-related features such as high surface area to volume ratio and highly porous interconnected network structure with tunable pore size (the pores refer to the spaces created between the fibers) [80, 81]. However, these characteristics may compromise the physical stability of the formulation. The high surface area exposed to the external environment can accelerate phase separation and crystallization of drug from the fibers. However, the physical instability and crystallization behavior in these nano- and microfibers are still poorly understood.

Spin coating is a rapid solvent-evaporation-based process that prepares thin and ultrathin films with controllable thickness (normally micrometer to nanometer thickness) on a substrate, as illustrated in Figure 15.8. It has been widely used in microfabrication in the semiconductor industry [85]. Unlike the traditional pharmaceutical film casting and film coating, the rate of solvent evaporation in spin coating is much higher because of the high spinning speed (normally 1000–10 000 rpm). This rapid solvent evaporation and solidification process can reduce the risk of clustering and phase separation of the drug in the films by shortening the time the system is not in the solid state (before the solvent has completely evaporated). With the advantages of high reproducibility, fast preparation, and precise control of the manufacturing process, spin coating has been used to prepare amorphous solid dispersions for experiments designed to provide a fundamental understanding of the physical stability of amorphous solid dispersions [82, 86–88]. For example, Ng *et al.* used spin coating to prepare solid dispersions containing model drugs including celecoxib, felodipine, fenofibrate, and carbamazepine and polymers with different hygroscopicities [82]. It has been reported that the key factors that affected the physical stability

Q9

Color Fig.: **15.8**

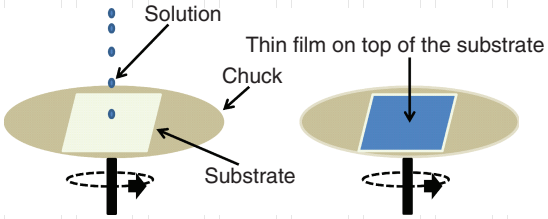

Figure 15.8 Procedure of using spin coating to prepare a thin film on a substrate.

of the solid dispersions under stressed humidity were the intrinsic physical stability of drugs alone and the hygroscopicity of polymers. In another study from the same group, drug migration from the bulk toward the surface of the spin-coated amorphous solid dispersion thin films of felodipine–PVP K29/32 was discovered during aging under stressed humidity [83, 87]. It has been reported that the film thickness can have significant effects on the crystal growth and hydrophobicities of the spin-coated crystalline polymeric films [82]. Therefore, it will be interesting to further investigate the relationship between the film thickness and the degrees of instability/crystallization on aging.

15.3 Conclusion

In a broad sense, disorder can be classified as any change of the molecular arrangement from its original form. If focusing on crystalline APIs, the degree of disorder increases with the change from crystal to crystal defects and eventually to the amorphous state. If focusing on semicrystalline polymers, the degree of disorder can be a decrease in the amount of crystalline domains in the polymer. In this chapter, commonly used and emerging pharmaceutical processing technologies were discussed with respect to their ability to create disordered states in the finished products either intentionally or unintentionally. Milling-based methods gradually build up the degree of disorder into the system, and significant accumulation of the disorder can eventually convert a crystalline material to an amorphous one. This is very different from the melting and solvent-based methods. Thermal melting and solvent-based methods start by introducing complete disorder into the systems either via melting the API with the excipients or dissolving them in a common solvent. The degree of disorder recovers during the second stage of the process, which is either cooling or drying. The conversion of disorder back to the low-energy crystalline state is often associated with physical instability of the formulations. A better understanding of the generation of disorders and their impact on the clinical outcome of the formulations requires a firm knowledge of the process and the characteristics of the material during and after processing.

References

1. Koivisto, M., Heinänen, P., Tanninen, V.P., and Lehto, V.P. (2006) Depth profiling of compression-induced disorders and polymorphic transition on tablet surfaces with grazing incidence X-ray diffraction. *Pharm. Res.*, **23** (4), 813–820.
2. Riippi, M., Tanninen, V., and Yliruusi, J. (2000) Effect of compression force on the crystal properties of erythromycin acistrate tablets. *Eur. J. Pharm. Biopharm.*, **50** (3), 365–371.
3. Feng, T., Pinal, R., and Carvajal, M.T. (2008) Process induced disorder in crystalline materials: differentiating defective crystals from the amorphous form of griseofulvin. *J. Pharm. Sci.*, **97** (8), 3207–3221.
4. Janssens, S., De Zeure, A., Paudel, A., Van Humbeeck, J., Rombaut, P., and Van den Mooter, G. (2010) Influence of preparation methods on solid state supersaturation of amorphous solid dispersions: a case study with itraconazole and eudragit E100. *Pharm. Res.*, **27** (5), 775–785.
5. Karmwar, P., Graeser, K., Gordon, K.C., Strachan, C.J., and Rades, T. (2011) Investigation of properties and recrystallisation behaviour of amorphous indomethacin samples prepared by different methods. *Int. J. Pharm.*, **417**, 94–100.
6. Weuts, I., Van Dycke, F., Voorspoels, J., De Cort, S., Stokbroekx, S., Leemans, R., Brewster, M.E., Xu, D., Segmuller, B., Turner, Y.T.A., Roberts, C.J., Davies, M.C., Qi, S., Craig, D.Q.M., and Reading, M. (2011) Physicochemical properties of the amorphous drug, cast films, and spray dried powders to predict formulation probability of success for solid dispersions: etravirine. *J. Pharm. Sci.*, **100**, 260–274.
7. Descamps, M., Willart, J.F., Dudognon, E., and Caron, V. (2007) Transformation of pharmaceutical compounds upon milling and comilling: the role of T_g. *J. Pharm. Sci.*, **96**, 1398–1407.
8. Willart, J.F., Carpentier, L., Danède, F., and Descamps, M. (2012) Solid-state vitrification of crystalline griseofulvin by mechanical milling. *J. Pharm. Sci.*, **101** (4), 1570–1577.
9. Trasi, N.S., Boerrigter, S.X., and Byrn, S.R. (2010) Investigation of the milling-induced thermal behavior of crystalline and amorphous griseofulvin. *Pharm. Res.*, **27** (7), 1377–1389.
10. Otte, A. and Carvajal, M.T. (2011) Assessment of milling-induced disorder of two pharmaceutical compounds. *J. Pharm. Sci.*, **100** (5), 1793–1804.
11. Willart, J.F. and Descamps, M. (2008) Solid state amorphization of pharmaceuticals. *Mol. Pharm.*, **5**, 905–920.
12. Elamin, A.A., Ahlneck, C., and Alderborn, G.C.N. (1994) Increased metastable solubility of milled griseofulvin, depending on the formation of a disordered surface structure. *Int. J. Pharm.*, **111**, 159–170.
13. Luisi, B.S., Medek, A., Liu, Z., Mudunuri, P., and Moulton, B. (2012) Milling-induced disorder of pharmaceuticals: one-phase or two-phase system? *J. Pharm. Sci.*, **101** (4), 1475–1485.
14. Qi, S., Weuts, I., De Cort, S., Stokbroekx, S., Leemans, R., Reading, M., Belton, P., and Craig, D.Q. (2010) An investigation into the crystallisation behaviour of an amorphous cryomilled pharmaceutical material above and below the glass transition temperature. *J. Pharm. Sci.*, **99** (1), 196–208.
15. Balani, P.N., Ng, W.K., Chan, S.Y., and Tan, R.B.H. (2010) Influence of excipients in co-milling on mitigating milling-induced amorphization or structural disorder of crystalline pharmaceutical actives. *J. Pharm. Sci.*, **99**, 2462–2474.
16. Gupta, M.K., Vanwert, A., and Bogner, R.H. (2003) Formation of physically stable amorphous drugs by milling with Neusilin. *J. Pharm. Sci.*, **92** (3), 536–551.
17. Bahl, D. and Bogner, R.H. (2006) Amorphization of indomethacin by co-grinding with Neusilin US2: amorphization kinetics, physical stability and mechanism. *Pharm. Res.*, **23** (10), 2317–2325.
18. Trasi, N.S. and Byrn, S.R. (2012) Mechanically induced amorphization

of drugs: a study of the thermal behavior of cryomilled compounds. *AAPS PharmSciTech*, **13** (3), 772–784.

19. Hu, Y., Macfhionnghaile, P., Caron, V., Tajber, L., Healy, A.M., Erxleben, A., and McArdle, P. (2013) Formation, physical stability, and quantification of process-induced disorder in cryomilled samples of a model polymorphic drug. *J. Pharm. Sci.*, **102** (1), 93–103.
20. Chattoraj, S., Bhugra, C., Telang, C., Zhong, L., Wang, Z., and Sun, C.C. (2012) Origin of two modes of non-isothermal crystallization of glasses produced by milling. *Pharm. Res.*, **29** (4), 1020–1032.
21. Willart, J.F., Dujardin, N., Dudognon, E., Danède, F., and Descamps, M. (2010) Amorphization of sugar hydrates upon milling. *Carbohydr. Res.*, **345** (11), 1613–1616.
22. Chieng, N., Zujovic, Z., Bowmaker, G., Rades, T., and Saville, D. (2006) Effect of milling conditions on the solid-state conversion of ranitidine hydrochloride form 1. *Int. J. Pharm.*, **327** (1–2), 36–44.
23. Otte, A., Zhang, Y., Carvajal, T., and Pinal, R. (2012) Milling induces disorder in crystalline griseofulvin and order in its amorphous counterpart. *CrystEngComm*, **14**, 2560–2570.
24. Kang, N., Lee, J., Choi, J.N., Mao, C., and Lee, E.H. (2014) Cryomilling-induced solid dispersion of poor glass forming/poorly water-soluble mefenamic acid with polyvinylpyrrolidone K12. *Drug Dev. Ind. Pharm.*, **22**, 1–11.
25. Al-Obaidi, H., Lawrence, M.J., Al-Saden, N., and Ke, P. (2013) Investigation of griseofulvin and hydroxypropylmethyl cellulose acetate succinate miscibility in ball milled solid dispersions. *Int. J. Pharm.*, **443** (1-2), 95–102.
26. Löbmann, K., Laitinen, R., Grohganz, H., Gordon, K.C., Strachan, C., and Rades, T. (2011) Co-amorphous drug systems: enhanced physical stability and dissolution rate of indomethacin and naproxen. *Mol. Pharm.*, **8** (5), 1919–1928.
27. Laitinen, R., Löbmann, K., Grohganz, H., Strachan, C., and Rades, T. (2014) Amino acids as co-amorphous excipients for simvastatin and glibenclamide: physical properties and stability. *Mol. Pharm.*, **11** (7), 2381–2389.
28. Löbmann, K., Strachan, C., Grohganz, H., Rades, T., Korhonen, O., and Laitinen, R. (2012) Co-amorphous simvastatin and glipizide combinations show improved physical stability without evidence of intermolecular interactions. *Eur. J. Pharm. Biopharm.*, **81** (1), 159–169.
29. Laitinen, R., Löbmann, K., Strachan, C.J., Grohganz, H., and Rades, T. (2013) Emerging trends in the stabilization of amorphous drugs. *Int. J. Pharm.*, **453** (1), 65–79.
30. Graeser, K.A., Strachan, C.J., Patterson, J.E., Gordon, K.C., and Rades, T. (2008) Physicochemical properties and stability of two differently prepared amorphous forms of simvastatin. *Cryst. Growth Des.*, **8**, 128–135.
31. Ke, P., Hasegawa, S., Al-Obaidi, H., and Buckton, G. (2012) Investigation of preparation methods on surface/bulk structural relaxation and glass fragility of amorphous solid dispersions. *Int. J. Pharm.*, **422** (1-2), 170–178.
32. Wojnarowska, Z., Grzybowska, K., Adrjanowicz, K., Kaminski, K., Paluch, M., Hawelek, L., Wrzalik, R., Dulski, M., Sawicki, W., Mazgalski, J., Tukalska, A., and Bieg, T. (2010) Study of the amorphous glibenclamide drug: analysis of the molecular dynamics of quenched and cryomilled material. *Mol. Pharm.*, **7** (5), 1692–1707.
33. Hu, Y., Gniado, K., Erxleben, A., and McArdle, P. (2014) Mechanochemical reaction of sulfathiazole with carboxylic acids: formation of a cocrystal, a salt, and coamorphous solids. *Cryst. Growth Des.* doi: 10.1021/cg401673z
34. Keen, J.M., McGinity, J.W., and Williams, R.O. III, (2013) Enhancing bioavailability through thermal processing. *Int. J. Pharm.*, **450** (1-2), 185–196.
35. Brown, T.D., Dalton, P.D., and Hutmacher, D.W. (2011) Direct writing by way of melt electrospinning. *Adv. Mater.*, **23** (47), 5651–5657.
36. Khan, N. and Craig, D.Q. (2004) Role of blooming in determining the storage stability of lipid-based dosage forms. *J. Pharm. Sci.*, **93** (12), 2962–2971.

37. Windbergs, M., Strachan, C.J., and Kleinebudde, P. (2009) Investigating the principles of recrystallization from glyceride melts. *AAPS PharmSciTech*, **10** (4), 1224–1233.
38. Windbergs, M., Strachan, C.J., and Kleinebudde, P. (2009) Understanding the solid-state behaviour of triglyceride solid lipid extrudates and its influence on dissolution. *Eur. J. Pharm. Biopharm.*, **71** (1), 80–87.
39. Qi, S., Marchaud, D., and Craig, D.Q. (2010) An investigation into the mechanism of dissolution rate enhancement of poorly water-soluble drugs from spray chilled gelucire 50/13 microspheres. *J. Pharm. Sci.*, **99** (1), 262–274.
40. Alonzo, D.E., Zhang, G.G., Zhou, D., Gao, Y., and Taylor, L.S. (2010) Understanding the behavior of amorphous pharmaceutical systems during dissolution. *Pharm. Res.*, **27**, 608–618.
41. Brough, C. and Williams, R.O. (2013) Amorphous solid dispersions and nano-crystal technologies for poorly water-soluble drug delivery. *Int. J. Pharm.*, **453**, 157–166.
42. Patterson, J., James, M., Forster, A., Lancaster, R., Butler, J., and Rades, T. (2004) The influence of thermal and mechanical preparative techniques on the amorphous state of four poorly soluble compounds. *J. Pharm. Sci.*, **94**, 1998–2012.
43. Forster, A., Hempenstall, J., Tucker, I., and Rades, T. (2001) The potential of small-scale fusion experiments and the Gordon-Taylor equation to predict the suitability of drug/polymer blends for melt extrusion. *Drug Dev. Ind. Pharm.*, **27** (6), 549–560.
44. Van den Brande, J., Weuts, I., Verreck, G., Peeters, J., Brewster, M., and Van den Mooter, G. (2004) DSC analysis of the anti-HIV agent loviride as a preformulation tool in the development of hot-melt extrudates. *J. Therm. Anal. Calorim.*, **77** (2), 523–530.
45. Cordeiro, P., Temtem, M., and Winters, C. (2013) Spray congealing: applications in the Pharmaceutical Industry. *Chim. Oggi-Chem. Today*, **31** (5), 69–73.
46. Passerini, N., Calogerà, G., Albertini, B., and Rodriguez, L. (2010) Melt granulation of pharmaceutical powders: a comparison of high-shear mixer and fluidised bed processes. *Int. J. Pharm.*, **391** (1-2), 177–186.
47. Weatherley, S., Mu, B., Thompson, M.R., Sheskey, P.J., and O'Donnell, K.P. (2013) Hot-melt granulation in a twin screw extruder: effects of processing on formulations with caffeine and Ibuprofen. *J. Pharm. Sci.*, **102** (12), 4330–4336.
48. Van Melkebeke, B., Vermeulen, B., Vervaet, C., and Remon, J.P. (2006) Melt granulation using a twin-screw extruder: a case study. *Int. J. Pharm.*, **326** (1-2), 89–93.
49. Alkhatib, H.S., Hamed, S., Mohammad, M.K., Bustanji, Y., Alkhalidi, B., Aiedeh, K.M., and Najjar, S. (2010) Effects of thermal curing conditions on drug release from polyvinyl acetate-polyvinyl pyrrolidone matrices. *AAPS PharmSciTech*, **11** (1), 253–266.
50. Sauer, D. and McGinity, J.W. (2009) Influence of additives on melt viscosity, surface tension, and film formation of dry powder coatings. *Drug Dev. Ind. Pharm.*, **35** (6), 646–654.
51. Cerea, M., Zheng, W., Young, C.R., and McGinity, J.W. (2004) A novel powder coating process for attaining taste masking and moisture protective films applied to tablets. *Int. J. Pharm.*, **279** (1-2), 127–139.
52. Sauer, D., Cerea, M., DiNunzio, J., and McGinity, J. (2013) Dry powder coating of pharmaceuticals: a review. *Int. J. Pharm.*, **457** (2), 488–502.
53. Luo, Y., Zhu, J., Ma, Y., and Zhang, H. (2008) Dry coating, a novel coating technology for solid pharmaceutical dosage forms. *Int. J. Pharm.*, **358** (1-2), 16–22.
54. Repka, M.A., Majumdar, S., Kumar Battu, S., Srirangam, R., and Upadhye, S.B. (2008) Applications of hot-melt extrusion for drug delivery. *Expert Opin. Drug Delivery*, **5** (12), 1357–1376.
55. Lang, B., McGinity, J.W., and Williams, R.O. III, (2014) Hot-melt extrusion - basic principles and pharmaceutical applications. *Drug Dev. Ind. Pharm.*, in press.
56. Breitenbach, J. (2002) Melt extrusion: from process to drug delivery

technology. *Eur. J. Pharm. Biopharm.*, **54** (2), 107–117.

57. Saerens, L., Vervaet, C., Remon, J.P., and De Beer, T. (2014) Process monitoring and visualization solutions for hot-melt extrusion: a review. *J. Pharm. Pharmacol.*, **66** (2), 180–203.
58. De Beer, T., Burggraeve, A., Fonteyne, M., Saerens, L., Remon, J.P., and Vervaet, C. (2011) Near infrared and Raman spectroscopy for the in-process monitoring of pharmaceutical production processes. *Int. J. Pharm.*, **417** (1–2), 32–47.
59. Qi, S., Belton, P., Nollenberger, K., Gryczke, A., and Craig, D. (2011) Compositional analysis of low quantities of phase separation in hot melt extruded solid dispersions: a combined atomic force microscopy, photothermal Fourier-transform infrared microspectroscopy and localised thermal analysis approach. *Pharm. Res.*, **28** (9), 2311–2316.
60. Yang, Z., Nollenberger, K., Albers, J., Craig, D., and Qi, S. (2013) Microstructure of an immiscible polymer blend and its stabilization effect on amorphous solid dispersions. *Mol. Pharm.*, **10** (7), 2767–2780.
61. Lauer, M.E., Siam, M., Tardio, J., Page, S., Kindt, J.H., and Grassmann, O. (2013) Rapid assessment of homogeneity and stability of amorphous solid dispersions by atomic force microscopy—from bench to batch. *Pharm. Res.*, **30** (8), 2010–2022.
62. Zema, L., Loreti, G., Melocchi, A., Maroni, A., and Gazzaniga, A. (2012) Injection molding and its application to drug delivery. *J. Controlled Release*, **159** (3), 324–331.
63. Sammoura, F., Kang, J.J., Heo, Y.M., and Lin, L. (2007) Polymeric microneedle fabrication using a micro injection molding technique. *Microsyst. Technol. J.*, **13**, 517–522.
64. Clark, M.R., Johnson, T.J., McCabe, R.T., Clark, J.T., Tuitupou, A., Elgendy, H., Friend, D.R., and Kiser, P.F. (2012) A hot-melt extruded intravaginal ring for the sustained delivery of the antiretroviral microbicide UC781. *J. Pharm. Sci.*, **101** (2), 576–587.
65. Gazzaniga, A., Cerea, M., Cozzi, A., Foppoli, A., Maroni, A., and Zema, L. (2011) A novel injection-molded capsular device for oral pulsatile delivery based on swellable/erodible polymers. *AAPS PharmSciTech*, **12** (1), 295–303.
66. Nagy, Z.K., Balogh, A., Drávavölgyi, G., Ferguson, J., Pataki, H., Vajna, B., and Marosi, G. (2013) Solvent-free melt electrospinning for preparation of fast dissolving drug delivery system and comparison with solvent-based electrospun and melt extruded systems. *J. Pharm. Sci.*, **102** (2), 508–517.
67. DiNunzio, J.C., Brough, C., Miller, D.A., Williams, R.O. III, and McGinity, J.W. (2010) Fusion processing of itraconazole solid dispersions by kinetisol dispersing: a comparative study to hot melt extrusion. *J. Pharm. Sci.*, **99** (3), 1239–1253.
68. Dinunzio, J.C., Brough, C., Hughey, J.R., Miller, D.A., Williams, R.O. III, and McGinity, J.W. (2010) Fusion production of solid dispersions containing a heat-sensitive active ingredient by hot melt extrusion and Kinetisol dispersing. *Eur. J. Pharm. Biopharm.*, **74** (2), 340–351.
69. Sollohub, K. and Cal, K. (2010) Spray drying technique: II. Current applications in pharmaceutical technology. *J. Pharm. Sci.*, **99** (2), 587–597.
70. Vehring, R. (2008) Pharmaceutical particle engineering *via* spray drying. *Pharm. Res.*, **25** (5), 999–1022.
71. Cal, K. and Sollohub, K. (2010) Spray drying technique. I: hardware and process parameters. *J. Pharm. Sci.*, **99** (2), 575–586.
72. Guns, S., Dereymaker, A., Kayaert, P., Mathot, V., Martens, J.A., and Van den Mooter, G. (2011) Comparison between hot-melt extrusion and spray-drying for manufacturing solid dispersions of the graft copolymer of ethylene glycol and vinylalcohol. *Pharm. Res.*, **28** (3), 673–682.
73. Tang, X. and Pikal, M.J. (2004) Design of freeze–drying processes for pharmaceuticals: practical advice. *Pharm. Res.*, **21**, 191–200.
74. Lai, F., Pini, E., Corrias, F., Perricci, J., Manconi, M., Fadda, A.M., and Sinico, C. (2014) Formulation strategy and

evaluation of nanocrystal piroxicam orally disintegrating tablets manufacturing by freeze-drying. *Int. J. Pharm.*, **467** (1-2), 27–33.

75. Santivarangkna, C., Aschenbrenner, M., Kulozik, U., and Foerst, P. (2011) Role of glassy state on stabilities of freeze-dried probiotics. *J. Food Sci.*, **76** (8), R152–R156.

76. He, X., Pei, L., Tong, H.H., and Zheng, Y. (2011) Comparison of spray freeze drying and the solvent evaporation method for preparing solid dispersions of baicalein with Pluronic F68 to improve dissolution and oral bioavailability. *AAPS PharmSciTech*, **12** (1), 104–113.

77. El-Badry, M. and Fathy, M. (2006) Enhancement of the dissolution and permeation rates of meloxicam by formation of its freeze-dried solid dispersions in polvvinylpyrrilidone k-30. *Drug Dev. Ind. Pharm.*, **32**, 141–150.

78. Felton, L.A. and Porter, S.C. (2013) An update on pharmaceutical film coating for drug delivery. *Expert Opin. Drug Delivery*, **10** (4), 421–435.

79. Porter, S.C. and Felton, L.A. (2010) Techniques to assess film coatings and evaluate film-coated products. *Drug Dev. Ind. Pharm.*, **36** (2), 128–142.

80. Sill, T.J. and von Recum, H.A. (2008) Electrospinning: applications in drug delivery and tissue engineering. *Biomaterials*, **29** (13), 1989–2006.

81. Zamani, M., Prabhakaran, M.P., and Ramakrishna, S. (2013) Advances in drug delivery via electrospun and electrosprayed nanomaterials. *Int. J. Nanomed.*, **8**, 2997–3017.

82. Qi, S., Moffat, J.G., and Yang, Z. (2013) Early stage phase separation in pharmaceutical solid dispersion thin films under high humidity: improved spatial understanding using probe-based thermal and spectroscopic nanocharacterization methods. *Mol. Pharm.*, **10**, 918–930.

83. Williams, G.R., Chatterton, N.P., Nazir, T., Yu, D.-G., Zhu, L.-M., and Branford-White, C.J. (2012) Electrospun nanofibers in drug delivery: recent developments and perspectives. *Ther. Delivery*, **3** (4), 515–533.

84. Chakraborty, S., Liao, I.C., Adler, A., and Leong, K.W. (2009) Electrohydrodynamics: a facile technique to fabricate drug delivery systems. *Adv. Drug Delivery Rev.*, **61** (12), 1043–1054.

85. Norrman, K., Ghanbari-Siahkali, A., and Larsen, N.B. (2005) 6 studies of spin-coated polymer films. *Annu. Rep. Prog. Chem. Sect. C: Phys. Chem.*, **101**, 174–201.

86. Van Eerdenbrugh, B., Baird, J.A., and Taylor, L.S. (2010) Crystallization tendency of active pharmaceutical ingredients following rapid solvent evaporation—classification and comparison with crystallization tendency from undercooled melts. *J. Pharm. Sci.*, **99**, 3826–3838.

87. Ng, Y.C., Yang, Z., McAuley, W.J., and Qi, S. (2013) Stabilisation of amorphous drugs under high humidity using pharmaceutical thin films. *Eur. J. Pharm. Biopharm.*, **84**, 555–565.

88. Van Eerdenbrughand, B. and Taylor, L.S. (2010) Small scale screening to determine the ability of different polymers to inhibit drug crystallization upon rapid solvent evaporation. *Mol. Pharm.*, **7**, 1328–1337.

89. Cui, W., Zhou, Y., and Chang, J. (2010) Electrospun nanofibrous materials for tissue engineering and drug delivery. *Sci. Technol. Adv. Mater.*, **11** (1), 014108.

Q10

"keywords/abstract

Dear Author,

Keywords and abstracts will normally not be included in the print version of your chapter but only in the online version (if not decided differently by Wiley-VCH).

Thank you!"

Abstract

Keywords

Affiliation for the Author: Sheng Qi
Q11 University of East Anglia, School of Pharmacy, Norwich, UK

Queries in Chapter 15

Q1. Please confirm if the heading levels are sequenced correctly.

Q2. We have slightly modified this sentence. Please check and confirm it is fine.

Q3. We have changed the expansion of 'hydroxypropyl cellulose' to 'hydroxypropyl methylcellulose' for matching with the 'HPMC'. Please confirm.

Q4. Figure 15.6 has not been cited in text. Please confirm if the citation provided by us is appropriate.

Q5. Please explain what these numbers in parentheses indicate.

Q6. Figure 15.7 has not been cited in text. Please confirm if the citation provided by us is appropriate.

Q7. Figure 15.7 is poor (Poor quality, image not clear) quality. Please check and provide the better quality figure.

Q8. As references 4 and 80 are identical, 80 has been replaced with 4 and subsequent references have been renumbered to maintain sequence in the text.

Q9. There is a mismatch in the author's name between the text citation (Ng *et al.*) and reference 82 (Qi *et al.*). Please check and provide the appropriate author.

Q10. Reference [old No. 86 = New No. 89] has not been cited in text. Please clarify as to where it should be cited (renumbering will be done by the typesetter).

Q11. Please provide institute, street name, and postcode for this affiliation.