Chapter 6
Hot-Melt Extrusion for Solid Dispersions: Composition and Design Considerations

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6.1 Introduction

Pharmaceutical hot-melt extrusion (HME) has been an area of great interest in academia and pharmaceutical industry alike since the 1980s (Crowley et al. 2007), with numerous patents and research papers having been published since then. However, extrusion technology is a very mature platform widely used in the polymer and food industries. Some examples of plastic products manufactured through extrusion include medical tubing, electric cables, pipes, and plastic bags, among others. In the food industry, the extrusion process, often referred to as extrusion cooking, is used to manufacture numerous products such as cereals, snacks, pet food, flours, and precooked mixtures for infant feeding (Singh et al. 2007).

Through the HME process, one or more active pharmaceutical ingredients (API) are blended with at least one molten excipient in an extruder. The API in the extrudate (or HME product) may exist in its crystalline or amorphous state. Some of the applications of pharmaceutical HME include products designed to promote oral absorption, sustained release (either for oral delivery or implants; Follonier et al. 1995), targeted release (Doelker 1993; Follonier et al. 1995; Andrews et al. 2008), and prevention of substance abuse (Oshlack et al. 2001; Arkenau-Maric and Bartholomaus 2008). Some of these applications are listed in Table 6.1, where the commercial status and the purpose of the HME process are summarized for several drug products.

HME is a continuous melt manufacturing process consisting of the elementary steps of solids conveying, melting, mixing, devolatilization, pumping, and pressurization for shaping (Tadmor and Gogos 2006; Todd 1998). The API, the polymer

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Table 6.1 Examples of drug products manufactured by the HME process

Name	API	Polymer excipient	Delivery form	Indication	Status[b]	HME purpose
Dapivirine–maraviroc	Dapivirine + maraviroc[a]	EVA[a]	Implant	Antiviral (HIV)	UD[a]	Shape
Lacrisert®	None	HPMC	Implant	Dry eye syndrome	M	Shape
NuvaRing	Etonogestrel + ethinyl estradiol	EVA[a]	Implant	Contraceptive	M	Shape
Zoladex	Goserelin acetate	PLGA	Implant	Prostate cancer	M	Shape
Implanon	Etonogestrel	EVA	Implant	Contraceptive	M	Shape
Ozurdex®	Dexamethasone	PLGA	Implant	Macular edema	M	Shape
Kaletra®	Lopinavir + ritonavir	PVP-VA	Tablet	Antiviral (HIV)	M	Amorphous dispersion
Norvir®	Ritonavir	PVP-VA	Tablet	Antiviral (HIV)	M	Amorphous dispersion
Eucreas®	Vildagliptin + metformin hydrochloride	HPMC	Tablet	Diabetes	M	Melt granulation
Zithromax®	Azithromycin	HPMC	Tablet	Antibiotic	M	Taste masking
Gris-PEG®	Griseofulvin	PEG	Tablet	Antifungal	M	Crystalline dispersion
Rezulin®	Troglitazone	PVP	Tablet	Diabetes	W	Amorphous dispersion
Palladone™	Hydrophone	EC + ERS	Tablet	Pain	W	Controlled release
Posaconazole	Posaconazole	HPMCAS	Tablet	Antifungal	M	Amorphous dispersion
Anacetrapib	Anacetrapib	–	–	Cardiovascular disease	UD	Amorphous dispersion

API active pharmaceutical ingredient, *EVA* ethyl vinyl acetate, *HPMC* hydroxypropyl methylcellulose, *HPMCAS* hydroxypropylmethylcellulose acetate succinate, *PLGA* poly(lactic-co-glycolic acid), *PVP-VA* polyvinyl pyrrolidone-co-vinyl acetate, *PEG* polyethylene glycol, *PVP* polyvinyl pyrrolidone, *EC* ethyl cellulose, *ERS* Eudragit® RS, *UD* under development, *M* marketed product, *W* withdrawn from the market

[a]Loxley 2010

[b]DiNunzio 2011

carrier, and other excipients are fed as solid particulates, either as a preblend or independently, through the hopper. Additional solids and/or liquids can be independently fed downstream. Solids are conveyed by one or more screws down the length of the extruder barrel, followed by melting of the polymer carrier. In the case of miscible systems, the API is progressively dissolved in the molten polymer. In the case of immiscible systems, a crystalline API is homogenously dispersed in the process stream. Devolatilization may be required to remove entrapped air, moisture, and/or residual solvent. Finally, pressure is generated and the molten blend is forced through the die with the desired shape. After the material exits the die, the process stream is then cooled and subjected to secondary processing steps, such as milling, pelletization, or direct shaping.

Although both single-screw and twin-screw extruders are widely used for polymer processing and have been utilized in pharmaceutical research, the following discussion is centered on the latter. Fully intermeshing corotating twin-screw extruders are of the greatest interest for pharmaceutical applications since they provide more efficient mixing, tight residence time distributions (RTD), and minimal material stagnation (McCrum et al. 1997; Tadmor and Gogos 2006).

As schematically shown in Fig. 6.1, the properties of the HME product, or extrudate, are a function of three groups of variables: (1) design variables, (2) process variables, and (3) material variables. It is important to point out that these three groups are not fully independent but strongly interrelated.

The design variables can be further subdivided into three groups: extruder, screw, and die design. A twin-screw extruder is schematically depicted in Fig. 6.2, and it consists of a heated barrel that encloses the screws, which convey the material forward and force it through the die. Extruders are primarily defined by the diameter of their screws and their length to diameter ratio (L/D). The barrel can be modular or fixed, and is independently heated and cooled by means of a control system.

Modular screws are often used since they provide an additional degree of freedom to the design space. Furthermore, screw configuration should be defined based on the formulation and process objectives. Screw configurations are built by combining the three basic types of screw elements: conveying, kneading blocks, and special mixing elements. Conveying elements are employed for material transport and pressure buildup. They also provide some degree of mixing through shearing and linkage or backflow. The main geometrical characteristics of conveying elements are pitch, flight angle, length, and number of flights. A comprehensive geometrical description of these elements and fully intermeshing twin-screw extruders has been published (Booy 1978). Kneading blocks consist of a stack of paddles, of a given thickness and offset angle. Depending on their design, kneading block sections may be conveying, neutral, or reversing and cause varying extents of polymer melting and mixing. Mixing is predominantly due to elongational flows (i.e., dispersive mixing) and the multiple divisions and recombinations (i.e., distributive mixing) of the process stream. Specialized mixing elements are sometimes used to promote dispersive or distributive mixing. Detailed description of the flow patterns and mixing mechanisms in diverse screw elements is out of scope for this discussion but can be found elsewhere (Brouwer et al. 2002; Ishikawa et al. 2002; Tadmor and Gogos 2006; Kohlgrüber and Bierdel 2008).

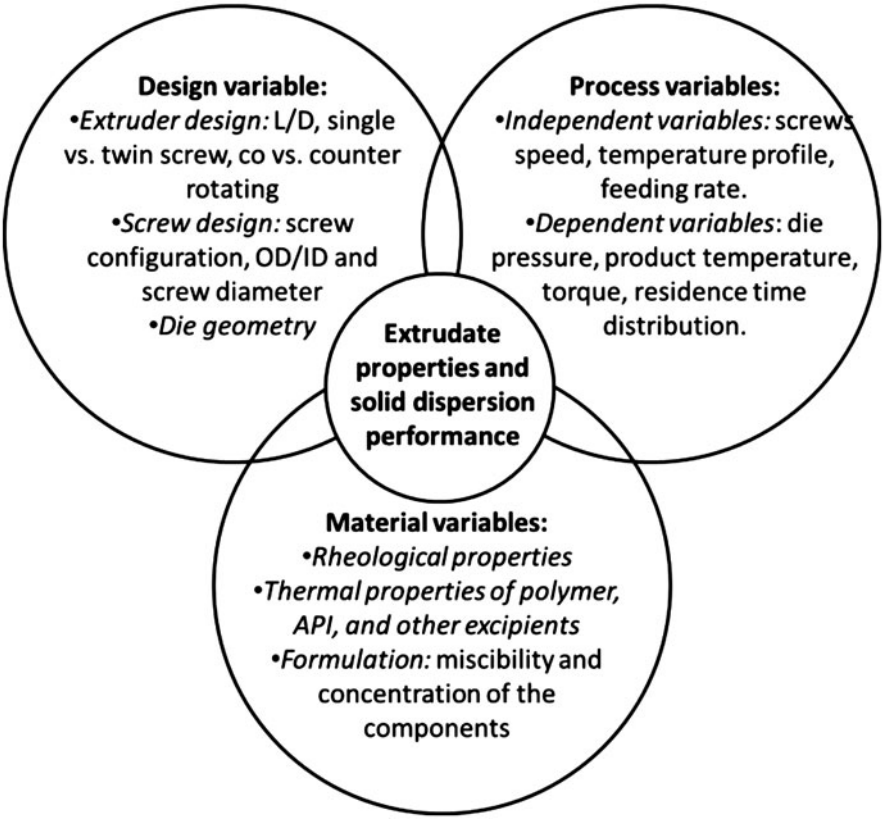

Fig. 6.1 Summary of the variables that affect the properties and performance of the extrudate or HME product

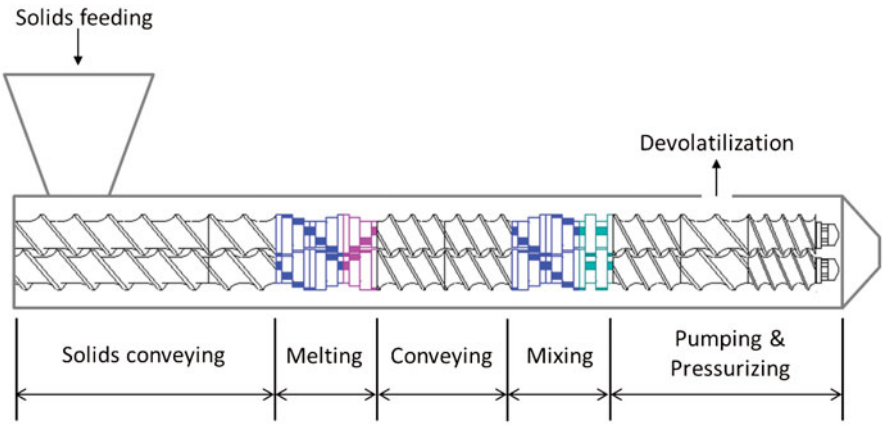

Fig. 6.2 Schematic representation of a twin-screw extruder and elementary steps

Process variables can be subdivided into two groups: (1) independent variables such as screw's rotating speed, temperature profile of the barrel, and feeding rates and (2) dependent variables such as product temperature or actual temperature of the process stream, RTD, pressure, and torque.

Typically, the barrel temperature profile is set at least 30 °C above the glass transition temperature (T_g) of the polymer or above its melting point, in the case of a semicrystalline polymer excipient. Furthermore, these temperatures are generally below the melting point of the API, although process temperatures can be above the API's melting point, if the components do not degrade. It is important to bear in mind that although the extruder barrel is heated, much of the energy utilized for melting is provided by the rotation of the screws—particularly at larger scales. As the solids are conveyed, heat is generated through frictional energy dissipation, followed by a combination of plastic and viscous energy dissipation in fully filled kneading blocks (Todd 1998; Tadmor and Gogos 2006).

Feeding rate in twin-screw extrusion is very important as it defines the manufacturing throughput. Twin-screw extruders are starve-fed, where the amount of material fed to the extruder does not completely fill its free volume. In general, conveying elements tend to be partially filled, while kneading blocks tend to be fully filled. The residence time of the melt in partially filled elements is solely dependent on the screw speed and screw element pitch; while in the fully filled sections, it is independent of the screw speed, i.e., only depends on throughput (Todd 1998). However, the length of the fully filled sections is a function of the screw speed. A practical implication of this is that the residence time of the material—for a fixed-screw configuration—is predominantly controlled by the feeding rate.

Finally, material variables will have a direct impact on the design and process variables. Both the properties of the individual components and those of phases formed during processing are important in the design of extrusion processes. For example, the melt viscosity of a polymer can be lowered by the addition of plasticizer or increased by the addition of an immiscible dispersed phase. This behavior was clearly shown (Yang et al. 2011) for an API–polymer binary system.

As such, it is clear that the design of extruded amorphous dispersions will be dependent on formulation and process considerations. The flexibility provided by the extruder yields unique opportunities to address many of the challenges faced during development. The subsequent sections detail the considerations for selection of the extrusion platform, classification of dispersion systems, formulation design, characterization, commercialization, integration within the supply chain, scale-up, inline monitoring through process analytical technologies (PAT), and implementation of extrusion operations within a quality-by-design (QbD) framework.

6.2 Enabled Technology Platform Selection

At its core, an amorphous solid dispersion formulation is simply a single-phase mixture of drug with other components. However, multiple paths exist for achieving that single-phase mixture, including mechanical activation, spray drying, and HME, among others. At a high level, all process routes to manufacture an amorphous

solid dispersion follow the same generalized set of activities: mixing of individual components followed by a quench step. In the case of spray drying, the mixing of individual components is achieved through dissolution of the components in a common solvent system, whereas the quench step is the actual spray drying process where atomized droplets are rapidly dried. In contrast to spray drying where mixing is relatively simple and achieved through dissolution in a solvent system, the melt extrusion process itself is where mixing takes place. For melt extrusion, quenching occurs following extrusion, where the extrudate is rapidly cooled by forced air, dry ice, chilled rolls, or other techniques.

Much has been written in the literature on the impact of amorphous solid dispersion *composition* on the stability or performance of the drug product, including studies covering the stability of polyethylene glycol (Zhu et al. 2013), the stability of PVP (Taylor and Zografi 1997), the stability of PVP-VA64 (Wang et al. 2005), the performance of HPMC (Suzuki and Sunada 1998), and the performance of HPMCAS (Friesen et al. **?**). Some published studies have examined the impact of *process route* on the stability or performance of amorphous solid dispersions with the same composition, including publications covering melt/quench methods relative to ball milling (Patterson et al. 2005), comparing HME to spray drying and ball milling (Patterson et al. 2007), evaluating HME and solvent coprecipitation (Dong et al. 2008), and examining spray drying relative to HME (Patterson et al. 2008). However, very few studies have examined the impact of *process parameters* on the stability or performance of amorphous solid dispersions having the same composition.

One seeking to determine the best process technology to leverage for a given amorphous solid dispersion often attempts to determine whether spray drying or HME is a more appropriate route. In some ways, the choice is straightforward. All else equal, an HME process occupies a smaller facility footprint, requires comparatively lower-cost capital equipment, enables higher throughput, and fits into many existing pharmaceutical processing suites (Breitenbach 2002). However, all else is generally not equal: both the process route and the process parameters themselves can substantially impact the stability or performance of the drug product. Any given process could result in a product of poor quality, and in some cases, several different processes can produce an amorphous solid dispersion with similar quality attributes.

Each process presents different challenges toward achieving the desired product. Amorphous solid dispersions manufactured by HME are often challenged by the ability to achieve a single-phase mixture, whereas this goal is rather easily achieved during spray drying by dissolving all components in a solvent system. Those formulations manufactured by spray drying may be challenged by the capability to maintain a single-phase mixture throughout the manufacturing process, given relative drying rates and the presence of residual solvent in the spray-dried product that may substantially plasticize the material. The HME process largely decouples the phase state of the amorphous solid dispersion from the physical properties of the particles generated through the use of a separate milling step. In contrast, the spray drying process largely links the phase state of the formulation to the physical properties of the resultant particles. Changing the size and density of the spray-dried particles requires changes in heat and mass transfer in the spray dryer, which may impact homogeneity and phase state.

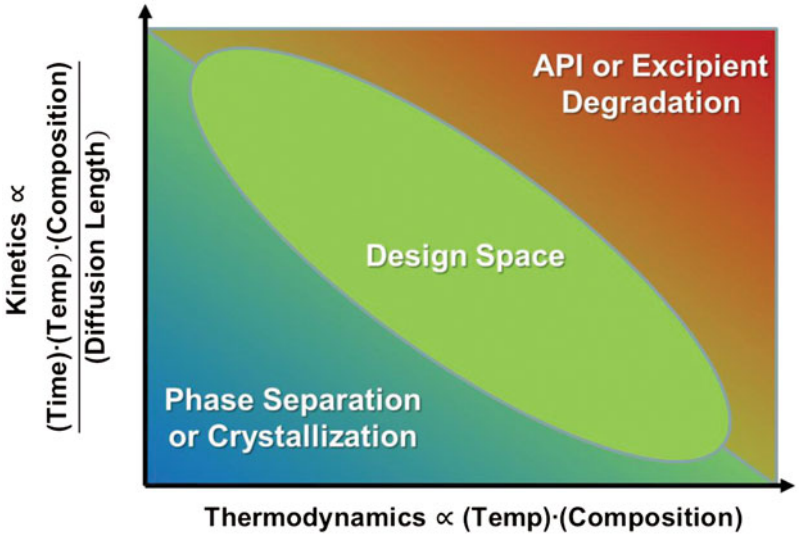

Fig. 6.3 Conceptual design space for an amorphous solid dispersion manufactured by hot-melt extrusion, where failure modes are depicted with respect to thermodynamic and kinetic variables

Achieving a single-phase mixture by HME requires a balancing of thermodynamic and kinetic driving forces, as shown by Fig. 6.3. From a thermodynamic perspective, both the temperature and composition of the formulation may impact its risk of crystallization or phase separation. From a kinetic perspective, single-phase mixtures require sufficient temperature, time, and surface area for diffusion to occur. These principles are made more complex by the reality that there is not a single temperature, time, composition, or surface area within the extruder. Instead, there is a distribution of temperatures and compositions, owing to a physical mixture of particles flowing through a barrel with axially varying screw profile, axially changing barrel temperature profile, and even radially different temperature and shear profiles within a given screw segment (Griffith 1962).

Too much energy input is not necessarily a good thing. Excessive time, temperature, or stress may result in degradation of API, polymer, or components. Limits of API degradants in drug products have been well established through International Conference on Harmonisation International Conference on Harmonization(ICH) guidelines (ICH Q3B(R2): Impurities in New Drug Products, 2006); however, degradation of excipients may play a more critical role for amorphous solid dispersions than for other drug products. Although nearly all pharmaceutical excipients are functional, the excipients present in the amorphous solid dispersion often link directly to the stability and performance of the formulation. Consequently, excipient degradation may result in loss of functionality, which could translate to a change in the stability or dissolution behavior of the drug product.

High melting point drugs usually present considerable challenges toward achieving a single-phase mixture while avoiding degradation of any components. Diffusion of the individual components into a single phase over the timescales relevant to a continuous process is facilitated by mixing all components in the liquid state, so drugs

with melting points in considerable excess of 200 °C require that the components in the extruder experience very high temperatures or be formulated with excipients that melt soluble materials far below the melting point of the pure API. Some polymers commonly utilized for amorphous solid dispersion formulations have been reported to degrade above 220 °C (Schenck et al. 2011), with some materials even showing instability as low as 150 °C. Thermally labile drugs also present a significant challenge to the extrusion of a single-phase formulation without the onset of degradation (Verreck et al. 2006a). In particular, the gap between the melting point of the crystalline drug and its onset of decomposition needs to be wide enough to ensure a sufficient operating window exists.

While high melting point and thermally labile drugs add complexity to HME process development, there are still opportunities to develop a process that ensures a single-phase mixture while avoiding degradation. Depending on specific interactions, polymers may depress the melting point of drugs considerably, such that these drug compounds will dissolve into the polymer at temperatures well below degradation onset (Marsac et al. 2006). Another opportunity to mitigate degradation risk is to incorporate components into the amorphous solid dispersion formulation whose sole function is to depress the melting point of the drug and enable lower processing temperatures (Ghebremeskel 2007). A liability with this approach is that the very components which facilitate processing may plasticize the resultant amorphous solid dispersion, potentially increasing the physical stability risk of the drug product during shelf life. A compelling response to this risk is the injection of supercritical fluid into the extruder barrel, which can dissolve into the formulation, temporarily depress the melting point, and subsequently evaporate from the extrudate (Nalawade 2006). This technique has the advantage of having no impact on the glass transition temperature of the amorphous solid dispersion on storage, thereby avoiding additional physical stability risk.

Another consideration in the selection of technology platform is the polymer chosen for the amorphous solid dispersion formulation. The fact that many pharmaceutical polymers degrade, crosslink, or lose functionality at high temperatures has already been discussed. However, the melt viscosity of a polymer is critical to the ability to extrude the amorphous solid dispersion within the capabilities of the extrusion equipment. The melt viscosity as a function of temperature and shear rate varies considerably across pharmaceutical polymers (Chokshi et al. 2005). Formulation melt viscosities in the range of 10–100,000 Pa s are generally acceptable for HME, although the range depends heavily on the torque limit capability of the particular extruder.

Process technology selection for the manufacture of amorphous solid dispersions requires consideration of the particular complexities of the drug and excipients. HME offers the possibility to manufacture drug products in a continuous, cost-effective manner, yet it presents unique challenges that must be tackled. Noting the significant interplay between formulation and process, a risk-based classification system has been developed to aid in the early assessment of dispersion success using melt extrusion.

6.3 Drug: Polymer Systems for Extrusion

The complexity of compounding an API and a polymer into an amorphous dispersion is dependent on the physical and mechanical properties of the constituent ingredients, and the processing conditions. Both thermodynamic and kinetic mixing considerations are at play during the formation of a solid dispersion in a hot-melt extruder. HME compounding classification schemes have been reported previously (DiNunzio et al. 2012; Liu et al. 2012). Categorization of formulations into two types of systems may provide insight into ultimate process development. The first system is characterized by the dissolution of solid API particles into a "liquid-like" polymer melt. The second system is described by the mixing of miscible liquids of differing viscosities. These two systems can be further subdivided based on the following system attributes: the melting point of the API, the extent of API melting point depression observed in the presence of the polymer, and the melt viscosities of the API and polymer. In this section, an expanded classification system for binary API/polymer amorphous dispersion compounding problems is presented based on the above attributes (Troup classification system; TCS) and summarized in Table 6.2. The main features of solid/liquid and liquid/liquid systems and details on each class are explained in the following subsections.

6.3.1 Classes I and II: Solid/Liquid Systems

Solid/liquid systems are categorized by high-melting-point APIs that exhibit negligible melting point depression in the presence of polymer. In class I systems, the polymer is highly viscous, while in class II systems, the polymer is inviscid. The system behavior of these two classes can be described as a solid drug dissolution problem (Liu et al. 2010), and can be understood in terms of the Noyes–Whitney equation (Noyes and Whitney 1897), given as Eq. 6.1:

$$\frac{dC(t)}{dt} = D_{api,polymer} \times A_{surface} \times \frac{[C_{sat} - C(t)]}{h \times V_{melt}} \tag{6.1}$$

where $D_{\text{api,polymer}}$ is the diffusion coefficient of the API in the polymer melt at the processing temperature, A_{surface} is the total surface area of the API in contact with the polymer melt, C_{sat} is the saturation solubility of the API in the polymer melt at the processing temperature, C is the concentration of API in the bulk polymer melt, h is the diffusion boundary layer thickness, and V_{melt} is the volume of the polymer melt. Analysis of Eq. 6.1 suggests that increasing API surface area, reducing the boundary layer thickness, and increasing convective mixing are required to drive homogeneity of solid/liquid systems. General processing guidelines for classes I and II systems are briefly described in the following subsections.

Table 6.2 Troup classification system characterizing the risk of dispersion production

Class	Melting temperature of API	Extent of melting point depression	Polymer system	Complexity	Phase attributes
I	High	Negligible	Viscous	Mixing degradation	Solid/viscous liquid
II	High	Negligible	Inviscid	Mixing degradation	Solid/inviscid liquid
III	High	Significant	Viscous	Mixing	Liquid/liquid
IV	High	Significant	Inviscid	Mixing	Liquid/liquid
V	Low	NA	Viscous	Mixing for extreme viscosity ratios	Liquid/liquid
VI	Low	NA	Inviscid	Mixing for extreme viscosity ratios	Liquid/liquid

API active pharmaceutical ingredient, *NA* not available

6.3.2 Class I: High T_{melt}^{API}, Negligible Melting Point Depression, and Viscous Polymer System

Class I systems require high processing temperatures and long residence times to fully compound the API and polymer into an amorphous dispersion. At these processing conditions, thermal degradation of the polymer and/or the API is often an issue. From Eq. 6.1, increasing the total surface area by jet-milling the API should improve processing performance by reducing the required residence time. Preblending the feedstock prior to melt extrusion may also improve processing performance by maximizing the initial amount of API in contact with bulk polymer. Distributive mixing sections in the extruder will promote drug dissolution into the bulk. Higher viscosity polymers are anticipated to be more challenging in these cases because it is more difficult to refresh the boundary layer during mixing in the extruder. The addition of low levels of melt-solubilizing polymers and/or plasticizers should be considered for this class.

6.3.3 Class II: High T_{melt}^{API}, Negligible Melting Point Depression, and Inviscid Polymer System

Similar to class I, class II systems also typically require high processing temperatures and long residence times to fully melt and disperse the API. Thermal degradation of the polymer and/or the API is again an issue. The inviscid polymers may possibly be prone to thermal degradation at these temperatures, but the lower viscosity should

lead to improved mixing performance due to rapid surface renewal of bulk polymer at the boundary layer during mixing. Both jet-milling the API and preblending the feedstock should improve processing performance. Distributive mixing sections are also recommended for this class. If the API dissolution rate is sufficiently high, lower temperature processing may be possible.

6.3.4 Classes III and VI: Liquid/Liquid Systems

In contrast to classes I and II, where the drug dissolution into the polymer dominates system behavior, classes III and VI are better characterized by liquid/liquid mixing phenomenon. In these cases, the API rapidly melts, forming discrete fluid pockets enriched with API in a continuous matrix of pure polymer melt. A disparity in viscosity ratio will transiently exist between the discrete API-enriched phase and the continuous polymer-enriched phase as the two components are mixed and as the API diffuses and dissolves. For a rigorous theoretical treatment of laminar mixing of homogeneous fluids, interested readers should refer to (Tadmor and Gogos 2006). Laminar mixing theory reveals that mixing in liquid/liquid systems is dependent on the total strain, the volume fraction of the minor component, and the initial striation thickness, in this case the droplet diameter. The final striation thickness, which is a measure of mixedness, as a function of these parameters is given in Eq. 6.2 (Tadmor and Gogos 2006), which is derived for an arbitrarily oriented surface element in a homogeneous simple shear flow field

$$r = \frac{2L}{3X_{vol}\gamma} = \frac{2r_0}{\gamma} \tag{6.2}$$

where r is the final striation thickness, L is the characteristic length, X_{vol} is the volume fraction of the minor component, γ is the total strain, and r_0 is the initial striation thickness. This simplified model shows that the key variable in liquid/liquid systems is the total strain allowed by the screw design and process conditions. Additionally, from inspection of Eq. 6.2, it is evident that the problem can be amplified if a low volume fraction of API is being incorporated. For nonhomogeneous liquid mixing, it is generally regarded that mixing a low-viscosity minor component into a viscous matrix or mixing high-viscosity minor component into a low viscosity matrix are the two most challenging scenarios (Rauwendaal 1998, 2002, Tadmor and Gogos 2006). The former case is the common situation for most pharmaceutical compounding problems. In liquid/liquid systems, the droplet breakup theory developed for immiscible systems (Grace 1982) could also partially apply, as there will be a transient surface tension difference between the discrete and continuous phases. In particular, glass-forming APIs in inviscid polymer systems may exhibit droplet breakup behavior. General processing guidelines for classes III and VI are briefly described in the following subsections.

6.3.5 Class III: High T_{melt}^{API}, Significant Melting Point Depression, and Viscous Polymer System

The melting point depression of the API/polymer systems exhibited in class III systems should result in more moderate processing temperatures compared to classes I and II. The complexity in this system arises from the potential for large differences in the viscosities of the API-enriched phase and the bulk polymer phase. Distributive mixing sections will be beneficial to reduce the length scale of discrete-phase API-enriched fluid droplets, and dispersive mixing may aid in API-enriched droplet deformation and breakage. In these systems, it may be useful to have a distributive mixing section, followed by a dispersive mixing section, then followed by a second distributive mixing section to homogenize the dissolving API into the polymer matrix.

6.3.6 Class IV: High T_{melt}^{API}, Significant Melting Point Depression, and Inviscid Polymer System

Class IV systems are simpler to process than class III systems due to the lower viscosity polymer, leading to a lower viscosity ratio and the potential for improved mixing efficiency with low-viscosity APIs. Less dispersive mixing should be required in this class compared to class III systems, as length-scale reduction should proceed more readily. However, APIs that can transform into a viscous glass requiring mixing of a viscous minor component into a lower viscosity matrix can complicate processing.

6.3.7 Class V: Low T_{melt}^{API} and Viscous Polymer System

Class V systems are analogous to class III systems in that they result in a liquid/liquid mixing problem. Class V systems should result in lower complexity due to the higher degree of freedom afforded by low melting point APIs to increase process temperatures above the melting point of the pure drug substance. Also, in the cases where the API plasticizes the polymer, further processing benefits may be realized, for example, lower absolute processing temperature and improve mixing efficiency. Again both classes III and V will benefit from both dispersive and distributive mixing sections. Complexity in this class may arise if a low-viscosity minor component needs to be compounded.

6.3.8 Class VI: Low T_{melt}^{API} and Inviscid Polymer System

This class is expected to be the least complex system to compound since it requires slower processing temperatures and should have improved mixing efficiency

by virtue of its lower viscosity polymer system. The low melting point APIs in classes V and VI should result in processing temperatures that are more a function of API properties than viscosity reduction of the polymer. These systems are less prone to thermal degradation issues and should be reasonably robust to changes in extrusion operating conditions.

6.4 Formulation Design

Formulation and process design for the production of solid solutions must be considered simultaneously. As discussed previously, the properties of the API have a significant influence on the way in which the dispersion is formed and also influence the thermodynamic end point for the process. In general, the TCS can be used to describe the relative risk for producing amorphous dispersions. While many examples exist in the literature covering classes IV–VI systems (Verreck et al. 2003, Keen et al. 2013, DiNunzio et al. 2010, Chokshi et al. 2005), only a few have been described for classes I–III (Hughey et al. 2010). Likely, the absence of examples for classes I–III is tied to the basic challenges of appropriately identifying and manufacturing these systems. However, even with these challenges, extrusion remains a preferred manufacturing technology for a number of solid dispersion products.

For extrusion, viewed as a mixing process at elevated temperature and subsequent quenching, it becomes possible to describe the phase behavior of the dispersion. Shown in Fig. 6.4, this diagram describes the melting temperature of the API as a function of composition as well as the glass transition temperature of the dispersion. Phase envelopes can also be described in this space, leading to a comprehensive understanding of dispersion behavior at relevant temperatures. Serving as a guide for design, additional kinetic factors must also be accounted for, which contribute to the final dispersion properties.

The concentration of API in a solid solution formulation is typically evaluated to understand the effect of drug loading on solid solution properties such as propensity for phase instability. The addition of some APIs directly influences properties critical to melt extrusion process design and development. For example, APIs influence melt rheology as plasticizers, anti-plasticizers, or fillers.

Compatibilizers, excipients that help promote miscibility or interactions between one component (often the API) and other components (e.g., the polymer; Work et al. 2004), may be incorporated into solid solution compositions. Compatibilizers may be added to manipulate solid-state properties and/or the properties of solid solutions upon dissolution. Surfactants often serve the role of compatibilizers in solid solution formulations, influencing dissolution behavior, and, ultimately, bioavailability.

The dependence of formulation properties (e.g., supersaturation maintenance upon dissolution) on both formulation and production process complicates aspects of early formulation screening. Specific formulation compositions may be erroneously disregarded because of the way in which they are prepared during screening. The use of heated ovens and thermogravimetric analysis (TGA) to simulate extrusion

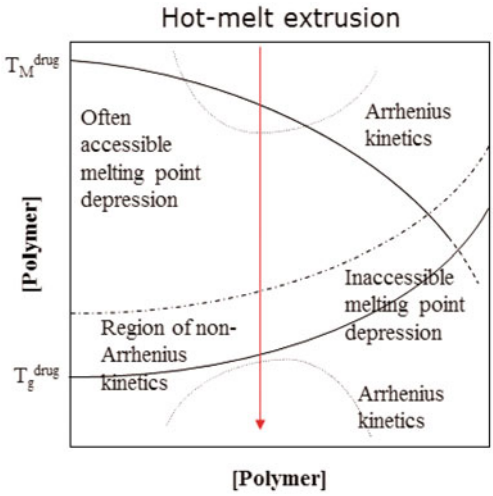

Fig. 6.4 Phase diagram of amorphous dispersion in temperature and composition space

can lead to relatively long exposures of formulations to heat compared to typical extrusion residence times. Extended heating times can lead to polymer and/or API degradation (DiNunzio et al. 2010). Polymers like HPMCAS do not appreciably mix during differential scanning calorimetry (DSC), making cyclical DSC experiments suboptimal for screening many formulations based on this polymer. Attempts have been made to experimentally improve miscibility assessment via thermal methods for polymers like HPMCAS by particle size reduction, cryomilling, and systematically varying heating rates (Sun et al. 2009, 2010; Tian et al. 2012; Mahieu et al. 2013a, 2013b). Solvent casting (Verreck et al. 2003), a technique directly amenable to high-throughput screening (Chiang et al. 2012), may require multiple solvents and/or relatively slow quench kinetics, both of which have the potential to lead to phase separation during preparation which could undesirably bias formulation definition.

Conversely, process constraints may lead to changes in formulations. Plasticizers, including surfactants (Ghebremeskel et al. 2007) and dissolved gases (Verreck et al. 2006a, 2007), may be employed in extrusion processing in order to reduce the temperature and/or stress required to form a homogeneous melt.

Given the complexity of amorphous dispersions, both in terms of criteria related to production as well as stability and bioperformance, it is necessary to develop such systems using a structured design approach. In this type of approach, outlined generally in Fig. 6.5, feedback between process performance, stability, and bioperformance are all necessary to define the optimum system (DiNunzio et al. 2012). This requires strong communication between multiple functions within an organization and also necessitates the appropriate characterization tools for performance assessment. When developing amorphous dispersion formulations, one can consider several paradigms based on the stage for which the technology is utilized. In general, many limitations exist that are prohibitive for implementation of extrusion in the early development space. Specifically, restrictions on equipment scale and small

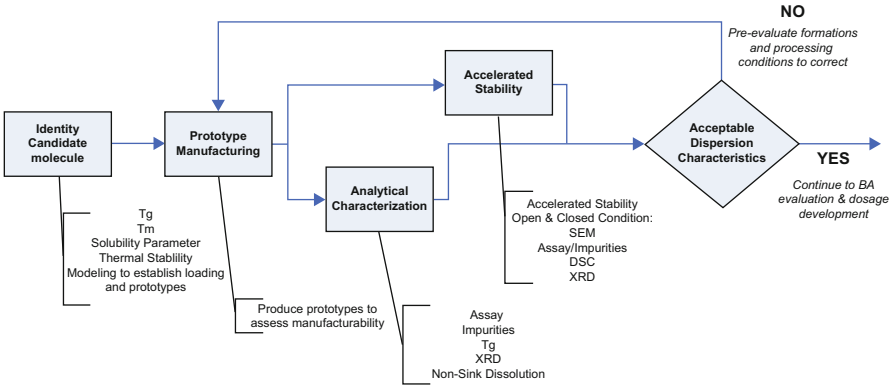

Fig. 6.5 Pathway for prototype dispersion development

batch size can make implementation logistically challenging. Additionally, restrictions based on API/polymer systems that were previously discussed can also limit the utility. As such, many organizations will adopt a strategy of developing dispersions using another processing technology, such as milling, coprecipitation, or spray drying, and then transitioning to extrusion to leverage process advantages for larger production runs. Alternatively, by nature of the properties of the compound and/or organizational philosophy, an end-to-end development of extrusion may be utilized. This section outlines the general approaches for designing melt-extruded solid dispersions under each of these paradigms, with a focus on compositional design to optimize manufacturability, bioavailability, and stability.

6.4.1 Early Formulation Development Considerations

Amorphous solid dispersions are leveraged at varying stages in development for a number of reasons. For extruded dispersions, a limited number of polymer systems summarized in Table 6.3 form the backbone of the compositional definition. In early development, they are most commonly used to support elevated exposures necessary for preclinical assessment and/or assure phase stability when a crystalline form is not readily isolated. At this stage of development, the amount of material available for development will be restricted. As discussed previously, this constraint can challenge the utility of extruded systems where minimum batch sizes are significantly larger than for development of spray-dried dispersions or coprecipitated material.

The small-scale characterization approaches are often conducted in an automated format where the dispersion is produced using solvent casting and then exposed to thermal cycling to simultaneously devolatilize and anneal the system (DiNunzio and Miller 2013). While an effective approach is to regulate the thermal history of the product, these types of approaches do not accurately reflect the quench rate kinetics

Table 6.3 Properties of common excipients used in solid dispersions

Polymer	T_g or T_m (°C)	Grades	Notes
Hypromellose	170–180 (T_g)	Methocel® E5	Non-thermoplastic API must plasticize Excellent nucleation inhibition Difficult to mill
Vinylpyrrolidone	168 (T_g)	Povidone® K30	API must plasticize Potential for H-bonding Hygroscopic Residual peroxides Easily milled
Vinylpyrrolidone–vinylacetate copolymer	106 (T_g)	Kollidon® VA 64	Easily processed by melt extrusion No API plasticization required More hydrophobic than vinylpyrrolidone Processed around 130 °C
Polyethylene glycol, vinyl acetate, vinyl caprolactam graft copolymer	70 (T_g)	Soluplus®	Newest excipient for melt-extruded dispersions Easily processed by melt extrusion Low T_g can limit stability Not of compendial status Stable up to 180 °C
Polymethacrylates	130 (T_g)	Eudragit® L100-55 Eudragit® L100	Not easily extruded without plasticizer Degradation onset is 155 °C Ionic polymer soluble above pH 5.5
Hypromellose acetate succinate	120–135 (T_g)	AQOAT®-L AQOAT®-M AQOAT®-H	Easily extruded without plasticizer Process temperatures 140 °C Ionic polymer soluble above pH 5.5 depending on grade Excellent concentration-enhancing polymer Stable up to 190 °C depending on processing conditions
Amino methacrylate copolymer	56 (T_g)	Eudragit® E PO	Processing at 100 °C Degradation onset is 200 °C Low T_g can limit stability
Methacrylic acid ester	65–70 (T_g)	Eudragit® RS Eudragit® RL	Extrudable at moderate temperatures (> 100°C) Excellent CR polymer
Poly(ethylene vinylacetate)	35–205 (T_m)	Elvax®	Extrudable at low temperatures (60 °C) Excellent controlled-release polymer but nonbiodegradable

Table 6.3 (continued)

Poly(ethylene oxide)	< 25–80 (T_m)	Polyox®	Mechanical properties ideal for abuse-deterrent applications and CR Process temperatures 70 °C Excellent CR polymer
Poly(lactic-co-glycolic acid)	40–60 (T_m)	RESOMER®	Low-melt viscosity for certain grades is challenging to process Biodegradation rate controlled by polymer chemistry Excellent for implantable systems

API active pharmaceutical ingredient, *CR* controlled release

associated with typical spray drying processes or the impact of mechanical energy associated with typical extrusion processes on the critical product attributes. Some researchers have utilized rheometers as surrogates to the extrusion process to assess material performance under a stress field (Yang et al. 2011). While able to simulate shear stresses in extrusion, they do not provide the distributive mixing experienced in extrusion operations. The maximum shear rate in an extruder can be estimated from the clearance between the screw and barrel (overflight; C), screw speed (N), and the outer diameter of the screw (D):

$$\frac{\pi DN}{C} = \dot{\gamma}.$$

The maximum shear rate is on the order of $1000\,s^{-1}$ for a typical intermeshing 16–18-mm corotating extruder ($D = 16$ mm; $N = 200$ revolutions/min; $C = 0.1$ mm). Alternative methods leveraging DSC to identify the solubility of drug in molten polymer (DiNunzio et al. 2010) have also been advocated as an approach to support selection of the optimum dispersion compositions; however, viscosity limitations associated with several pharmaceutical polymers may inhibit sufficient diffusion during the timescale of the experiment. Forming a homogeneous composition during prototype screening is a critical first step in designing amorphous dispersions. Assessing the stability and bioperformance of these compositions is needed to define the compositional design space that will result in successful products. While methods like TGA and stressed stability can provide insight into the performance (Hughey et al. 2010), there is not an effective way to conduct all of these tests in a truly representative fashion without direct manufacturing on an extrusion platform.

Supporting formulation identification at this stage can be facilitated by small-scale characterization and manufacturing of prototype batches using customized low-volume extruders. To address the scale limitations, a number of small-scale extrusion options are available, ranging in size from 3 to 16 mm that are capable of producing batch sizes as low as 5 g. At this size, geometric similarity to pilot and production scale units may not be preserved as designs are engineered to maximize yield and minimize batch size. However, these systems do serve an important role by providing a representative platform for assessing formulation performance using

melt extrusion. Within these systems, a design approach can be implemented through stepwise manufacturing of probe formulations. Supported by early characterization that identifies the optimum formulation for dissolution performance and stability, manufacturability attributes can be assessed in the early development space and used to identify compositions of interest for extrusion development. During the extrusion process, the performance is evaluated based on the operating temperatures and motor loads that will be predictive of larger batch production. Additionally, samples of the dispersion are analyzed for attributes covering the physical and chemical stability of components in the formulation. The scope of this characterization may also be more limited at this stage, focusing primarily on API stability during production and initial assessment of amorphous form generation. Homogeneous and stable dispersions can be further evaluated at this point via dissolution behavior and preclinical pharmacokinetic studies. In this manner, critical attributes related to bioperformance and stability can be optimized, in addition to setting a basis for development of manufacturability attributes in later development.

6.4.2 Pilot-Scale Development Considerations

Optimized formulations developed for clinical trials will typically be produced on larger-scale extrusion equipment than the equipment used during early screening. As extruders transition between the lab and pilot scale, a number of geometric differences can drive changes in performance. These differences, including changes in screw type (i.e., conical to parallel), element design difference (for example, outer to inner diameter ratio), and feed method (manual vs. volumetric vs. gravimetric), can all influence the energy input to the system and the approach for scaling. It is not generally possible to quantitatively map the operating space from these early-screening extruders to pilot-scale extruders because of these differences. Experience and empirical correlations more typically guide process development as programs transition between these disparate pieces of equipment.

Maintaining a constant maximum shear stress between extruders is often not possible because of the exceptionally small clearances that would be required to do this for screening scale extruders. These smaller extruders are often shorter to minimize their free volume (maximizing yield), which necessarily means they will be more limited in the amount of distributive mixing that can be incorporated into the extrusion process. As a result, small-scale equipment may provide misleading results with respect to the mixing that can be achieved readily using larger-scale extruders. Reducing the feed rate can compensate for the reduced mixing in these small-scale extruders. However, many benchtop systems are manually fed or fed with poor control due to the relatively low feed rates required. Variable feed rates inherently cause variation in both the residence time and specific energy input the processed material experiences. The ability to effectively cool or heat the product via the barrel wall with the smaller-scale extruders often used in early pharmaceutical development (e.g., < 16 mm) can lead to challenges with process scale-up.

In order to address these limitations, development at the pilot scale may be necessary prior to current good manufacturing practice (cGMP)—particularly for products requiring a narrow processing window (e.g., where significant degradation is observed near temperatures required to ensure a homogeneous glass is formed). Development and optimization are designed around addressing issues associated with energy input and residence time through formulation and process modification, where uniformity of the dispersion and thermal stability of the formulation are paramount. As such, characterization techniques designed to determine the physical and chemical stability of the drug and polymer are routinely utilized. Specific chemical approaches include gel permeation chromatography, infrared (IR)-coupled gel permeation chromatography (DiNunzio et al. 2010), and chemometric titration (DiNunzio et al. 2010), all of which are intended to determine backbone and side-group changes. Advanced characterization of solid-state properties which are discussed in more detail in the following section are also used at this stage to provide a more comprehensive understanding of molecule distribution and molecular interactions that govern performance of the system.

The extrusion RTD will often be characterized at this stage to provide a baseline for the process and assess the impact of process changes that are conducted to yield a final optimized system. In one approach, the effect of a bolus tracer is measured at the discharge of the extruder, by (i) visual determination with colored tracer, (ii) offline analysis using a chemical tracer, and/or (iii) inline analysis using a chemical tracer. With any of these techniques, it is possible to extract mean and moment information about the distribution that can be related back to the performance. In a recent example of this, Keen et al. (2013) characterized RTDs of corotating and counter-rotating extruders, highlighting performance differences between the units as shown in Fig. 6.6. In general, process modifications (as opposed to compositional modifications) are the most preferred approach to address manufacturing challenges facing prototype formulations. The section below discusses options for addressing two of the most common challenges observed at the early stage of extrusion development: (i) formulation modifications to expand processing windows and (ii) compositional changes to reduce chemical impurity formation during extrusion.

Plasticizers have been well documented for their ability to reduce processing temperatures during extrusion, which translates into a wider operational space (DiNunzio et al. 2010). Although many plasticizers are liquids at room temperature, addition can easily be facilitated by pregranulation or direct injection during extrusion. Solid-state plasticizers, such as citric acid, can also provide a convenient way to reduce processing temperature while facilitating addition via gravimetric feeders (Schilling et al. 2007). However, careful consideration must be given when adding plasticizers into a formulation as the material will also reduce the glass transition temperature of the dispersion, thereby potentially negatively impacting stability and/or dissolution of the dispersion. One method for addressing this is with the use of transient plasticizers, such as supercritical carbon dioxide, where the gas is injected into the processing section under supercritical conditions. Within this environment, the injected material behaves as a supercritical fluid, facilitating molten flow of the melt while functioning as a molecular lubricant. On discharge from the die, the material

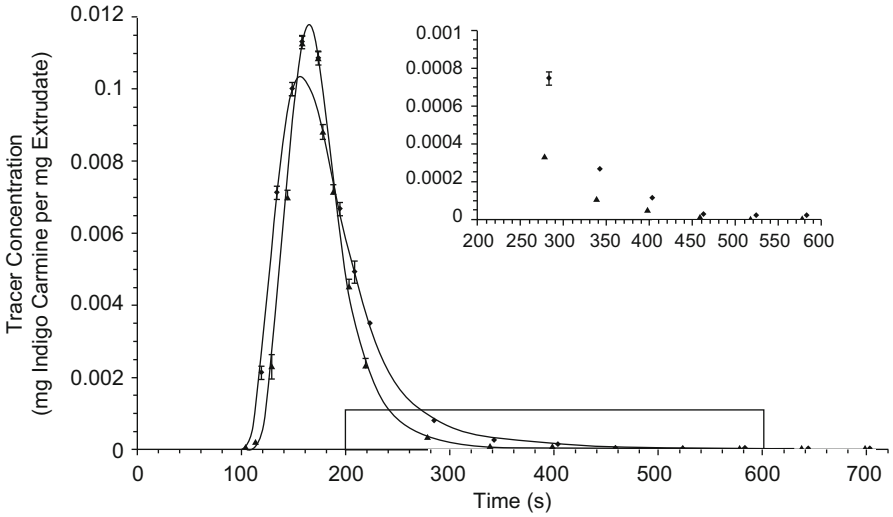

Fig. 6.6 Residence time distribution of corotating and counter-rotating extruders

experiences a dramatic pressure drop that drives a rapid expansion of gas within the melt and creates a foam structure as the additive leaves the system. By this mechanism, supercritical fluids or subcritical gases added directly to the extruder or incorporated separately provide reductions in melt viscosity through transient plasticization (Verreck et al. 2007).

Beyond plasticizers, it is also well known that polymer selection influences molten solubility of drug substances in a system. Careful selection of polymer type has been shown to improve solubilization and reduce impurity formation during thermal processing (DiNunzio et al. 2010). Adapting this approach, researchers have recently illustrated the utility of polymer blends for enhancing the processing characteristics of solid dispersion formulations by incorporating low levels of melt-solubilizing polymer into the dispersion (Albano et al. 2012). This addition allows for greater levels of drug substance to be dissolved in the molten polymer, which provides a viable approach for expanding the operational space of extrusion when dealing with group classes I and II systems. Importantly, because many polymers have high glass transition temperatures, often > 100°C, the polymeric additive will generally have less impact on physical stability when compared with plasticizers or surfactants that are typically characterized by low T_g's. However, care must be given to maintain levels of the solubilizing polymer below which they would impact bioperformance aspects associated with the primary polymer system.

Addressing the chemical impurity formation during extrusion is also generally achieved through process modification by altering the mechanical energy input and residence time of the process. However, it may not be possible to adjust these attributes independently of the composition while balancing requirements for amorphous material formation and minimization of impurity formation. Formulations may

also be modified to incorporate additives, such as pH modifiers and antioxidants, that help to reduce degradation during the process (Crowley et al. 2007). These materials provide a means to reduce impurity formation by altering the local environment or scavenging free radicals that would drive decomposition. Another important point to take note of is the purity of the starting materials since many pharmaceutical polymers, such as polyvinylpyrrolidone and polyethylene oxide, have high levels of peroxides, which can be detrimental at elevated temperatures. Although antioxidants can improve performance of extruded dispersions, many vendors now supply high purity grades of these excipients that can also aid in performance. Careful selection of the composition, therefore, begins with the identification of appropriate raw materials and continues on to additives that facilitate manufacturing.

6.5 Solid-State Characterization of Melt-Extruded Amorphous Dispersions

Solid-state characterization of amorphous solid dispersion systems prepared by HME is essential to understand their physical behavior. Several tools and techniques to detect physical failure modes such as crystallization or amorphous–amorphous phase separation will be outlined with an emphasis on the strengths and weaknesses of each approach. Characterization tools such as thermal methods may help to inform process development, specifically the phase diagram, inherent restrictions in processing space, and potential thermal liabilities. Finally, approaches aimed at understanding the fundamentals of amorphous solid dispersions will be discussed. In particular, tools and techniques which offer insight into the thermodynamics and molecular mobility of amorphous systems will be emphasized.

6.6 Detection of Crystallization and Amorphous–Amorphous Phase Separation

Demonstrating the absence of physical failure most often requires the application of multiple characterization tools and techniques. Detectability of relevant failure modes must be demonstrated along with the absence of failure at all relevant processing and storage conditions. The two most common modes of failure are crystallization and amorphous–amorphous phase separation. Crystallization is most often detected using X-ray powder diffraction (XRPD). The exceptional discriminating power of XRPD is largely the result of amorphous materials, lacking in long-range order, giving no constructive interference of incident X-rays. Relevant crystalline forms of the API most often display peaks which are resolved from those peaks associated with excipients used in the formulated product. The absence of API peaks, therefore, provides strong evidence for the stability of the amorphous solid dispersion.

Other spectroscopic techniques may also be used to detect crystalline API in the amorphous matrix. Solid-state nuclear magnetic resonance (ssNMR) spectroscopy can be used to push limits of detection exceptionally low when the API contains an atom which is of high natural abundance and is present exclusively in the API. For instance, ^{19}F and ^{31}P sometimes present exclusively in the API and data can be acquired with reasonable speed. Raman spectroscopy most often provides discriminating power as a result of the API having unique chemical moieties and, therefore, unique vibrational bands as compared to most excipients. Differences between the crystalline and amorphous forms in some instances allow for excellent limits of detection (Sinclair et al. 2011). Advances in nonlinear spectroscopy may provide yet another tool in the solid-state pharmaceutical scientist's toolbox (Strachan et al. 2011). Second-harmonic generation (SHG) operates under the principle that crystalline materials possessing a chiral space group will double the frequency of the incident radiation. Amorphous materials show no second-harmonic signal, and therefore, the discriminating power of SHG can be exceptional (Wanapun et al. 2010, 2011; Kestur et al. 2012). In the presence of finished dosage forms, excipient interferences have been observed. Coupling SHG with two-photon fluorescence may provide additional discriminating power (Toth et al. 2012).

Although the above approaches may all be amenable to detection of crystallization in finished products, they can also be used to characterize the HME (i.e., prior to downstream processing). Further, many other techniques are often applied exclusively to the HME intermediate. For instance, optical microscopy offers excellent detectability of crystalline material in transparent extrudates. Dielectric analysis (DEA; Alie et al. 2004; Bhugra et al. 2007, 2008) and thermally stimulated current IR spectroscopy (Shah et al. 2006; Rumondor and Taylor 2010), atomic force microscopy (AFM; Lauer et al. 2013; Marsac et al. 2012; Price and Young 2004), and calorimetric methods have also been used to detect crystallization from an amorphous matrix (Baird and Taylor 2012; Pikal and Dellerman 1989; Avella et al. 1991).

Phase separation into two amorphous phases may also be of concern. Most generally, a property which discriminates between the amorphous dispersion and a physical mixture of each of the component amorphous materials can be leveraged to detect amorphous phase separation. In practice, detecting amorphous–amorphous phase separation can be very difficult. This is because amorphous materials inherently present analytical signatures which are less well defined as compared to the crystalline counterpart. Further, amorphous phase separation will not often present as well-defined phases of discrete composition as is the case for crystallization. Instead, it is likely that a distribution of compositions may be observed, making detectability very difficult. Most often, DSC is used to detect the presence of multiple amorphous phases (Lu and Zografi 1988). Specifically, if the glass transition temperature (T_g) of each component of the dispersion is unique and if the T_g shows a strong functional dependence with composition, phase separation may be detected with DSC. Alternatively, if the components have similar T_g's or if the compositional dependence of T_g is subtle near the target composition, detection may be difficult. Further, the measurement itself may homogenize the sample, the samples may have an inherently

small change in heat capacity across the T_g, or the distribution of molecular environments may be very broad as a result of the distribution of molecular weight in the components which make up the solid dispersion. These and other difficulties may present challenges in measuring a well-defined T_g and are not necessarily unique to DSC. Nevertheless, there is a clear need to consider orthogonal approaches to measure the phase separation. Mathematically transformed X-ray data may be used to understand the phase behavior of amorphous solid dispersions. Specifically, the X-ray signal from amorphous materials may be used to produce a pair distribution function (PDF) via Fourier transformation with the results describing the probability of finding two atoms separated by a specific interatomic distance. Mixing, of course, influences the result and provides useful information about the miscibility of a system or lack thereof (Newman et al. 2008). Vibrational spectroscopy can also be used to detect amorphous phase separation. When interactions between species within the mixture manifest as a change in the frequency and distribution of vibrational modes, this may be detected using approaches such as IR spectroscopy (Rumondor et al. 2009; Marsac et al. 2010; Rumondor and Taylor 2010; Rumondor et al. 2011). Raman spectroscopy has also shown sensitivity to detect amorphous phase separation. In one example, two solid dispersions prepared at different HME processing conditions showed differences in physical stability despite both displaying a single T_g (Qian et al. 2010). Confocal Raman spectroscopy was used to explain the varying degrees of compositional homogeneity between the samples. Although Raman mapping is quite time consuming, nonlinear approaches such as broadband coherent anti-Stokes Raman scattering may expedite the collection process significantly (Hartshorn et al. 2013). In addition to detecting crystalline material within an amorphous matrix, ssNMR may also be used to demonstrate compositional heterogeneity. For instance, two-dimensional correlation techniques and 1H T1 relaxation methods are showing utility in understanding amorphous systems (Pham et al. 2010). Dynamic mechanical analysis (DMA) has found great utility in the study of polymer processing and may be extended to pharmaceutical systems (Karabanova et al. 2008; Carpenter et al. 2009; Szczepanski et al. 2012). DEA and thermally stimulated current have also been shown to provide sensitivity in understanding the homogeneity of the amorphous phase (Power et al. 2007; Shmeis et al. 2004a). Yet another approach, AFM, has been shown to detect amorphous phase separation in samples presented as thin films. For instance, felodipine and polyvinylpyrrolidone were shown to phase separate as indicated by changes in surface roughness and phase shifts after exposure to high relative humidity (Marsac et al. 2010). In another study, differences in HME processing conditions were shown with AFM. Specifically, preparation of a solid dispersion at two processing conditions showed differences in the homogeneity as measured by AFM. The material produced at the higher temperature showed a signal more similar to a control sample with the lower temperature signal showing signs of heterogeneity (Lauer et al. 2013).

Regardless of the method used and the mode of failure detected, all approaches share the common issues of having to discriminate the API from the excipients. Further, desired and undesired phases must show reasonable discrimination and therefore

the limit of detection is inherently a function of the system. Most often, several techniques must be explored in parallel during development before a commercial quality control approach that balances the ease of measurement and discriminating power is selected.

Characterization Informs Process Development and Provides Insight into the Fundamentals of Amorphous Solid Dispersions

Characterization of HME-based solid dispersions is not solely motivated by the need to directly measure physical failure. By extension, characterization tools and techniques provide insight into the fundamental properties which facilitate physical failure. For instance, measures of the thermodynamic properties and modes of motion associated with amorphous systems serve to better assess risk of physicochemical failure. Also, as was noted above, in several instances, although the material may be rendered amorphous, the differences in length scale of mixing may manifest as differences in performance, and, thus, characterization tools also inform process development.

Process space can be better understood through construction of the phase diagram and definition of temperature boundaries where failure modes occur. Various characterization approaches may be used to define phase boundaries and robust processing space. For instance, consider a binary API–polymer system. The liquidus line defining equilibrium between the crystalline API and the molten binary API–polymer phase represents the lowest temperature at which the extruder can be operated while still achieving a homogeneous single-phase amorphous solid dispersion system. This line can be generated via approaches such as melting point depression experiments and variations thereof (Marsac et al. 2006,. 2009; Marsac 2006, 2009; Mahieu et al.; Tao et al. 2009; Tian et al. 2009; Sun et al. 2010). However, it is often difficult to access the thermodynamic end state for highly viscous samples and so the kinetics of mixing should always be considered when interpreting DSC results. In the extruder, the combination of dispersive mixing, distributive mixing, and thermal homogenization expedites the formation of a single-phase amorphous system. Viscosity measurements as a function of shear rate and temperature may inform screw design but may also provide insight into the location of the liquidus line for materials of high viscosity. Once a homogeneous system is achieved, cooling below the liquidus line creates a thermodynamic driving force for crystallization. DSC may be used to understand the tendency for a material to crystallize on cooling below the liquidus line (Baird and Taylor 2012). The kinetics of crystallization is system dependent and inhibited by increased viscosity of the material below the liquidus line. Further, the temperature dependence of viscosity as T_g is approached can vary significantly across materials and so the risk of crystallization is case dependent. Yet another important limitation in extrusion is the temperature at which thermal liabilities become relevant over the timescale of the extrusion run. Samples from the DSC experiments may be analyzed by appropriate chemical assays to determine risk. Further, thermogravimetric experiments may be conducted with various time–temperature profiles and assays conducted with the same end in mind. A view of the liquidus line, the glass transition temperature as a function of composition, and the temperature at which thermal degradation exists provides a baseline understanding of processing limitations.

Applying thermodynamic principles to unstable amorphous systems allows for a more complete understanding of the driving forces associated with various failure modes. The tools used to measure these failure modes were discussed above, and here the focus is on how these tools can be used to measure fundamental thermodynamic properties of the amorphous systems. Melting point depression experiments not only provide definition of the phase boundary as discussed above, they also provide insight into the thermodynamic changes which occur as a result of mixing. Specifically, the extent of melting point depression reflects the change in chemical potential of the API, as shown in Fig. 6.7. The greater the melting point depression, the greater the reduction in chemical potential of the drug in the molten phase (Marsac et al. 2006, 2009). More recently, a method for measuring the chemical potential of an API in the presence of a polymer at room temperature was developed. Specifically, solution calorimetry provides a direct method to measure the heat of mixing drugs and polymers and can be used to calculate the solubility of an API in a polymer matrix at room temperature (Marsac 2012). Thermodynamics provides insight into the driving force for crystallization, but mobility facilitates crystallization. Although physical stability risk is most often considered negligible below the T_g, examples of sub-T_g crystallization exist (Vyazovkin and Dranca 2007), nucleation may occur during production of amorphous materials (Baird et al. 2010), and growth rates of crystalline materials may exceed those expected based on diffusion control by an order of magnitude at temperatures below the T_g (Hikima et al. 1995; Ishida et al. 2007; Sun et al. 2008a, 2008b; Yu 2006). These results, among others, have motivated the research toward linking molecular mobility with crystallization tendency. Many of the tools outlined above offer access to various modes of molecular mobility and may offer fundamental insight into the motions linked to physicochemical changes. Most generally, if the activation energy associated with a particular molecular motion matches the activation energy associated with a failure mode, this provides strong evidence that the two are linked. Many of the tools and techniques outlined above can also be used to access various timescales of motion. Most notably, DEA offers access to motions spanning the range of about 10^{-11}–10^{4} s, the complimentary TSC approach offers access to motions which occur over timescales of roughly 20–300 s, and ssNMR provides insight into motions on the order of 10^{-11}–10^{3} s (Ediger et al. 1996; Correia et al. 2001). In some instances, these approaches have shown some success in linking sub-T_g motions with crystallization tendency, but this remains an area of active research (Alie et al. 2004; Shmeis et al. 2004a, 2004b; Bhugra et al. 2007, 2008; Bhattacharya and Suryanarayanan 2009; Dantuluri et al. 2011; Bhardwaj and Suryanarayanan 2012a; Bhardwaj et al. 2013).

Given the versatility of current amorphous characterization techniques, it is clear that a range of resolutions and data can be generated on amorphous dispersions. As discussed previously, within a risk-based development approach, it becomes possible to triage testing to yield the appropriate balance of resolution and resource utilization so that the extruded product can be successfully positioned for commercialization.

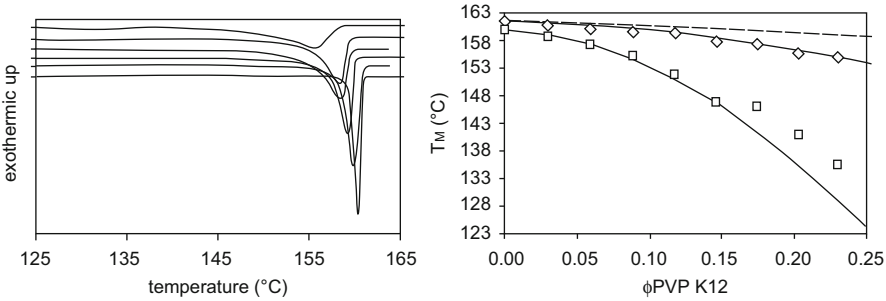

Fig. 6.7 Melting point depression as a function of drug loading for amorphous dispersions for indomethacin using onset (*square*) and offset (*diamond*) data. (Reproduced with permission from Marsac et al. 2009)

6.7 Mechanical Properties of Melt-Extruded Amorphous Dispersions

The mechanical properties of amorphous solid dispersions prepared by HME are an important yet often overlooked feature of these materials. The impact of an extrudate's mechanical properties is realized in further downstream processes such as particle size reduction and compaction.

The particle size distribution resulting from a milling operation is primarily determined by both the method of particle size reduction as well as the mechanical properties of the material such as fracture toughness, elastic modulus, and hardness. Thus, two extrudate samples with different mechanical properties milled under the same conditions will yield different particle size distributions. Beyond the intrinsic properties of the system, the mechanical behavior of extruded material is also affected by features of the bulk extrudate itself such as air bubbles, particle inclusions, or other defects that can increase the apparent brittleness of the material. Foamed extrudate, for example, could have different milling behavior as compared to a nonfoamed extrudate of the same composition.

The milled extrudate's particle size is often a critical quality attribute for the drug product performance for many reasons. It is well known that the dissolution rate of a particle is determined in part by the particle's size and surface area. For polymer-based materials such as extrudate, particle size can influence phenomena such as swelling and gelling, which may or may not be desirable for the product performance. Particle size may also affect powder flow in feeders and hoppers and can result in segregation risks that impact content uniformity in the final drug product.

In addition to particle size reduction, roller compaction and tableting are other downstream processes that will likely to be impacted by the mechanical properties of the milled extrudate. In the case of tableting, the extrudate may be subjected to localized high stresses which can induce particle breakage, elastic deformation, and/or plastic flow that affect compactability and tablet hardness.

Amorphous solid dispersions are prepared primarily with amorphous and/or semicrystalline materials, and therefore, the mechanical behavior of the extrudate is generally viscoelastic in nature. The materials' viscoelasticity implies a strain-rate dependence of the mechanical response and time-dependent mechanical behavior such as creep and stress relaxation. For example, in cases of high strain rates, these materials tend to be more brittle than under slower strain rates where viscous flow and other molecular relaxations can dissipate the energy without fracture. Thus, high strain rates are beneficial for particle size reduction operations.

Some of the important mechanical property descriptors of polymeric materials such as hot-melt extrudate are as follows:

- Elastic modulus: Stiffness, resistance to deformation, analogous to the spring constant in Hooke's law.
- Yield strength: The stress at which the behavior deviates from the linear elastic region and permanent plastic deformation is achieved.
- Ductility: The amount of plastic deformation that occurs before fracture.
- Fracture toughness: The resistance to fracture in the presence of a crack.
- Hardness: Resistance to localized plastic deformation.
- Creep modulus: A measure of the continued, time-dependent strain for a constant applied stress.

Mechanical testing of hot-melt extrudate can be performed on a variety of equipment typically used to test other types of materials. Loading configurations such as tensile, three-point bend, and cantilever deflection can assess different mechanical properties of the material under different stress states. If quasi-static methods are used, tests may be performed under different strain rates to assess viscoelastic effects of mechanical properties as discussed above. From a practical standpoint, the specimen tested should have uniform dimensions devoid of defects and ideally be of regular cross-sectional shape such as a circle or rectangle, enabling accurate determination of the cross-sectional area and the stress state for a given applied load. Perhaps the most ubiquitous device for testing polymers and therefore, hot-melt extrudate is the DMA. In addition to the ability to perform quasi-static tests in multiple loading configurations, a DMA can also test materials with oscillatory loading with varying frequency, temperatures, and even relative humidity for some models. The complex modulus obtained from a dynamic test can be separated into its elastic (storage modulus) and viscous (loss modulus) components. With the ability to ramp temperature during the test, changes in the mechanical properties can be assessed as a function of temperature and frequency, thus enabling not only temperature-dependent mechanical properties but also other sub-T_g relaxations that other techniques such as DSC may not be sensitive enough to detect. When amorphous polymers are heated through their glass transition, the elastic modulus can drop by a few orders of magnitude, and since the glass transition is related to changes in molecular dynamics, the transition temperature itself as measured with DMA will be a function of the applied strain rate with increases in T_g observed with increasing strain rates.

In addition to temperature, other environmental factors such as relative humidity can have a strong impact on the mechanical properties of the extrudate as many of

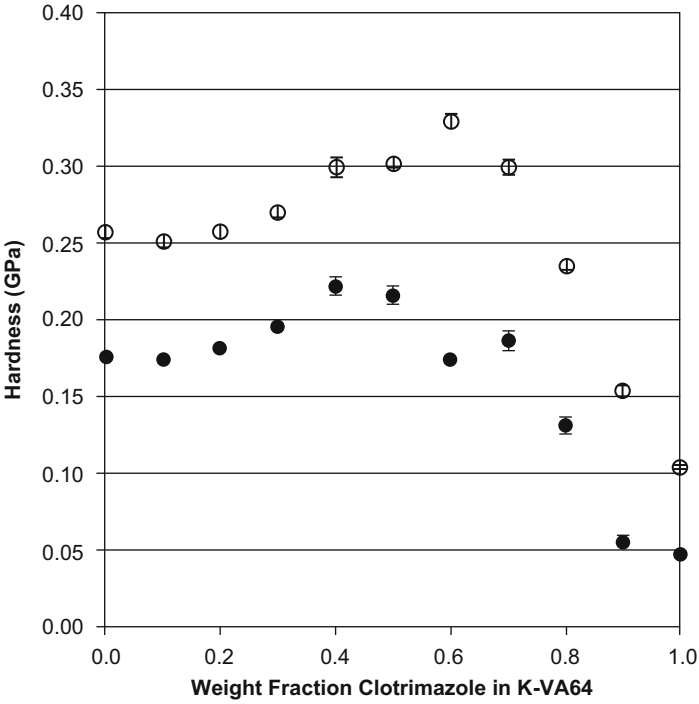

Fig. 6.8 Hardness versus weight fraction of clotrimazole in Kollidon VA 64 measured by nanoindentation at 18 % (o) and 49 % (o) relative humidity

the polymers used in the process tend to be hygroscopic. With some exceptions, water generally acts as a plasticizer for these polymers, lowering the glass transition temperature and reducing mechanical properties, such as modulus and hardness. It is important to control the relative humidity during mechanical tests performed on extrudates and also to be aware of the storage conditions the materials were exposed to prior to testing. For example, if extrudate is stored under desiccated conditions but tested at ambient laboratory conditions, the mechanical properties could change over time as the materials slowly absorb moisture. For accurate measurement and comparison between samples, it is recommended to equilibrate the materials at desired environmental conditions and then test at the same. Equilibration times will depend on the thickness of the samples and rates of moisture diffusion into and out of the sample.

A final consideration with respect to mechanical properties of hot-melt extrudate is the composition of the amorphous solid dispersion itself. Just as water content described above can impact the mechanical properties of the material, so can the other components such as plasticizers, surfactants, and the API itself. In one study, the effect of both API loading and humidity on the mechanical properties of amorphous solid dispersions was determined using nanoindentation and nanoDMA (Lamm et al 2012). This is illustrated in Fig. 6.8, where dispersions of clotrimazole and

copovidone were tested, and it was found that adding the drug to the polymer actually increased the hardness and modulus of the materials up to approximately 50 % drug loading despite the fact that glass transition temperature decreased with increasing drug load. This phenomenon, known as anti-plasticization, can have significant impact on the materials performance in downstream processes as discussed above. For all the extrudate compositions tested, increasing humidity lowered the hardness and modulus of the dispersions, thus highlighting water's plasticizing effects on the dispersions.

Beyond this, there are also a limited number of examples describing mechanical properties that can be used to indirectly relate mechanical properties of extrudates to milling and compression performance. In a recent study, using three-point bend analysis of extruded parts, the modulus, yield strength, and toughness of materials were characterized with particular properties ascribed to the downstream processability of these materials (DiNunzio et al. 2012). For HPMCAS, a material known to be particularly challenging to mill, both brittle and ductile behavior was observed. As drug loading increased, the yield strength and toughness decreased; however, the modulus remained largely unchanged, explaining why drug loading may favorably influence milling performance of these systems. When compared to other extruded polymers, specifically copovidone and amino methacrylate copolymer, a significantly greater toughness is observed for HPMCAS that falls in line with the millability of these systems. Additional characterization of polyethylene glycol showed no brittle failure of the sample, only a continuous deformation. This behavior, unique to polyethylene oxide among the systems studied, illustrated why this material exhibits challenges during milling operations and can provide significant benefits for abuse-deterrent formulations.

6.8 Summary

Among process options for commercial amorphous solid dispersion generation, HME is often preferred due to its continuous nature, small manufacturing footprint, and lack of solvents. Preclinical development may require alternative processes, but these can often be transitioned to HME. Designing HME amorphous solid dispersions requires a thorough understanding of polymer, plasticizer, and surfactant selection, extrusion equipment design, and process parameters, guided by increasingly effective characterization tools to assure drug particle dispersal and dissolution into the matrix and stabilization throughout the shelf life of the product to finally deliver an effective dose to the patient. Furthermore, the limitations of the use of HME are quickly being overcome by application of formulation understanding and the use of supercritical fluids to allow processing of high melting point APIs with additional understanding of mechanical properties, leading to improved milling efficiency and compaction performance.

By building on the extensive product and process design experience of the polymer and food industries, pharmaceutical development is now able to add its unique

considerations to incorporate HME as a core capability for commercial manufacturing. As will be described in a following chapter, HME can be rapidly scaled up based on product and process design space understanding after successfully demonstrating drug product quality in early development.

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