Chapter 3
Overview of Amorphous Solid Dispersion Technologies

Harpreet Sandhu, Navnit Shah, Hitesh Chokshi and A. Waseem Malick

3.1 Introduction and Background

A survey of recent literature shows considerable growth in the application of amorphous solid dispersion (ASD) to solve solubility-related challenges in product development (Williams et al. 2010, 2013; Repka et al. 2013). This growth is primarily driven by three factors:

a. development and expansion of acceptable excipients especially at the dose level that is needed for solid dispersion,
b. application of newer technologies, and
c. enhanced understanding of amorphous systems using predictive analytical tools for stability and dissolution.

The earlier developments in ASD were hindered by the lack of scientific understanding of the metastable high-energy form and the availability of suitable technologies (Sekiguchi et al. 1964). For the purpose of this chapter, the processing technologies are classified into two main classes primarily, i.e., solvent based or fusion based. A schematic of this classification is shown in Fig. 3.1 to help orient the readers (Miller 2012). Based on their maturity, selected technologies are covered in this chapter with a goal to provide the necessary tools to help select an appropriate technology for a specific application.

H. Sandhu (✉)
Merck & Co., Inc., 556 Morris Avenue, Summit, NJ 07901, USA
e-mail: harpreet.sandhu@merck.com

N. Shah
Kashiv Pharma LLC, Bridgewater, NJ, USA

H. Chokshi
Roche Pharma Research & Early Development, Roche Innovation Center, New York, NY, USA

A. W. Malick
Pharmaceutical and Analytical R&D, Hoffmann-La Roche Ltd., Nutley, NJ, USA

N. Shah et al. (eds.), *Amorphous Solid Dispersions,*
Advances in Delivery Science and Technology, DOI 10.1007/978-1-4939-1598-9_3

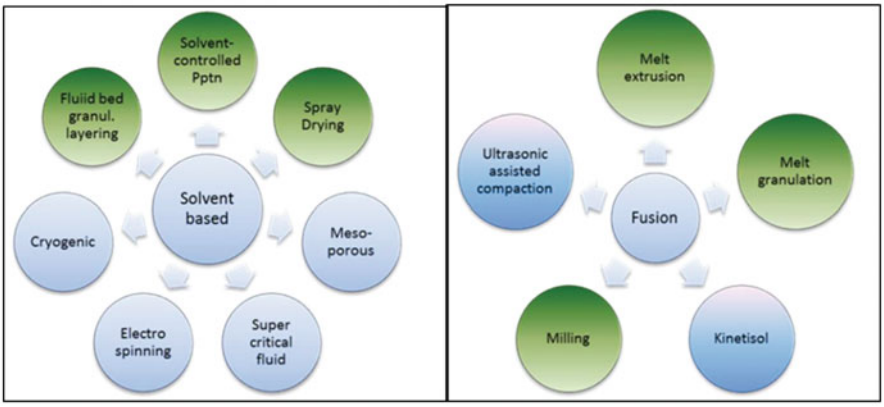

Fig. 3.1 Commonly used processing technologies in the manufacture of amorphous solid dispersion (ASD)

- **Solvent-based technologies** listed below rely on the preparation of a solution of the drug together with the stabilizing component:
  - Spray drying: Rapid removal of the solvent in a controlled environment (temperature and pressure) that is accelerated by generating high surface area
  - Fluid bed granulation/layering/film coating: Removal of solvent in various conventional pharmaceutical equipments
  - Coprecipitation: Solvent-controlled precipitation technologies, e.g., micropre-cipitated bulk powder (MBP), evaporative precipitation into aqueous solution (EPAS), Nanomorph, and flash precipitation, etc.
  - Supercritical fluid- based technologies and its variations such as FormulDisp®
  - Cryogenic processing, e.g., spray freeze drying (SFD) and thin film freezing (TFF)
  - Electrospinning: Drawing nanofibers from solution or molten material under high electrostatic voltage
  - Rotating jet spinning: Combination of centrifugation and pinning to produce nanofibers
- Fusion-based technologies where the drug and the stabilizing component are heated and mixed:
  - Melt granulation
  - Melt extrusion
  - KinetiSol: High-shear mixing combined with high temperature
  - Milling: High-shear milling/cryogrinding with and without excipients, e.g., Biorise®
  - Deposition of molten material on a carrier by hot-melt coating in a fluid bed process, e.g., Meltdose®

3.2 Solvent Evaporation

A key prerequisite for ASD is the elimination of drug's crystallinity and the best means to achieve that state is by dissolving the crystalline drug in a suitable solvent. In some cases, it may be possible to obtain pure amorphous drug but due to stability considerations the drug is generally processed with a polymer that stabilizes the amorphous form through mechanical and physicochemical interactions. An ideal means to achieve coprecipitation involves the solubilization of active pharmaceutical ingredient (API) and polymer in a common solvent followed by solvent removal. Typically, solubility of a drug in organic solvents drives the selection of stabilizing polymer and the process. The design of a formulation using solvent evaporation process generally consists of the following sequential steps:

- Solvent selection
- Selection of polymer and additives
- Selection of an evaporation method that produces ASD with acceptable residual solvent levels

To get a better insight into these processes, each of these steps is discussed in the following sections.

3.2.1 Solvent Selection

For successful application of solvent-based techniques, adequate solubility in organic solvents is critical for generating an ASD. In most cases, the solubility screen conducted during preformulation studies forms the basis for selecting a solvent. The criteria for solvent selection include solubility of API and polymer in a common solvent, drying efficiency of the solvent, acceptable level of residual solvents (based on International Conference on Harmonization classification), and desired shelf-life stability. From thermodynamic perspective, the drying of solvent involves complex interplay of heat and mass transfer and depends primarily on the supply of heat and efficiency of vapor removal. On a process level, the drying efficiency depends on the solvent evaporation rate that in turn depends on the boiling point, specific heat of solution, heat of vaporization, surface area, vapor pressure, percent solid content, and solution viscosity (Abeysena and Darrington, 2013).

Drying is an energy-intensive process that requires careful selection of a solvent that can provide adequate solubility of drug and polymer and is easy to remove. From the thermal perspective, the amount of heat required to remove a solvent represents the sum of latent heat of vaporization (ΔH_{vap}), heat required to raise the temperature to the boiling point, and losses in the process (Murugesan et al. 2011). Assuming that energy loss is an equipment factor and will be similar for different solvents, the heat required (Q_H) to remove a solvent can be estimated by ΔH_{vap} and $C_p \Delta T$:

$$Q_H = C_{P^*}(T_b - T_{RT}) + \Delta H_{\text{vap}} \times \frac{1000}{\text{Mol weight}},$$

Table 3.1 Drying-related properties of some commonly used solvents

Solvent	Mol wt (g/mol)	Heat capacity (J/g °C)	Heat of vaporization (kj/mol)	Boiling point (°C)	Vapor pressure @20 °C (kpa)	Heat energy required to evaporate 1 kg solvent (J)
Water	18	4.18	40.7	100	2.3	2596
Ethanol	46	2.44	38.7	78	5.8	983
Acetone	58	2.17	29.1	70	24	610
Dimethylsulfoxide	78	1.96	52.9	189	0.06	1009
Dimethylacetamide	87	2.0	46.2	165	0.3	828
N-methylpyrrolidone	99	1.7	54.5	204	0.04	846

where C_p is specific heat capacity, T_b is the boiling point, and T_{RT} is room temperature.

A summary of the relevant thermophysical properties of commonly used solvents is provided in Table 3.1. In addition to boiling point and heat of vaporization, vapor pressure of the solvent is also critical in assessing the drying efficiency as that determines the surface renewal efficiency. Understanding the temperature-dependent changes in vapor pressure can provide useful insights into the means of improving drying efficiency. It has been shown that solvents such as water, toluene, n-heptane, and N-methylpyrrolidone (NMP) are difficult to remove because the increase in vapor pressure as a function of temperature is very slow. Furthermore, it is also important to note that the properties summarized in Table 3.1 are for pure solvents and can vary significantly depending on the additives and their interactions with the solvents.

Driven by the desire to maximize API solubility and for optimization of drying efficiency, on many occasions the formulation scientists resort to using mixed solvents. Although considered an annoyance from the perspective of purification, the azeotropes are preferred for ASD in the event a pure solvent cannot be used. In the absence of azeotropes, the differences in the evaporation rates of binary solvents may result in variable supersaturation of the precipitating material thus potentially resulting in phase separation. A list of some commonly used solvents that can form azeotrope is provided in Table 3.2 for reference. When using mixed solvents for ASD, it is likely that much more extensive work will be required to optimize the right combination and ascertain its impact on product quality to derisk potential problems during manufacturing and scale-up.

In the course of selecting a suitable solvent for ASD preparation, it is important to ensure that material is chemically and physically stable in the solvent. The intent of solvent selection is to convert crystalline material into amorphous form, however, some solids may form solvates or the residual solvent may lower the glass transition temperature (T_g) of the material resulting in unfavorable stability. The stability needs

Table 3.2 Listing of commonly used solvents with respect to their ability to form azeotrope (http://en.wikipedia.org/wiki/Azeotrope_(data), Accessed 10 Dec 2013)

Solvents	Boiling Point of Solvent (°K)	Azeotropic Temp (°K)	Azeotropic Composition (%w/w)
Ethanol:Water	352/373	352	96:4
Acetone:Water	330/373	Zeotropic	Zeotropic
Water:Acetone:Chloroform	373/330/334	334	4:38:58
Ethanol:Tetrahydrofuran	352/339	339	97:3
Ethanol:Ethyl acetate	352/350	345	69:31
Dichloromethane:Water	313/373	312	99:1
Dichloromethane:Ethanol	313/352	313	95:5

to be established to ensure that sufficient hold time can be achieved especially during scale-up where the run times can extend over days.

3.2.2 Selection of Polymer and Other Additives

Primary criterion for the selection of a polymer for ASD by solvent evaporation method depends on its solubility in the solvent. The other criteria which are also important include miscibility with API in the solid state, ability to yield high-drug loading, supportive toxicological data package, and its impact on achieving and maintaining high supersaturation. These additional criteria are covered in details in the other chapters. A brief summary of different polymers and the solvents that have been used for various applications is provided in Table 3.3. Solvent-based processes provide options to include other additives, such as surfactant or secondary stabilizers, to augment product quality. Feed solution ranging from solution to suspension can be processed by spray drying process; however, for ASD manufacture it is desirable that all components are in the dissolved state. From a downstream processing perspective, most spray-dried intermediates require densification to improve the density and flow properties prior to manufacturing the final dosage form. The predominant consolidation mechanism for amorphous materials especially with relatively large proportion of polymer is plastic deformation (Iyer et al. 2013). Choice of the polymer, any additives and their relative amounts in the feed solution, and the characteristics of the final amorphous intermediate may impact critical properties of the material such as particle size and density that could have significant effect on downstream processing.

Table 3.3 Relevant properties of commonly used pharmaceutical polymers

Polymer	Commercial product/late-stage experience (ASD)	Thermal properties T_g (°C)	Solubility in solvent
Hypromellose	Sporanox®, Fluid bed coating on non-pareil seeds	170–180	Ethanol:dichlormethane (1:1, 2:1) Methyl acetate:methanol (1:1)
Hydroxypropylcellulose acetate succinate	InCivek®and Kalydeco® by spray drying, Zelboraf®by coprecipitation, Noxafil DR® (HME)	100–110	Ethanol, methanol, dichloromethane, chloroform
Methacrylic acid copolymers (Eudragit L100, S100)	No known product as ASD, used in controlled relase product	> 150	Acetone, ethanol, methanol Ethanol:dichlormethane (1:1)
Amino methacrylate copolymer (Eudragit EPO)	Taste-masking application	48	Acetone, ethanol, methanol, ethyl acetate, methyl ethyl ketone, dichloromethane, tetrahydrofuran
Povidone (PVP)	Cesamet®) granulation with ethanol (Conine 1980), Rezulin®(HME)	175 (K30) 180 (K90)	Acetone, ethanol, methanol, ethyl acetate, methyl ethyl ketone, dichloromethane, tetrahydrofuran
Copovidone (PVP/VA)	Kaletra® and Norvir® made by HME	106	Acetone, ethanol, methanol, ethyl acetate, methyl ethyl ketone, dichloromethane, tetrahydrofuran
Polyethylene glycol	GrisPEG® melt granulation	Tm = 55–63 (PEG6000)	Acetone, ethanol, methanol, ethyl acetate, methyl ethyl ketone, dichloromethane, tetrahydrofuran
Poloxamers	Late-stage experience as nanoparticles and crystalline dispersion	Tm = 52–57 (P188)	Acetone, ethanol, methanol, ethyl acetate, methyl ethyl ketone, dichloromethane, tetrahydrofuran
Polyvinyl acetate phthalate	Primary use in tablet coating	NA	Ethanol, ethyl acetate, methanol Ethanol:dichloromethane (1:1)
Cellulose acetate phthalate	NA	160–170	Acetone, methyl ethyl ketone, ethyl acetate
Hypromellose phthalate	NA	133–137	Acetone, ethanol:dichlormethane (1:1) methanol, ethyl acetate, methyl ethyl ketone, dichloromethane, tetrahydrofuran
Soluplus®	NA, primarily used in melt extrusion	70	Acetone, methanol, ethanol, dichloromethane

ASD amorphous solid dispersion, *HME* hot-melt extrusion

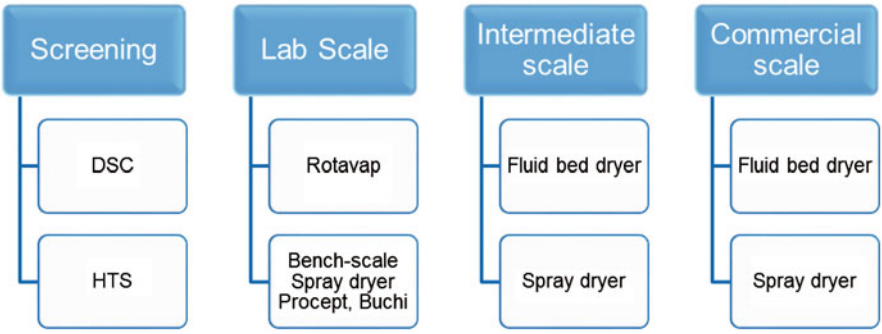

Fig. 3.2 Selection of solvent removal process

3.2.3 Selection of Solvent Evaporation Process

There are several literature reports demonstrating the role of solvent removal process in the development of ASD (Joe et al. 2010; Miller and Gil 2010). The choice of solvent evaporation process is influenced by the scale, the stability of the formulation, and the availability of equipment. Commonly used solvent removal processes in the pharmaceutical industry are shown in Fig. 3.2. Even though spray drying is the most efficient, well understood, and established process for ASD, other methods are also frequently used. Fluid bed drying includes either spray granulation or fluid bed layering on inert beads. The granulated product can be converted to tablets or capsules although the multiparticulate pellets produced by fluid bed processes are generally more suitable for encapsulation.

Owing to its suitability for high-throughput screening, solvent evaporation is the most widely used process during preformulation screening for optimal selection of solvent, polymer, and drug loading. Because of the small sample volume (typically few microliters) and the efficiency of solvent removal process, the screening studies tend to simulate the spray drying process fairly well. However, in the chronicles of ASD development, the weakest link between preformulation screening and the manufacture of small-scale batches has been the availability of suitable laboratory-scale equipment. Rotary evaporators that are used in early development may lead to false negatives for compounds with high crystallization tendency and the small-scale spray dryers suffer from low yield. It is generally recognized that compounds with low tendency for crystallization can be manufactured by any solvent evaporation process but the rate of solvent removal and the long exposure time to high-temperature conditions pose serious challenges for compounds with high crystallization tendency. Due to the solvent removal efficiency and single-stream continuous processing, spray drying offers the most favorable conditions for manufacture of ASD. With recent developments in the design of spray dryers, spray drying can now be realized across all scales ranging from laboratory to commercial. The laboratory-scale spray dryer supplied by ProCepT® can work with volumes as low as 1 mL to 24 L with more than 90 % yield (ProCepT 2014). One of the challenges with all solvent-based techniques

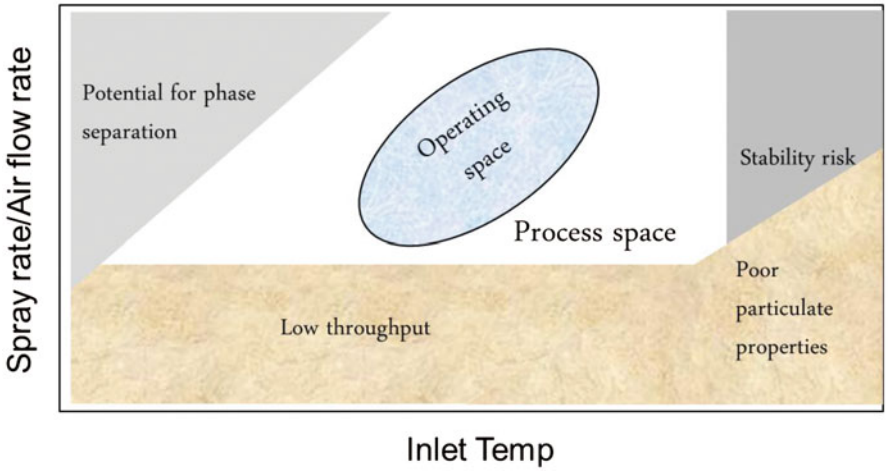

Fig. 3.3 Spray drying design space

is the complete removal of solvent. In addition to the safety concerns, the residual solvent can have a detrimental effect on the stability of the product. Therefore, spray drying is usually followed by secondary drying. Processes ranging from tray drying to fluid bed have been used to achieve the desired level of residual solvent. Among the various modes of solvent removal, spray drying has become the most widely adopted process. The key features of spray drying processes that are relevant for design and development of an ASD product are listed below:

- Design of spray dryer: Closed-loop versus open-loop systems
- Atomization and nozzle design: Rotary, multi-fluid pneumatic (two to four fluids), pressure, and ultrasonic nozzles
- Drying gas: Type (cocurrent versus current orientation) and air volume
- Feed material: Solid content, foaming, viscosity, solvent system, T_g, and stability
- Collection system: Cyclone, filter bags, and electrostatic precipitators
- Secondary drying: Tray drying, fluid bed drying, rotary, agitated dryer, and fluidized spray drying
- Downstream processing: Densification, compaction, agglomeration, dissolution, and stability

The product quality and particulate properties can be controlled by optimizing the process variables. Types of equipment setups that can be used to support the development of ASD product from early screening phase to commercial scale are shown in Fig. 3.2 and the key processing variables are shown in Fig. 3.3 (Appel 2009).

3.3 Hot-Melt Extrusion

From the discovery of ASD, the two methods that have dominated the literature are solvent evaporation and melt extrusion (fusion-based method). Although spray drying continues to be an important technology, the commercial success achieved with melt extrusion has placed hot-melt extrusion (HME) at the top of the technology list. This stems from the specific advantages of the HME process that provides solvent-free continuous processing, modularity, and ability to produce a close-to-final product. Comprehensive discourses focusing on the application of melt extrusion in the pharmaceutical industry have been the subject of several research-based textbooks that have become available in the recent past (Ghebre-Selassie et al. 2003; Douroumis 2012 and Repka et al. 2013). The following section provides an overview of the formulation and process considerations in the development of the HME process. The key areas that need special consideration are listed below and elaborated further in the text:

- Selection of polymer, additives, and drug loading
- Selection of extruder and the processing conditions
- Downstream processing and performance optimization

3.3.1 Selection of Polymer, Additives (Plasticizer, Flow Aid and Surfactant), and Drug Loading in HME

The use of a polymer in ASD development is primarily for stabilizing the amorphous form, but in the case of the HME it is critical for processing as well. The molten polymer provides a medium in which the drug is either solubilized or dispersed. Therefore, in addition to improving the performance (dissolution and stability) of the product, the polymer also serves as an enabler for processing. Key characteristics of the polymer and the overall composition that are suitable for melt extrusion can be summarized as:

- Melting point and/or T_g of the drug
- Melting point and/or T_g of the polymer
- Molecular weight and melt viscosity of the polymer
- Specific interactions between drug and polymer leading to plasticization or antiplasticization, especially in the molten state
- Thermal stability of the components at the processing temperature
- Properties of additives such as physical state, melting point, miscibility, and stability
- Particulate properties of the polymer

A systematic analysis of potential drug:polymer blends may provide insight into the selection of a suitable polymer, e.g.:

- Solubility parameter estimation and differential scanning calorimetry (DSC) help assess the drug:polymer miscibility and determine drug loading.
- Rheological studies provide key insights into the viscoelastic properties and potential torque-limited extrusion.
- Assessment of the plasticizer to improve processability (lowering processing temperature or reducing torque).
- Microscopic investigation, especially atomic force microscopic and light microscopic methods, in characterization of the extrudates.
- Dissolution studies to monitor the rate and extent of solubility enhancement as well as to determine the need for surfactants.

Utilizing the melting point depression data from DSC, it is possible to calculate the Flory–Huggins interaction parameter that can then be used to construct the temperature–composition phase diagram for a binary system. The maximum drug loading that can be achieved in the solid dispersion that provides acceptable dissolution performance depends on the thermal (T_m/T_g ratio) and hydrophobic properties of the compound (log*P*). Based on the trend analysis of the available data, an empirical relationship has been proposed that demonstrate that drug substance with log*P* less than 6 and T_m/T_g ratio less than 1.3 may accommodate payloads as high as 50 % w/w (Friesen et al. 2008; DiNunzio 2013).

Plasticizer Plasticizers are low molecular weight additives that may be used in the HME process to help lower the processing temperature or reduce the melt viscosity of formulations containing high-melting actives or high molecular weight polymers. The processing of ASD by HME has been envisioned to occur in either the solubility regime or miscibility regime. In most cases, it is the molten API that is mixed with the molten polymer to produce an ASD. For some challenging compounds that do not have adequate solubility in the molten polymer, plasticizers are added to the formulation to aid in the process. Since plasticizers can have a negative impact on other aspects of the product such as dissolution, physical stability, T_g, hygroscopicity, chemical stability, appearance, and milling, their use in the formulation should be based on balancing and optimizing their effect on both processing and performance of the ASD.

A list of commonly used plasticizers is summarized in Table 3.4. Selection of the plasticizer is based on its intended functionality in the formulation such as reducing the processing temperature or reducing the melt viscosity. An ideal plasticizer is a temporary plasticizer that imparts the desired processing advantage but is removed from the formulation before final processing to minimize its negative impact. Supercritical carbon dioxide (CO_2), low boiling solvents, and reagents that can evaporate or sublime are all being evaluated for this purpose (Verreck et al. 2005; Desai 2007). In some cases, drug itself may provide adequate plasticization of the polymer (Zhu et al. 2002).

Table 3.4 Commonly used processing aids: plasticizers, surfactants, and flow aids in HME processing

Class	Type	Name/functionality	Mode of addition
Plasticizer	Liquid	Triethyl citrate Tributyl citrate Triacetin Polyethylene glycol 400 Acetyl tributyl citrate Dibutyl sebacate Solutol HS15 Cremophor EL and\RH40	Preblending could be challenging and may require preprocessing either by high-shear mixing or crude HME processing Through liquid addition port
	Solid	Low-melting drugs (does not belong because of title of table) Methyl paraben Citric acid PEG 8000 Stearic acid Glyceryl behenate Soluplus	Preblending feasible May be added through a different port
			May require large amount 5–10 % to achieve desired benefit May also act as flow aid
	Gaseous	Supercritical fluid (CO_2)	Are added via liquid addition port
		Low-boiling solvents (Acetone/ethanol/ethyl acetate)	Requires optimal screw design to prevent backflow
		Camphor	Engineering controls required in the facility

Table 3.4 (continued)

Class	Type	Name/functionality	Mode of addition
			Mostly act as temporary plasticizers, but residual solvent control may be needed
Surfactants	SPANS	Sorbitan esters of long-chain fatty acids	Mostly added in preblend but can be metered via dedicated feed port
	Poloxamer	Block co-polymer PEO-PPO	May impact T_g and other quality attributes
	Tween	Polyoxyethylene derivatives of sorbitan esters (C12-C18)	Pure docusate sodium is semisolid but a powder form is available that contains sodium benzoate
	Labrasol	PEG-8 Caprylic/Capric Glycerides	May require lower processing temperatures due to chemical stability
	Gelucire 44/14, 50/13	Lauroyl polyoxylglycerides Stearoyl polyoxylglycerides	Usage amount should consider permissible daily intake
	Docusate sodium	Dioctyl sodium sulfosuccinate	
	Sodium lauryl sulfate	Strong surfactant	
	Vitamin E TPGS	–	
Flow aid	Mannitol/isomalt	Commonly used pharmaceutical excipients	They may be added in powder blend to improve feeding efficiency of poor-flowing powders
	Starch/maltodextrin		
	Colloidal silica	Flow aid	

HME hot-melt extrusion, *TPGS* tocopheryl polyethylene glycol

Surfactant Despite having successfully converted the crystalline drug to amorphous form, the HME product may not always provide the desired dissolution advantage. This is attributed to the poor wetting of the extrudate caused by hydrophobicity of the drug and the low porosity of the extrudates. Inclusion of a surfactant in the formulation improves the dissolution properties resulting in improved bioavailability of the product (Rosenberg et al. 2005; Mosquera-Giraldo et al. 2014). Listing of the commonly used surfactants is provided in Table 3.4. The key considerations in terms of selection criteria include impact on stability, daily usage limit, and processing feasibility.

Flow Aids A key consideration in the development of HME process is being able to uniformly feed the extruder. The consistent feed rate depends on the flow properties of the material. Depending on the number of feeders used, the drug and the polymer can be fed either as a common blend or separately through different feeders. To ensure the uniformity of blend, it is important to closely match the particulate properties of the drug and the polymer. A milling step may be required to ensure that drug and polymer are adequately mixed prior to extrusion.

To aid in the dissolution of API in the molten polymer, micronized API is frequently used in the extrusion process. However, this poses challenges in terms of poor flow and electrostatic charges that may limit the feeding of the API:polymer blend to the extruder. The low bulk density of the powder blend may further compromise the feeding efficiency giving rise to feed rate fluctuations and process instability. Commonly used pharmaceutical excipients shown in Table 3.4 can be included in the HME formulation to aid in the flow of material. Since some of these materials are crystalline in nature, they may affect the miscibility of drug in the polymer or simply increase the analytical complexity.

Thus, formulation design requires judicious selection of each component while considering their impact on the desired and undesired attributes of the product.

3.3.2 Selection of Extruder and the Processing Conditions

From the early days of introduction of melt extrusion processing in the pharmaceutical world, co-rotating twin-screw extruders have dominated this technology owing to their superior efficiency of mixing and self-wiping action ensuring first-in-first-out material flow. Several extruder types and sizes are available to achieve the desired product attributes that meet the phase-dependent needs of the product. Small-scale extruders provide an API-sparing option to support early studies such as pharmacokinetic (PK) feasibility or range-finding toxicology. These, however, may not always reflect the actual shear stress that the product will be subjected to during intermediate to large-scale manufacturing. Some of the challenges faced during small-scale manufacturing using a laboratory-scale extruder (degradation or incomplete conversion to amorphous form) may be resolved with larger extruders due to more efficient material flow and controlled residence time and residence time distribution. Typically,

extruders greater than 12 mm provide representative extrusion conditions for scale-up with respect to the geometric similarity between total length, screw geometry, shear conditions, feeding mechanism, temperature of zones, and die dimension. The key equipment considerations in the development of an extrusion process include:

- Selection of extruder type (corotating versus counter rotating, motor power, and gear box)
- Length/diameter ratio (L/D ratio)
- Die design, size, and number of openings
- Feeding mechanism, number, and type of feeders including liquid injection port
- Optimization of screw geometry (distribution of kneading and conveying zones across the screw length)
- Temperature of each zone
- Online processing of extrudates: Cooling belt, pelletization, milling, and chillers
- Calendaring or direct shaping of materials such as films, implants, or tablets
- Downstream processing of the extrudates

A key consideration in the development of scalable process requires maintaining geometric similarity, i.e., L/D ratio and the degree of fill. Similar L/D ratios along with temperature and screw design across the barrel length provide comparable temperature and shear stress profiles. And the comparable degree of fill ensures consistent residence time and residence time distribution. This ensures that product is exposed to similar energy as given by the following equation:

$$\text{Specific energy}(SE) = \frac{K_{wm} EG_{\%} TS_{\%} \frac{RPM\text{run}}{RPM\text{max}}}{Q_n},$$

where SE is kw/h/kg, K_{wm} is motor power in kw (horsepower/1.34), $EG_{\%}$ efficiency of the gear system (95 %), $TS_{\%}$ (percent of torque and is formulation specific), RPM_{run} is the screw speed during the run and RPM_{max} the maximum feasible for the machine, Q_h is the feed rate (kg/h). Since most of the parameters are equipment specific, the two process variables are screw speed and feed rate.

Owing to its direct impact on the performance and efficiency of the process, feed rate is an important factor to consider during development. Representative feed rates that can be geometrically scaled up ensure reproducibility of the process and product. Multiple feeders can be used to improve the throughput as long as the product robustness has been established in that feed rate range.

Screw Design (Screw Elements and Shaft) The unique feature of melt extrusion process is its modularity and the prime illustration of that is in the design of screw configuration. In most pharmaceutical operations, the screw design consists of three elements: conveying, mixing, and zoning. Each of these regions can be moved, lengthened, or shortened with relative ease to achieve desired product characteristics. Conveying elements are low-shear elements, however, mixing elements depending on the design can generate significant shear and result in distributive mixing whereas zoning elements are primarily included to block the backflow especially in case of gas or supercritical fluid addition. Screw design can be optimized to accomplish uniform

mixing, modify residence time, and/or to improve the chemical stability of thermally labile compounds. The screw elements are assembled on the shaft that controls the amount of torque being transferred from the motor to the product. Optimal design of screw shaft can further improve the extrusion efficiency by ensuring that the extruder power is effectively transferred to move the screws especially for high-viscosity products.

3.3.3 Downstream Processing and Performance Optimization

The most common type of output from pharmaceutical extrusion process is a spaghetti-shaped extrudate that may appear as transparent glass for pure amorphous material and has characteristically high density. For manufacture of standard oral dosage forms, after adequate cooling, these extrudates are generally milled to obtain granules. The granules are mixed with other excipients such as disintegrant, compression aid, and lubricant for either encapsulation or compression into final dosage form. Contrary to spray-dried material, HME granules possess excellent flow properties requiring minimal lubrication. However, HME granules generally have very poor compaction characteristics that are attributed to low porosity of the extrudates and ductile properties of the polymeric systems. Process modification, such as inclusion of supercritical fluids in the extrusion, increases the porosity of the extrudates that has favorable effect on the compaction properties. Thus, process and material properties play an important role in achieving the desired quality attributes ranging from appearance, integrity, and dissolution. Some of the issues encountered during development and possible means of resolution are summarized below:

- **Low T_g product and milling**: Ideally, selection of polymer and drug loading takes into consideration the T_g, specifically for physical stability purposes, however, in some instances it may not be possible to improve the T_g. Products with low T_g ($T_g < 50\,°C$), may not be suitable for conventional milling by impact mills such as hammer mill due to the potential of melting and blinding of the screen. In such cases, lowering the density of extrudate with inclusion of volatile solvents or supercritical CO_2 may improve the milling behavior. Alternatively, air jet milling or cryo-milling may provide viable options to address the milling issues with the extrudates. Particle size reduction may also improve the porosity of the granules thus helping with compaction.
- **Slow dissolution**: Despite using the same formulation composition, HME products when compared to ASD manufactured by other techniques, such as spray drying or microprecipitation, may provide slower dissolution rate (Dong et al. 2008). The slow dissolution rate is attributed to low surface area of the particle (low porosity surface and particle size). Several examples have been cited in the literature that uses surfactants in the formulation to overcome the dissolution problem. High hydrophilic–lipophilic balance (HLB) surfactants such as docusate sodium, d-α-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS),

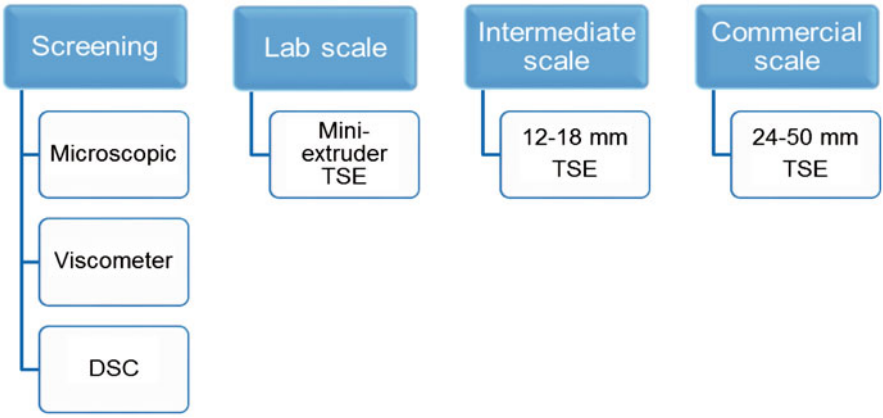

Fig. 3.4 Types of extruders used during product development

spans, tweens, cremophor, sodium laurylsulfate, and poloxamer are frequently used to improve the dissolution rate. As mentioned earlier, the selection of surfactant requires a systematic assessment of the allowable use limit, thermal stability, physical stability, and dissolution. The processing factors such as particle size reduction, use of superdisintegrants, and foaming agents in the extrusion can also help in improving the release rate by increasing the surface area and porosity.

- **Poor compaction**: Although milling of the extrudates may produce fine particles but due to low inherent porosity and ductility of polymers, for most part HME granules result in tablets of low tensile strength. This can be overcome by increasing the porosity of the extrudates either by the use of foaming agents or adding materials with brittle fracture characteristics during extrusion or prior to compression.

Figure 3.4 shows the equipment train that has been commonly used in the industry during different stages of development and Fig. 3.5 shows the key processing considerations during the development of HME process (Schenck et al. 2011).

3.4 Microprecipitation: MBP

The microprecipitation technology is especially suited for APIs that do not have adequate solubility in volatile organic solvents, and/or are thermally labile either due to high melting point or poor stability. According to Yalkowski, solubility of a compound can be estimated by its crystal structure (melting point and heat of fusion) and hydrophobicity (Yang et al. 2002). It has been observed that some compounds with high crystal lattice energy present solubility challenges in all types of solvents, i.e., aqueous as well as pharmaceutically acceptable cosolvents and vehicles. These brick dusts-like molecules have been shown to dissolve in polar solvents like dimethylacetamide (DMA), dimethylformamide, dimethylsulfoxide, and NMP.

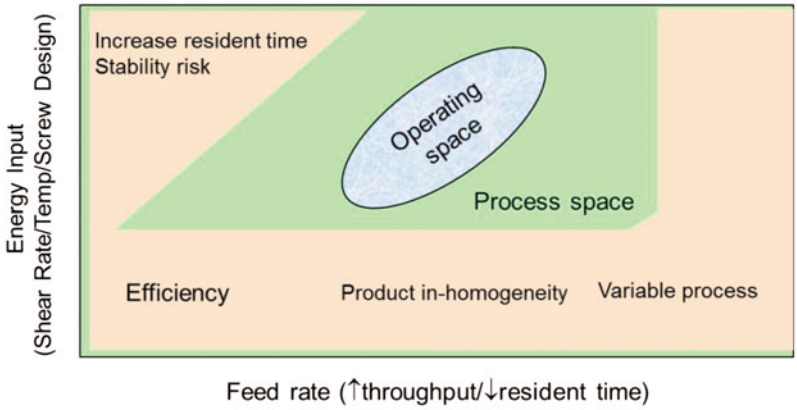

Fig. 3.5 Design space consideration during development of the hot-melt extrusion (HME) formulation

Such compounds are not suitable for either melt-based processes because of thermal stability or spray drying due to of the high boiling points of these solvents. Microprecipitation takes advantage of the solubility of the API and polymer in these polar solvents to produce amorphous form of API by solvent-controlled precipitation (Shah et al. 2012, 2013).

A schematic of the process is shown in Fig. 3.6 where a solution of the drug and polymer (ionic) is slowly added into a large volume of antisolvent to induce precipitation. The rapid precipitation conditions achieved due to insolubility of drug and polymer in the antisolvent as well as low processing temperature help preserve the amorphous form. From conceptual perspective, it can be visualized that the particle formation in microprecipitation occurs by extraction of solvent by the antisolvent. Because of high solubility of DMA in aqueous fluid, the extraction process is highly efficient resulting in amorphous particles with high porosity and superior wetting characteristics compared to spray drying. Although some work has been done using organic solvents as antisolvents, the most advanced systems use aqueous-based antisolvents to induce precipitation (Kadir 2012). Figure 3.7 shows a hypothetical scheme proposing the mechanism of particle formation during spray drying as well as the microprecipitation process. It appears that due to the formation of a skin on the surface of the particle, the rate of solvent removal could drop substantially in spray drying whereas this is not a concern in microprecipitation where the porous structure produced due to solvent removal is filled with aqueous fluid (antisolvent) which further promotes the solvent exclusion.

The salient features of the microprecipitation technology include:

Advantages:

- Suitable for challenging compounds (low solubility in volatile organic solvents and high melting point).
- Low temperature processing.

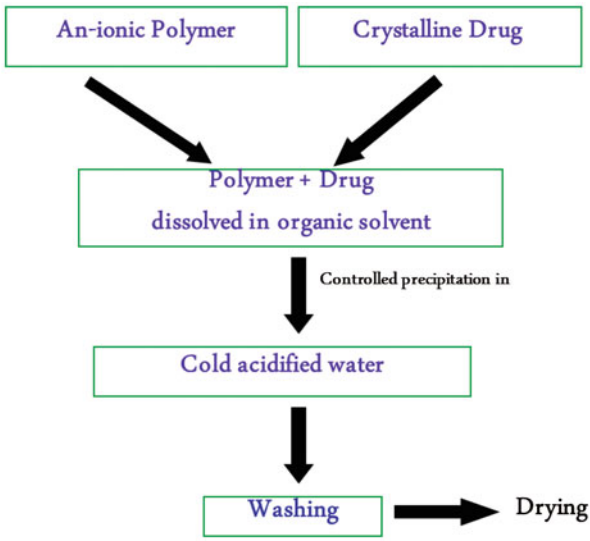

Fig. 3.6 Schematic of a microprecipated bulk powder (MBP) process

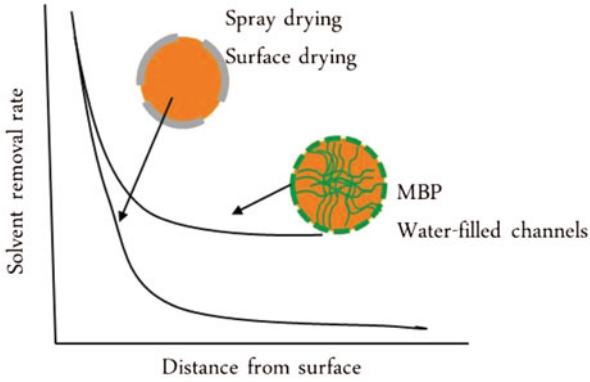

Fig. 3.7 Particle formation during solvent removal process by spray drying versus microprecipitation

- Suitable across different scales with high yield (few milligrams to thousand kilos).
- Superior particulate properties enable compaction and dissolution with least amount of external additives.
- Reduction in the need for plasticizers or surfactants.
- Rapid rate of quenching may provide higher drug loading.
- Ionic polymers used in creating MBP may impart superior stability (ionic interactions and low water activity).

Limitations:

- Some pH-sensitive compounds may not have an adequate window for processing due to pH-dependent solubility and stability.
- Ionic polymers release drugs in certain region of the gastrointestinal tract that may limit the applicability for drugs with narrow window of absorption.

- Removal of the nonaqueous solvent is by extraction but the final drying of the material containing water is generally performed in forced-air oven or a fluid bed dryer. Heat and moisture during final drying may promote recrystallization.

3.4.1 MBP Methodology

The key components of MBP technology involve two main aspects: preparation of amorphous dispersion and downstream processing to make the final product.

- Preparation of ASD:
  - Dissolution of API and polymer in a common solvent
  - Selection of antisolvent: Solubility and stability of API and polymer in solvent and solvent-rich-antisolvent phase
  - Precipitation conditions (pH, temperature, shear, solvent to antisolvent ratio, and time)
  - Mode of addition
  - Batch versus continuous processing
  - Washing of the precipitate to remove the residual solvents
  - Isolation of the precipitate
  - Drying of the precipitate
- Downstream processing:
  - Milling/sizing
  - Encapsulation or compaction
  - Coating

3.4.2 Preparation of ASD

Even though it is counter-intuitive to use an aqueous phase as antisolvent for the preparation of ASD, appropriate conditions can be generated that provide adequate supersaturation for both the polymer and API to induce rapid precipitation. The current literature is primarily based on using the pH condition that allows the precipitation of ionic polymers. Commonly used polymers include hypromellose acetate succinate, L, M, H grades, cellulose acetate pthalate, cellulose acetate butyrate, polyvinyl phthalate, hypromellose pthalate, polymethacrylates (Eudragit L100–55, Eudragit L100, Eudragit S-100, and Eudragit EPO). Use of low temperature, low solvent–antisolvent ratio, and appropriate shear help in maximizing the precipitation efficiency. As shown in Fig. 3.7, due to the differences in the mechanism of solvent removal process the surface properties of the two materials are also different. The MBP material produced by solvent exchange process has high porosity and better wetting compared to spray-dried or melt-extruded material that imparts better compaction and dissolution, thus reducing the need for additives such as compaction and wetting agents. Furthermore, due to the rapid quenching of the solution phase

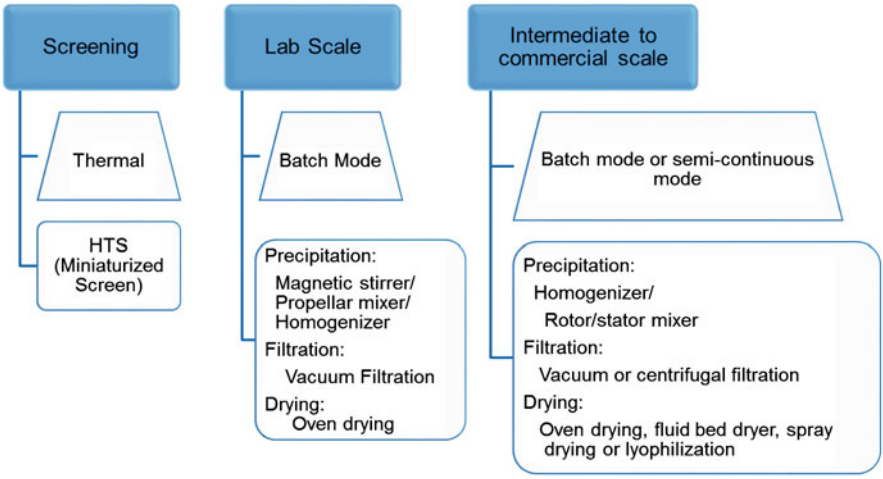

Fig. 3.8 Selection of precipitation, filtration**,** and drying methodologies at different scales

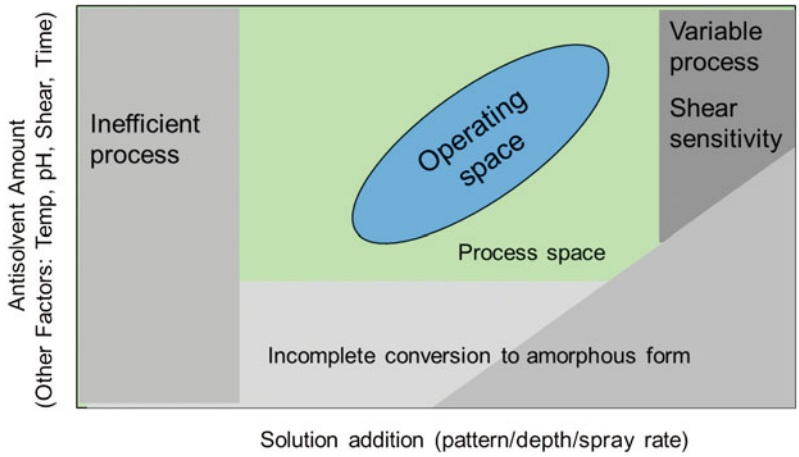

Fig. 3.9 Design space considerations during microprecipitation process design (solvent to antisolvent ratio and mixing). Other relevant factors related to supersaturation include pH, temperature, time, and shear

in solid state, it is also possible to increase the drug loading to as high as 70 % for some compounds. A general overview of the various processing options that can be used during different stages of development is summarized in Fig. 3.8 and the key processing aspects are shown in Fig. 3.9.

3.4.3 Downstream Processing

Depending on the particulate properties, the material may be of low bulk density (~0.1–0.3 g/cc) and densification may be required for further processing. Although MBP is primarily produced from aqueous media, once isolated and dried, the product requires appropriate protection from humidity and water due to physical stability of the amorphous form. Therefore, dry granulation is the preferred method to achieve the desired attributes of the granulates.

Several variations of the solvent-controlled precipitation have been evaluated to produce ASD, e.g., EPAS, Nanomorph, flash nanoprecipitation, and controlled precipitation (CP). In EPAS, the solution of drug and polymer is atomized into a heated aqueous solution, where the solvent (generally dichloromethane) is evaporated by the heated antisolvent (Vaughn et al. 2005). Due to the use of heated aqueous fluid as antisolvent, this process is limited to solvents such as dichloromethane that can be easily evaporated and because precipitation occurs at elevated temperature, it may not be suitable for the stability of ASD. Modification of EPAS process, CP involves in-line removal of solvent by vacuum distillation. The CP process also uses low boiling point solvents such as methanol as the preferred solvent. Alternatively, use of organic solvents as antisolvents has also been examined in technologies such as Nanomorph but robust development into a commercially viable product needs to be demonstrated (Keck and Muller 2006). Along with the selection of appropriate solvent/antisolvent pair and the processing conditions, these systems may be preferred to produce nanocrystals rather than amorphous dispersions.

3.5 Supercritical Fluid Processing

Over the past two decades, utility of supercritical fluids (SCF) has gained substantial momentum in the pharmaceutical industry. Although customarily used in the food industry for extraction (caffeine, essential oils, etc.) or in separation science for purification, the SCF offer promising opportunities in the development of specialized drug delivery systems such as particle design, nanoparticles, and amorphous dispersions. The key advantage of using supercritical fluids lies in their liquid- and gas-like properties that provide excellent media for solubilization with very low solvent burden. Due to the flexibility in designing the system, SCF can be used either as a solvent or antisolvent depending on the solubility of API and the stabilizing polymer. Its applications to ASD development is as diverse as the technology itself, e.g.:

- **HME:** As a processing aid in HME, SCF can serve multiple purposes ranging from lowering the melt viscosity, lowering processing temperature, modifying solubility of the drug in the molten polymer, and increasing the porosity of the extrudates that can improve dissolution and compaction.

- **Spray drying:** As an extraction solvent, SCF can be used to extract residual solvents from spray-dried material.
- **Microprecipitation:** As a stand-alone system, depending on the solubility, SCF may be used as a solvent or an antisolvent for microprecipitation technology that is akin to rapid expansion of supercritical solvent (RESS) or SCF as an antisolvent for precipitation (SAS).

Depending on how SCF is used, several techniques have evolved over the years especially in the particle engineering area. The commonly used variations of different processes are delineated below:

- Rapid expansion of supercritical solutions (RESS)
- Gas antisolvent precipitation (GAS)
- Supercritical antisolvent precipitation (SAS)
- Precipitation with compressed fluid antisolvent (PCA)
- Solution-enhanced dispersion by supercritical fluids (SEDS)
- Precipitation from gas-saturated solutions (PGSS)

Although there are very few case studies where SCF has been evaluated for production of ASD, the literature is rich with its application in particle engineering areas such as nanoparticles, and applications requiring low-temperature processing. Few examples showing the utility of RESS in producing amorphous particles include cefuroxime axetil (Varshosaz et al. 2009), ibuprofen, and indomethacin (Pathak et al. 2004). Similarly, there are few examples demonstrating the potential of using SAS techniques to produce ASD, e.g., itraconazole (Lee et al. 2005), rifampicin (Reverchon et al. 2002) and amoxicillin (Kalogiannis et al. 2005). While some formulation and processing factors may be similar for SAS or RESS system, it is critical to optimize the temperature and pressure in the SCF chamber to ensure that solubility conditions are fine-tuned to induce rapid supersaturation to ensure the precipitation of amorphous system.

The formulation and processing factors that can be tailored to customize the product attributes include:

- Use of cosolvents
- Nozzle dimension, spray rate, temperature, and pressure
- Conditions in the extraction chamber
  - Temperature
  - Pressure
  - Volume
  - Precipitation in aqueous phase with stabilizers (surfactants and polymers)

The selection of SCF technology to produce ASD depends primarily on the solubility of API and polymer in the most commonly used SCF, supercritical CO_2. Further formulation modification may be necessary to achieve desired particle morphology, e.g., polymers and surfactants are widely used to deagglomerate the particles and improve dissolution. Application of SCF in the development of ASD is still in its infancy, however, based on the flexibility in designing the process and properties of the SCF, it offers great potential for future advancement. For instance:

- Supercritical fluids could potentially enable the fastest rate of quenching and hence may open new possibilities in the solubilization space especially for challenging compounds.
- Differential solubility of API and polymer in the SCF may provide novel means of stabilizing the amorphous form.
- Processing temperatures may be suitable for thermo-labile compounds.
- By process design, the true particle size can be controlled in the submicron to nano range, thus offering dual advantage in improving the dissolution rate.

Once a suitable amorphous system has been produced, the downstream processing considerations will need to be addressed. Based on the nanoparticles work that has been conducted in this field, it is apparent that the amorphous product produced by the SCF will generally be of low density and high porosity and further densification will be required to make final dosage form.

3.6 KinetiSol

Poor aqueous solubility is a growing challenge in the pharmaceutical industry. Although several technologies have been successfully developed to produce commercially viable products, there is still a need for newer technologies that can be applied to challenging compounds and/or provide additional benefit of simplifying the process or increasing drug load. KinetiSol® is a promising new technology that has specific advantage for compounds that cannot be processed with more established processes such as ASD and HME. Similar to microprecipitation technology, KinetiSol is developed to address the processing needs of difficult compounds that are limited by either high melting point and/or low solubility in volatile organic solvents (DiNunzio et al. 2010; Hughey et al. 2010).

The core aspect of the technology is a specific type of equipment that has been used in the plastic industry to mix high-melting, high-viscosity products. The primary mechanism of making amorphous form is a variation of the fusion method. Similar to HME, it utilizes the frictional and shear energy to melt the drug and polymer blend. However, its distinguishing features are the intensity of mixing that causes material to melt within few seconds as opposed to HME where total residence time can vary from 30 s to few minutes. Faster heat transfer and melting result in shorter exposure time to high temperature that is specifically useful for high-melting and thermo-labile compounds. Due to the short exposure times, chemically labile compounds can be processed by KinetiSol® (Miller et al. 2012). Although this technology is in the early stages of development, prototype equipment have already been designed to provide insights into scale-up and production. Laboratory-scale equipment is generally run in batch mode to conserve the API, however, the pilot- and production-scale equipment are being designed to run in semicontinuous mode with relatively high-throughput rate

In addition to being suitable for thermo-labile compounds, the short exposure to high temperature also expands the range of polymers that are generally not stable

for high-temperature HME. From a downstream processing perspective, the material appears to be similar to HME and requires particle size reduction prior to processing into the final dosage form. Additives such as plasticizer and wetting agents may also be included to improve product performance.

3.7 Ultrasonic-Assisted Compaction

To harness the full potential of amorphous systems for all types of chemical compounds, alternate technologies are constantly being added to the toolbox. Ultrasonic-assisted compaction is a modified tabletting process that can provide heat, pressure, and shear due to ultrasonic energy to the powder mixture during compaction. The application of ultrasound to solubility enhancement is based on the fusion method and in some ways mimics the extrusion process (Fini et al. 1997; Sancin et al. 1999). The ultrasonic frequency vibration is applied at the same time as compaction force. The key features of the technology include:

- Need small amount of material to conduct feasibility.
- Eliminates need for downstream processing since the manufacturing process delivers the final product.
- Current tablet presses may be retrofitted with the needed components.
- Product may show some inhomogeneity due to lack of distributive mixing with ultrasonic energy.
- The low porosity of compressed tablet may require use of hydrophilic fillers to improve the dissolution rate that may be at the expense of drug/polymer interactions.

A schematic of the process is shown in Fig. 3.10 with a representative tablet sample showing amorphous glass. Although research in this area is still limited, if successful, this may be a useful tool for early screening and for minimization of downstream processing.

3.8 Cryogenic Processing

Bottom-up particle engineering technologies based on cryogenic processing such as SFD, spray freezing into liquid, and TFF can produce amorphous nanostructured aggregates (Yang 2010). Cryogenic technologies involve use of cryogens such as liquid nitrogen to introduce a change in the temperature of the solubilized system that causes supersaturation, nucleation, and precipitation. Use of cryogens combined with a particular mechanism of addition can produce very high cooling rates thus resulting in rapid quenching of the amorphous form. These technologies are further classified based on the differences in the type of injection devices (capillary, rotary, pneumatic, and ultrasonic), location of nozzle (spray into the liquid or applying

Fig. 3.10 Amorphous compacts generated using ultrasound-assisted compaction unit

the solution onto cryogenic substrate), and the composition of the cryogenic liquid (hydrofluoralkanes, liquid nitrogen, liquid argon, compressed CO_2). Generally, these technologies involve rapid freezing of the solvent that can then be removed by sublimation, thus producing a powder. These techniques are particularly useful for temperature-sensitive materials such as proteins and peptides. Key considerations in applying these technologies are:

- Formation of feed solution: For amorphous processing, a solution formulation is preferred over suspension or emulsion. The total solid content may affect particulate properties.
- Ease of lyophilization of solvents: Solvents with high vapor pressure, melting point close to room temperature, high viscosity, and low toxicity. Commonly used solvents include acetonitirile, dioxane, and t-butanol.
- Due to the nature of the process, it may be possible to obtain amorphous materials at relatively high drug loading; however, stability during storage and dissolution may still limit the drug loading.
- Downstream considerations will be similar to spray-dried material.

3.9 Electrospinning and Rotating Jet Spinning

Analogous to HME, electrospinning is also a widely used technique in the polymer industry. A schematic of electrospinning process is shown in Fig. 3.11. A polymer solution is drawn through a capillary tube that is subjected to an electric field. As the electric field increases, the feed solution forms a Taylor cone at the tip of the capillary. Once the electric field overcomes the surface tension of the solution, the polymer solution is ejected as an electrically charged jet. Due to the increase in surface area, the solvent evaporates leaving thin filaments of material (50 nm to 5 microns). These fibers are then collected on collector screens for further processing. This technique has been applied for pharmaceutical systems by several researchers

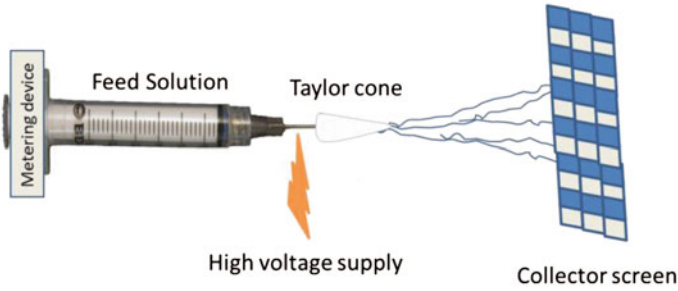

Fig. 3.11 Schematic of the electrospinning process

(Verreck et al. 2003; Nagy 2010). For amorphous processing, drug and polymer are generally dissolved in a common solvent similar to spray drying. Key factors in the processing include:

- Selection of the common solvent (generally ethanol is used).
- Electric potential from 16 to 24 kV has been used in some case studies.
- Downstream processing of fibers may be performed by milling.

Although this technique relies on solvent-based processing, the ability to form nanofibers can provide further advantage compared to other processing techniques. As the research in this area grows, there will be an opportunity to better understand the properties of pharmaceutical materials under high electric voltage. For most application in the literature, solvent-based processing has been evaluated, but nonsolvent-based processing using polymer melt is also feasible.

Rotating jet-spinning process is an evolution of the "cotton-candy" manufacturing equipment and uses centrifugal force of the rotor to create thin fibers that are deposited on the receiving chamber. Instead of a sugar solution, the drug:polymer solution in a suitable solvent is sprayed through the rotating jet. As shown in Fig. 3.12, the apparatus consists of a perforated reservoir containing polymer solutions attached to a motor. When the reservoir is spun about its axis of symmetry at a rate that exceeds the capillary and centrifugal forces, a viscous jet is ejected from a small orifice (Badrossamay et al. 2014). This jet is thrown outwards along a spiral trajectory as the solvent evaporates due to the creation of a high surface area. While moving, it is extended by centrifugal forces and solvent evaporates at a rate dependent on the diffusion coefficient of solvent through the polymer (Mellado et al. 2011). Compared to spray drying, the key limitations of this process may be the ability to remove the residual solvents to a satisfactory level, batch mode processing and downstream processing.

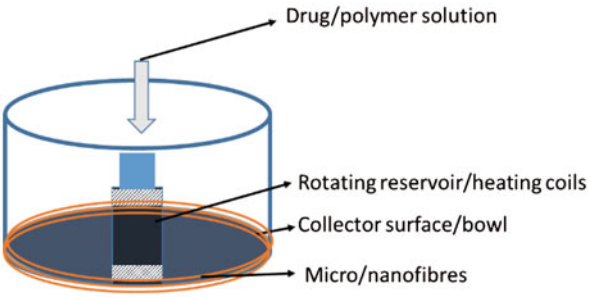

Fig. 3.12 Overview of the rotating jet-spinning process

3.10 Milling and Cryogrinding

Particle size reduction has been known to reduce crystallinity and induce amorphous characteristics for a long time (Mura et al. 2002). Since the naked amorphous API does not have adequate physical or chemical stability, co-grinding with polymers or stabilizers has also been used. Because milling is a standard unit operation in solid dosage form processing, this appears to be the most convenient means to produce the amorphous form, however, this simplicity comes with much higher risks. Due to the fact that milling is a top-down approach, there is always a risk that some material may exist in a nanocrystalline state that could act as seeds to induce nucleation and cause reversion of amorphous form to crystalline state. Several studies have been conducted to evaluate different milling mechanisms as well as stabilizers albeit with limited success. Media milling such as ball mill or cryo-milling with wide range of excipients such as Neusilin (magnesium aluminometasilicate), crospovidone, sodium chloride, or sugar (Gupta et al. 2002, 2003) have met with limited success. Although not claimed as one hundred percent amorphous, an anti-inflammatory product has been successfully manufactured using SoluMatrix® technology that involves dry milling the crystalline drug with a hydrophilic carrier (iCeutica 2014). Similarly, another milling technology that involves media milling in the dry state with crospovidone has been employed in a commercially available drug product (Perret 2014) by Aptalis. Considering that dry milling may have challenges for compounds with a high tendency to convert, it may be suitable for compounds that are inherently amorphous or have low tendency to crystallize. The products where drug could exist as a mixture of amorphous and nanocrystalline forms present much higher development risk and require stringent controls to ensure product consistency.

3.11 Hot-Melt Coating/Granulation

In an effort to extend the concept of lipid solubilization to produce solid dosage forms, a solution of drug substance in molten lipid is either coated or dispersed on an inert carrier (Faham et al. 2000; Holm et al. 2007). Several technologies have been

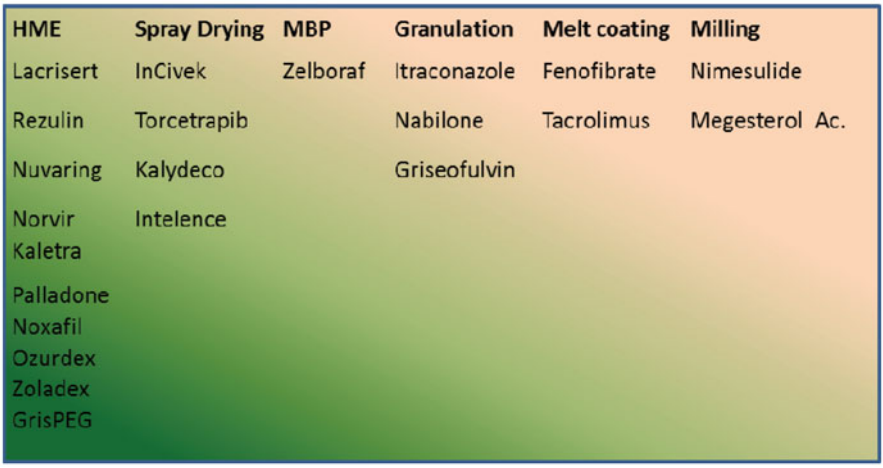

Fig. 3.13 Distribution of compounds and technologies based on late-stage experience (all formulations may not be amorphous solid dispersion (ASD))

developed where amorphous drug can be trapped in the molten lipid which is cooled during processing. The fluid bed processing used for this purpose is retrofitted with a temperature-control setup to ensure that the product can be maintained in the molten state. Depending on the carrier, the processing conditions and the properties of the drug, the amorphous form of the drug may be obtained by these processes. However, it is critical to ensure that molten feed material is stable for the duration of the process and the quality of amorphous material is consistent and reproducible. Since drug and polymer melt requires spraying, these technologies are generally limited to polymers that melt at relatively low temperature and have relatively low melt viscosity such as poloxamers and/or high HLB gelucires. Generally, these carriers are not highly regarded as suitable stabilizers for amorphous form.

3.12 Process Selection Guide

The path to making an amorphous form requires two basic types of processes, i.e., either dissolve the crystalline form in a suitable solvent or melt the crystalline form with the stabilizing polymer. Numerous variations have been developed in each of these two categories to match the compound's properties, product needs, and organizational preference. Several compounds are in development using one of the many ASD technologies; however, melt extrusion and spray drying are leading the way with regard to the number of commercially successful products (see Fig. 3.13). The chart also depicts the degree of difficulty in assuring the conversion to complete amorphous form with some technologies. For example, technologies such as milling and spray coating perform similar to nanocrystalline formulations rather than the true

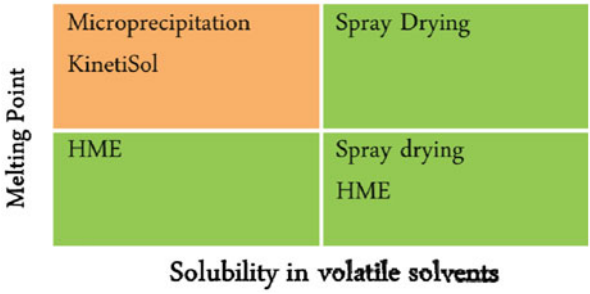

Fig. 3.14 Empirical guide to select a solid dispersion technology based on physicochemical properties of the active pharmaceutical ingredient (API)

amorphous form. Some of the newer technologies on the horizon have yet to meet the rigors of full-scale development as well as regulatory challenges to demonstrate their utility.

Usually the solubility in volatile organic solvents and melting point serve as the first level screen. The selection paradigm based on these two attributes is shown in Fig. 3.14. Compounds with melting point below 200 °C are generally suitable for melt extrusion and compounds with solubility of 10 mg/mL or greater in low boiling point solvents such as ethanol and acetone may be suitable for spray drying. Microprecipitation and KinetiSol provide alternate options for compounds that are not suitable for melt extrusion or spray drying due to processing difficulties.

3.13 Summary

As a first principle, it may be possible to estimate the solubility advantage that can be gained by completely destroying the crystalline lattice of a compound; however, it does not necessarily predict the impact on dissolution and bioavailability. Despite having totally similar X-ray amorphous structure and no apparent melting endotherm, the material produced by one process could have a widely different PK behavior than the material produced by another method. In some cases, the differences are attributed to certain physical properties of the amorphous material such as porosity but in other cases they are truly due to the type of interactions that may occur in solvent-based systems versus nonaqueous melts resulting in different product performance (Dong et al. 2008; Huang et al. 2011; Tominaga 2013). Therefore, the challenge to select the right processing method goes beyond the ability to make the amorphous material. In cases wherever multiple methods are possible, the selection criteria should take into consideration bioavailability followed by other factors such as stability, robustness, downstream processing, organizational capability, and cost. Important considerations in the selection of the processing technologies include:

- Physicochemical properties of the compound, e.g., solubility in aqueous, volatile, and other organic solvents
- Thermal stability of the compound and the polymer
- Extent of improvement in bioavailability

- Selection of stabilizing polymer and other processing aids
- Formulation complexity and ability to achieve highest drug loading
- Availability of equipment train from laboratory scale to commercial scale
- Product robustness (processability, amorphous stability, and dissolution performance)

References

Abeysena I, Darrington E (2013) Understanding evaporation and concentration technologies labmate. http://www.labmate-online.com/articles/laboratoryroducts/3/dr_induka_abeysena_application_specialist_rob_darrington_product_manager_genevac_ltd_ipswich _uk.this_paper_explains_the_basic_principles_of_evaporation_and_concentration_and_outlines _some_of_the_commonly_used_technologies._it_also_reviews_the_wid/understanding_evaporation_and_concentration_technologies/1442/. Accessed 12 Dec 2013

Appel L (2009) Amorphous solid dispersion. http://www.pharmatek.com/pdf/PTEKU/Jul302009.pdf. Accessed Dec 2013

Badrossamay MR, Balachandran K, Capulli AK, Golecki HM, Agarwal A, Goss JA, Kim H, Shin K, Parker KK (2014) Engineering hybrid polymer-protein super-aligned nanofibers via rotary jet spinning. Biomater 35(10):3188–3197

Conine JW (1980) Of ethanol insoluble pharmaceutically acceptable excipients, US 4195078 A. Mar 25, 1980

Desai D (2007) Solid-state plasticizers for melt extrusion. Ph.D., University of Rhode Island

DiNunzio JC, Miller DA (2013) Formulation development of amorphous solid dispersions prepared by melt extrusion. In: Repka MA, Langley N, DiNunzio J (eds) Melt extrusion. AAPS advances in the pharmaceutical sciences series, vol 9. Springer, New York, pp 161–204

DiNunzio JC, Brough C, Miller DA, Williams RO III, McGinity JW (2010) Applications of KinetiSol dispersing for the production of plasticizer free amorphous solid dispersions. Eur J Pharm Sci 40(3):179–187

Dong Z, Chatterji A, Sandhu H, Choi DS, Chokshi H, Shah N (2008) Evaluation of solid state properties of solid dispersions prepared by hot-melt extrusion and solvent co-precipitation. Int J Pharm 355(1–2):141–149

Douroumis D (2012) Hot melt extrusion: pharmaceutical applications. Wiley, Chichester

Faham A, Prinderre P, Piccerelle P, Farah N, Joachim J (2000) Hot melt coating technology: influence of Compritol 888 Ato and granule size on chloroquine release. Pharmazie 55(6):444–448

Fini A, Fernandez-Hervas MJ, Holgado MA, Rodriguez L, Cavallari C, Passerini N, Caputo O (1997) Fractal analysis of beta-cyclodextrin-indomethacin particles compacted by ultrasound. J Pharm Sci 86(11):1303–1309

Friesen DT, Shanker R, Crew M, Smithey DT, Curatolo WJ, Nightingale JA (2008) Hydroxypropyl methylcellulose acetate succinate-based spray-dried dispersions: an overview. Mol Pharm 5(6):1003–1019

Ghebre-Sellassie I, Martin CE, Zhang F, Dinunzio J (2003) Pharmaceutical extrusion technology, drugs and the pharmaceutical sciences (Series editor Swarbrick J)

Gupta MK, Tseng YC, Goldman D, Bogner RH (2002) Hydrogen bonding with adsorbent during storage governs drug dissolution from solid-dispersion granules. Pharm Res 19(11):1663–1672

Gupta MK, Vanwert A, Bogner RH (2003) Formation of physically stable amorphous drugs by milling with Neusilin. J Pharm Sci 92(3):536–551

Holm P, Buur A, Elema MO, Møllgaard B, Holm JE, Schultz K (2007) Controlled agglomeration, Google Patents

Huang J, Li Y, Wigent RJ, Malick WA, Sandhu HK, Singhal D, Shah NH (2011) Interplay of formulation and process methodology on the extent of nifedipine molecular dispersion in polymers. Int J Pharm 420(1):59–67

Hughey JR, DiNunzio JC, Bennett RC, Brough C, Miller DA, Ma H, Williams RO III, McGinity JW (2010) Dissolution enhancement of a drug exhibiting thermal and acidic decomposition characteristics by fusion processing: a comparative study of hot melt extrusion and KinetiSol dispersing. AAPS PharmSciTech 11(2):760–774

iCeutica's SoluMatrix Technology (2014) http://www.iceutica.com/solumatrix. Accessed 12 Dec 2013

Iyer R, Hegde S, Zhang YE, Dinunzio J, Singhal D, Malick A, Amidon G (2013) The impact of hot melt extrusion and spray drying on mechanical properties and tableting indices of materials used in pharmaceutical development. J Pharm Sci 102(10):3604–3613

Joe JH, Lee WM, Park YJ, Joe KH, Oh DH, Seo YG, Woo JS, Yong CS, Choi HG (2010) Effect of the solid-dispersion method on the solubility and crystalline property of tacrolimus. Int J Pharm 395(1–2):161–166

Kadir MF, Sayeed MSB (2012) Drug Delivery strategy: coprecipitation method of solid dispersion: a formulaion stratgey for poorly soluble drugs. LAP LAMBERT Academic, Saarbrücken

Kalogiannis CG, Pavlidou E, Panayiotou CG (2005) Production of amoxicillin microparticles by supercritical antisolvent precipitation. Ind Eng Chem Res 44(24):9339–9346

Keck CM, Muller RH (2006) Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. Eur J Pharm Biopharm 62(1):3–16

Lee S, Nam K, Kim MS, Jun SW, Park JS, Woo JS, Hwang SJ (2005) Preparation and characterization of solid dispersions of itraconazole by using aerosol solvent extraction system for improvement in drug solubility and bioavailability. Arch Pharm Res 28(7):866–874

Mellado P, McIlwee HA, Badrossamay MR, Goss JA, Parker K, Mahadevan L (2011) A simple model for nanofiber formation by rotary jet-spinning. ACEEE

Miller D, Gil M (2010) Spray-drying technology. In: Williams RO III, Watts AB, Miller DA (eds) Formulating poorly soluble drugs. AAPS advances in the pharmaceutical sciences series, vol 9. Springer, New York, pp 363–442

Miller D, DiNunzio JC, Hughey JR, Williams RO III, McGinity JW (2012) KinetiSol®: a new processing paradigm for amorphous solid dispersion systems. Drug Dev Deliv 11(2011):22–31

Mosquera-Giraldo LI, Trasi NS, Taylor LS (2014) Impact of surfactants on the crystal growth of amorphous celecoxib. Int J Pharm 461(1–2):251–257

Mura P, Cirri M, Faucci MT, Gines-Dorado JM, Bettinetti GP (2002) Investigation of the effects of grinding and co-grinding on physicochemical properties of glisentide. J Pharm Biomed Anal 30(2):227–237

Murugesan S, Sharma P, Tabora JE (2011) Design of filtration and drying operations. In: Am Ende DJ (ed) Chemical engineering in the pharmaceutical industry: R & D to manufacturing. Wiley, Hoboken, pp 315–346

Nagy ZK, Nyul K, Wagner I, Molnár K, Marosi G (2010) Electrospun water soluble polymer mat for ultrafast release of Donepezil HCl. eXPRESS Polym Lett 4(12):763–772

Pathak P, Meziani MJ, Desai T, Sun YP (2004) Nanosizing drug particles in supercritical fluid processing. J Am Chem Soc 126(35):10842–10843

Perret S, Venkatesh G (2014) Enhancing the bioavailability of insoluble drug compounds: innovations in pharmaceutical technology. http://www.iptonline.com/articles/public/IPT. Accessed 20 Jan 2014

ProCept Information Brochure (2014) Spray dryer. http://www.procept.be/spray-dryer-chiller. Accessed 20 Jan 2014

Repka MA, Langley NA, DiNunzio J (2013) Melt extrusion materials, technology and drug product design. AAPS advances in the pharmaceutical sciences series, vol 9. Springer, New York

Reverchon E, De Marco I, Della Porta G (2002) Rifampicin microparticles production by supercritical antisolvent precipitation. Int J Pharm 243(1–2):83–91

Rosenberg J, Reinhold U, Liepold B, Berndl G, Alani L, Ghosh S, Brietenbach J (2005) A solid pharmaceutical dosage formulation comprising lopinavir, European Patent, Abbott Laboratories. EP 2283844 A1

Sancin P, Caputo O, Cavallari C, Passerini N, Rodriguez L, Cini M, Fini A (1999) Effects of ultrasound-assisted compaction on Ketoprofen/Eudragit S100 mixtures. Eur J Pharm Sci 7(3):207–213

Schenck L, Troup GM, Lowinger M, Li L, McKelvey C (2011) Achieving a hot melt extrusion design space for the production of solid solutions. Chemical engineering in the pharmaceutical industry: R & D to manufacturing. Wiley, Hoboken, pp 819–836

Sekiguchi K, Obi N, Ueda Y (1964) Studies on absorption of eutectic mixture. II. Absorption of fused conglomerates of chloramphenicol and urea in rabbits. Chem Pharm Bull (Tokyo) 12:134–144

Shah N, Sandhu H, Phuapradit W, Pinal R, Iyer R, Albano A, Chatterji A, Anand S, Choi DS, Tang K, Tian H, Chokshi H, Singhal D, Malick W (2012) Development of novel microprecipitated bulk powder (MBP) technology for manufacturing stable amorphous formulations of poorly soluble drugs. Int J Pharm 438(1–2):53–60

Shah N, Iyer RM, Mair HJ, Choi DS, Tian H, Diodone R, Fahnrich K, Pabst-Ravot A, Tang K, Scheubel E, Grippo JF, Moreira SA, Go Z, Mouskountakis J, Louie T, Ibrahim PN, Sandhu H, Rubia L, Chokshi H, Singhal D, Malick W (2013) Improved human bioavailability of vemurafenib, a practically insoluble drug, using an amorphous polymer-stabilized solid dispersion prepared by a solvent-controlled coprecipitation process. J Pharm Sci 102(3):967–981

Tominaga K (2013) Effect of manufacturing methods used in the stability or amorphous solid solutions and predictions to test them. Ph.D., University of Rhode Island Dissertations and Master's Theses

Varshosaz J, Hassanzedh F, Mahmoudzadeh M, Sadeghi A (2009) Preparation of cefuroxime axetil nanoparticles by rapid expansion of supercritical fluid technology. Powder Technol 189(1): 97–102

Vaughn JM, Gao X, Yacaman MJ, Johnston KP, Williams RO III (2005) Comparison of powder produced by evaporative precipitation into aqueous solution (EPAS) and spray freezing into liquid (SFL) technologies using novel Z-contrast STEM and complimentary techniques. Eur J Pharm Biopharm 60(1):81–89

Verreck G, Chun I, Peeters J, Rosenblatt J, Brewster ME (2003) Preparation and characterization of nanofibers containing amorphous drug dispersions generated by electrostatic spinning. Pharm Res 20(5):810–817

Verreck G, Decorte A, Heymans K, Adriaensen J, Cleeren D, Jacobs A, Liu D, Tomasko D, Arien A, Peeters J, Rombaut P, Van den Mooter G, Brewster ME (2005) The effect of pressurized carbon dioxide as a temporary plasticizer and foaming agent on the hot stage extrusion process and extrudate properties of solid dispersions of itraconazole with PVP-VA 64. Eur J Pharm Sci 26(3–4):349–358

Williams RO III, Watts AB, Miller DA (2010) Formulating poorly soluble drugs. Springer, New York

Williams HD, Trevaskis NL, Charman SA, Shanker RM, Charman WN, Pouton CW, Porter CJ (2013) Strategies to address low drug solubility in discovery and development. Pharmacol Rev 65(1):315–499

Yang G, Ran Y, Yalkowsky SH (2002) Prediction of the aqueous solubility: comparison of the general solubility equation and the method using an amended solvation energy relationship. J Pharm Sci 91(2):517–533

Yang W, Owens DE III, Williams RO III (2010) Pharmaceutical cryogenic technologies. In: Williams RO III, Watts AB, Miller DA (eds) Formulating poorly soluble drugs. AAPS advances in the pharmaceutical sciences series, vol 9. Springer, New York, pp 443–500

Zhu Y, Shah NH, Malick AW, Infeld MH, McGinity JW (2002) Solid-state plasticization of an acrylic polymer with chlorpheniramine maleate and triethyl citrate. Int J Pharm 241(2):301–310