Chapter 13
Downstream Processing Considerations

Susanne Page and Reto Maurer

13.1 Introduction

Independent of the manufacturing technology used to create the amorphous solid dispersion and the anticipated route of administration, downstream processing is required to convert it into the final dosage form. For an oral application of a drug, tablets are the preferred solid dosage form followed by capsules. The development objective is captured in the target product profile (TPP) and the quality target product profile (QTPP) as these define the intended release mode, the type and acceptable size of dosage form, the anticipated shelf life, and storage conditions. They therefore set the framework for the formulation scientists, to help define the most important critical quality attributes such as dissolution kinetics, chemical and physical stability, appearance, and mechanical properties.

Dissolution Kinetics: In most cases, the drug substance is desired to be released immediately from the tablets or capsules, and only on rare occasions, an extended or pH-dependent drug release is envisaged. In both cases, the mechanism for achieving the supersaturation potential of the solid amorphous dispersion needs to be maintained in the final dosage form. Therefore, the formulator needs to have a clear understanding of all the factors that have an influence on the dissolution kinetics and the supersaturation potential. The amount of drug released determined in a standard dissolution test is the sum of different processes occurring all at the same time, namely release of the drug from the amorphous solid dispersion, nucleation, and crystal growth. The amount of drug released per time (dW/dt) is directly proportional to the diffusion coefficient (D), the surface area of the solid (A), the difference between the saturation concentration (c_s) and the concentration of drug in solution at time t (c_t), and indirect proportional to the diffusion layer thickness (L) as by Noyes and Whitney and Nernst and Brunner (Dokoumetzidis and Macheras 2006). The

S. Page (✉) · R. Maurer
Formulation Research and Development, F. Hoffmann-La Roche Ltd., Basel, Switzerland
e-mail: susanne.page@roche.com

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impact of the surface area on dissolution kinetic was illustrated by comparing the dissolution rate of cefdinir tablets obtained from spray drying (SD) or a supercritical anti-solvent (SAS) process (Park et al. 2010), and by another example of solid dispersions containing indomethacin (IMC) and polyethylene glycol 6000 (PEG 6000; Ford and Elliott 1985). Interestingly, the fastest release is not always obtained from the smallest particles (Ford and Elliott 1985). This observation could be explained by the fact that not only the amount of drug substance released per time is quite high for very small particles but also nucleation and subsequently crystal growth are fast. In particular, this aspect is important when the solid dispersion needs to be milled/micronized prior to the downstream processing. The surface area or particle size distribution of such systems might be a critical material attribute (CMA), and needs to be carefully investigated and subsequently controlled. Besides the particle size of the amorphous solid dispersion, the selection of type and amount of excipients present in the final dosage form will also have a major effect on both the downstream processing itself and the drug release profile. As an example, the investigations from Lepek et al. illustrate this point. They compared the effect of lactose and microcrystalline cellulose (MCC) during direct compression of formulations containing amorphous telmisartan, and showed improved flowability as well as compressibility for the final blends containing microcrystalline cellulose. Further investigations showed that the disintegration time ranged from 30 s for the formulation containing sodium carboxymethyl starch, 1 min for croscarmellose sodium and starch glycolate, up to 30 min for formulations with potato starch (Lepek et al. 2013). The dissolution kinetic of the final drug product also depends on the ratio between the solid dispersion and the excipients in the drug product, and on the processing conditions during downstream manufacturing, like roller compaction and compression force. Furthermore, the dissolution of the final product might change upon storage as described below.

When an amorphous component is exposed to high temperature and/or relative humidity above glass transition temperature (T_g), the amorphous system transforms to a rubbery state. Molecules in rubbery state are mobile and can form interparticle bridges or form particle aggregates, often resulting in particle fusion (Descamps and Palzer 2007). This effect of particle fusion can be magnified in amorphous solid dispersion particles with large surface area (Matteucci et al. 2007; Alonzo et al. 2011; Shah et al. 2013).

Amorphous solid dispersions, particularly amorphous microprecipitated bulk powder (MBP) or spray-dried powder, have large surface area. For example, a surface area of 23–24 m^2/g was obtained for amorphous MBP solid dispersion of vemurafenib (Shah et al. 2013). Similarly, surface areas in the range of 23–51 m^2/g were obtained for itraconazole (ITZ) MBP with drug loading in the range of 33–50 % (Matteucci et al. 2007). In general, the large surface area powder dissolves faster than small surface area powder following the equation from Noyes and Whitney and Nernst and Brunner. However, in the case of amorphous dispersion, dissolution phenomenon is not straightforward. Because of potential particle fusion under stress condition, amorphous solid dispersion with large surface area can actually dissolve slower than small surface area if amorphous solid dispersion fused together to hard aggregates.

The fusion of amorphous polymer particles above their T_g is a slow coalescence process most likely driven by surface energy, which reduces the free volume and the total surface area (Rosenzweig and Narkis 1983; Palzer 2011). Since amorphous dispersions often have a polymeric component, the sintering of amorphous polymer colloids occurs at/or above the T_g which is dependent on the particle size and packing fraction within the polymer as determined by the melt viscosity (Mazur et al. 1997).

Chemical and Physical Stability: Due to the fact that the drug substance is present in a high-energy amorphous form in the formulation, the chemical stability of the system might be altered compared to formulations containing the crystalline drug substance. Furthermore, the polymer itself can interact with and trigger instability with the active pharmaceutical ingredient (API) as shown by Dong and Choi for hydroxypropyl methylcellulose acetate succinate (HPMCAS). This polymer may undergo hydrolysis under harsh processing conditions (e.g., heating at 140 °C up to 5 h) with the generation of succinic acid and acetic acid, which can form ester bonds with the hydroxyl groups present in the API. This was shown by the authors for model compound A, where the succinate esters of the model compound and its epimer were found in the product, as well as for dyphylline (Dong and Choi 2008).

Recrystallization of the drug substance can be triggered by absorption of water/presence of moisture, and energy input in the form of heat or mechanical stress. The absorption of water by the amorphous solid dispersion leads to a decrease in the T_g of the system as the T_g of water is very low (− 137 °C), and an increase in molecular mobility due to disruption of intermolecular hydrogen bonds (Ahlneck and Zografi 1990). Water can be present in the amorphous solid dispersion itself in the form of residual moisture, or it can be introduced into the system by the moisture bound to excipients and water used as a processing liquid, for instance, during film coating. Energy is transferred to the amorphous solid dispersion upon milling, compaction, and compression of the material. A direct energy transfer occurred when jet or high peripheral-speed pin mills (e.g., shock action mills) were used for milling (Colombo et al. 2009). Further down, the material is either directly filled into capsules, compressed into tablets (if the bulk density is reasonably high), or dry granulated. In case of dry granulation and tablet compression, the pressure applied to the system can induce amorphous–amorphous phase separation in these systems (Ayenew et al. 2012a), and increase the extent of crystallization (Ayenew et al. 2012b). Recrystallization of the drug substance can also be triggered when a film coat is applied; besides the aforementioned effect of water, the temperature used in the process should be selected carefully. Finally, the packaging configuration for the final drug product needs to be selected to maintain stability over the shelf life of the product.

Physical and Mechanical Properties: Depending on the manufacturing technology used for the manufacture of the amorphous solid dispersion, the material will have different physical properties clearly impacting flow and compression behavior of the material. Comparing spray-dried powders, for instance, with milled extrudates will reveal the difference of both materials. The smaller spray-dried particles have a higher tendency towards cohesion and thus impacting powder flow. On the other

hand, the material has a higher porosity compared to the dense extrudates, making tablet compression easier. In addition to the physical and mechanical properties of the materials, those properties of the material subject to an applied stress are clearly of importance for the whole downstream processing process. Iyer et al. (2013) compared polymers, such as copovidone and HPMCAS, with other excipients such as lactose, MCC, or dibasic calcium phosphate anhydrous (DCP-A) and showed that the polymers itself exhibit compression pressures on the low, but acceptable end of the spectrum (solid fraction; SF = 0.85). MCC and lactose are in the typical range, and DCP-A requires extremely high compression pressures in order to obtain the same solid fraction (for DCP-A the value was extrapolated to SF = 0.85). Modification of the polymers by either SD or hot-melt extrusion (HME) led to an increase in the compression pressure by 24 % in case of spray-dried HPMCAS, 61 % in case of melt-extruded HPMCAS and a decrease of approximately 10 % upon extrusion of copovidone. The same authors also investigated the tensile strengths of the materials at a solid fraction of 0.85, and observed a decrease of tensile strength for the melt-extruded polymers compared to the polymer as is, whereas an increase in tensile strength was observed for the spray-dried HPMCAS, indicating an enhanced ability to form strong compacts. Further tests showed that in addition to compression pressure and tensile strength, other parameters such as dynamic hardness, brittle fracture index and dynamic bonding index were also altered by either SD or HME (Iyer et al. 2013).

The following sections will give a detailed overview on the downstream processing of the amorphous solid dispersions manufactured by different technologies. Overall, it can be concluded that the downstream process should avoid the use of water, higher temperatures and pressures as much as possible.

13.2 Downstream Processing of Hot-Melt Extrudates

HME is a fusion-based technology widely used for manufacturing of amorphous intermediates where the API is molecularly dispersed in a stabilizing polymer matrix. The number of polymers approved for pharmaceutical applications is limited and a preferred polymer may have a number of inherent challenges in terms of processability, dissolution performance, and downstream processing. For example, commonly used polymers like Eudragit® L100-55 and povidones of higher molecular weights show a high melt viscosity and can only be extruded with the incorporation of adequate plasticizers. In some cases, the API itself has a significant plasticizing effect on the polymer.

The high-energy amorphous state of the HME intermediate is facilitated by applying shear stress and thermal energy to a physical powder blend in order to overcome the crystal lattice of the drug and to soften the polymer allowing fusion with excipients. The extrusion process is followed by an immediate solidification or cooling step in order to freeze the glassy state and immobilize the incorporated API molecules.

The obtained extruded intermediates is normally not considered to be the final drug product as it usually appears as solid strands or films of undefined length which

either have to be shaped, cut, or milled in order to process it further into the desired final solid dosage form. Contrary to other manufacturing technologies for amorphous solid dispersions, extrudates are dense particles, having a high bulk density, enabling capsule filling with a powder blend or direct compression.

13.2.1 Powder Blends and Direct Compression

Direct Shaping of Extrudates: In the literature, the most prominent dosage forms described for solid dispersions made by HME are tablets and capsules. The simplest approach to produce tablets is to cut the solidified strands manually into cylindrical mini-matrices (Bruce et al. 2007; Schilling et al. 2008; Read et al. 2010; Dierickx et al. 2012). This direct shaping process is well suited for small batch sizes where the weight uniformity of the particles can be assured by individual weight check. For large batch sizes, direct shaping and automated calendaring is much more challenging as it must be preceded by a steady and nonpulsatile HME process facilitating consistent strand or film dimensions.

Milling of Extrudates: Feng et al. (2012) and Jijun et al. (2010) prepared tablets simply by blending a defined sieve fraction of the pulverized extrudates with functional excipients and directly compressing it with a single-punch press. Jijun et al. (2010) showed that the particle size of the milled extrudates had an impact on the dissolution kinetics as well as the flowability of the final powder blend for direct compression. They showed that dissolution of finer particles was inferior compared to the performance of the coarser sieve fraction and the flowability declined with particle size reduction (Jijun et al. 2010). The same group also investigated the downstreaming process by comparing the quality and performance of direct compressed tablets with tablets generated via wet granulation of the milled extrudates (Jijun et al. 2011). The wet granulation process initiated recrystallization upon storage resulting in a different dissolution release profiles.

Deng et al. produced HME strands of 2 mm diameter which were resized using a Fitz® Mill comminutor. The resulting powder was mixed with filler, disintegrants, and lubricants and directly compressed to tablets. Different superdisintegrants were used in order to investigate the impact on the dissolution kinetics. Alternatively, they prepared pellets of 1 mm thickness by utilizing a pelletizer. The pellets were simply filled into hard gelatin capsules and used for dissolution testing as well (Deng et al. 2013). In another example, Kindermann et al. milled the HME strands with an ultra-centrifugal mill and used the 355–500-μm sieve fraction to prepare double-layer tablets with tailor-made release profiles (Kindermann et al. 2012).

Read et al. used a cryogenic mill for the amorphous ketoprofen extrudates to produce particle with a mean size of 15–250 μm. The milled fraction reached 100 % dissolution after approximately 600 min while the manually cut rods eroded slowly resulting in only 50 % dissolution in the same time span. Cryogenic milling can be of advantage in cases where low-melting polymers have to be milled or when obtained strands show lack of brittleness (Read et al. 2010).

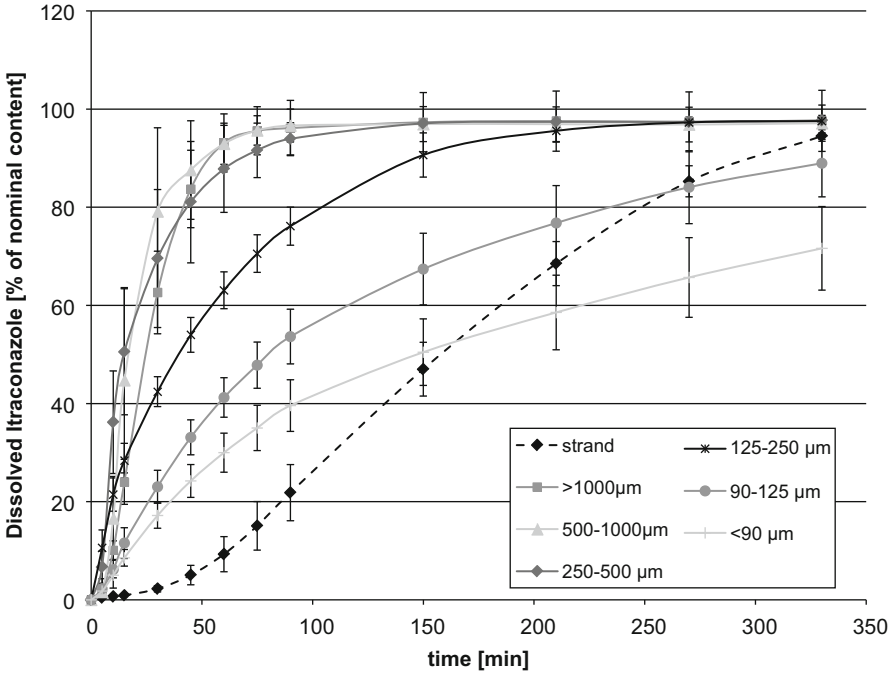

Fig. 13.1 Itraconazol (ITZ) release from hot-melt extrudates in dependence of particle size. (USP2 basket, simulated gastric fluid)

The impact of particle size on the dissolution performance was also observed for amorphous ITZ–Soluplus® extrudates. Samples of defined sieve fractions as well as samples of the unmilled strands were compared (simulated gastric fluid, $n = 6$). The results (Fig. 13.1; data not published) clearly showed that after 100 min, the API from milled particles with a mean particle size above 250 µm was fully dissolved, whereas the dissolution from finer particles was significantly slower and incomplete. The unmilled strands were steadily eroding resulting in almost 100 % dissolution after 330 min. For this formulation, coarser particles were more beneficial than finer grades, potentially as a result of polymer swelling or concurrent recrystallization effects.

Effect of Excipients: The composition and powder properties of the initial blend of API, polymer, and additional excipients not only impact the extrusion process but also the downstream process. The formulation has to exhibit sufficient flowability in order to facilitate a steady extrudate flow and screw fill degree ensuring uniform HME strands and an acceptable throughput. Many of the available pharmaceutical polymers show poor flowability and therefore the addition of flow aids like silicone dioxide or application of free-flowing polymers and excipients have to be considered. Godderis et al. investigated the flow properties and bulk density of ternary systems containing drug substance, Eudragit® E100, and surfactant tocopheryl polyethylene

glycol succinate (TPGS). By estimating the Hausner ratio and the Carr index, the best excipient ratio was evaluated with respect to the flowability (Goddeeris et al. 2008). The need for free-flowing excipients for pharmaceutical HME is also recognized by the polymer manufacturers. For example, Soluplus® was developed as dissolution and solubility enhancer especially for HME applications and shows favorable flow properties.

Another important aspect is the bulk density of the initial blend. If the bulk density is too low, the feeding unit, which is usually based on a twin-screw system, becomes the limiting part of the equipment with regard to throughput and screw fill degree. Therefore, the formulator is requested to balance between sufficient flow properties, bulk density, and particle size distribution which should be similar for all ingredients in order to avoid demixing.

The advantages of a drug substance formulated as a solid dispersion is sometimes not reflected in the final dosage form as many hydrophilic polymers tend to swell and form gel matrices when exposed to aqueous environment. This effect can change the dissolution kinetics from the targeted immediate-release profile to a slower erosion process. One option to improve the dissolution rate of such formulations is to reduce the solid dispersion content in the final solid dosage form by adding large amounts of a diluent like fine MCC (DiNunzio et al. 2012) or lactose (Jijun et al. 2011) as external phase to the milled extrudates before direct compression. These excipients act as spacers increasing the porosity and prevent formation of slowly disintegrating gel structures. Here the formulator has to be aware that the drug load in solid dispersion is already reduced since normally it contains substantial amounts of stabilizing polymer.

A different approach to overcome polymer gelling is to add inorganic salts like potassium bicarbonate. They can facilitate dehydration and precipitation of the polymers in aqueous environment which is reflected by an improved dissolution profile (Hughey et al. 2013).

Another possibility to adjust the dissolution kinetics is to incorporate specific excipients directly into the extrudate. Water-soluble pore former like mannitol (Deng et al. 2013), citric acid, and sucrose (Schilling et al. 2008) as well as water-soluble polymers like hypromellose, polyethylene oxide (Read et al. 2010), or poloxamers (Zhu et al. 2006) can be extruded together with the API and stabilizing polymer and these have also been shown to improve the dissolution rate.

13.2.2 Film Coating

As a last step in the downstream process, tablet coating should be given due consideration specifically in regard to preventing hygroscopic solid dispersions from moisture uptake or facilitating a targeted release profile. Jijun et al. described coating of HME-based tablets with an Opadry® amb coat (Jijun et al. 2010, 2011). In this case, the physicochemical properties of the amorphous API should be carefully monitored in order to exclude recrystallization during the coating procedure.

13.3 Downstream Processing of Spray-Dried Powders

Spray-dried powders often exhibit relatively small particles representing a large surface area, low bulk density, and often show poor flowability. Therefore, often a pre-compaction step is needed during downstream processing in order to increase the bulk density to a level which later allows tablet compression or capsule filling. At the same time, this reduces the surface area of the material which could have an impact on the drug release rate, especially when appropriate attention is not given to the formulation composition.

The powder characteristic, e.g., flowability, particle size, and bulk density, of the spray-dried material can be improved using an internal fluid bed in the spray dryer. Alternatively, other manufacturing technologies such as fluid bed coating/layering or spray granulation, where the organic solution containing the drug substance and the polymer is sprayed onto a carrier, can be used.

13.3.1 Powder Blends, Dry Granulation and Compression

Effect of Excipients: One issue which is often described in the literature for unformulated or poorly formulated capsule or tablet formulations containing spray-dried powders is the formation of hard plugs that inhibit dissolution. Langham et al. investigated the dissolution behavior of spray-dried amorphous solid dispersions of felodipine and copovidone, and showed that compaction leads to a significant decrease in the rate and extent of dissolution, which is drug-load dependent (Langham et al. 2012). Fakes et al. showed that the dissolution rate for amorphous material relative to the crystalline drug slowed down upon exposure to the aqueous dissolution medium, and that this may be attributed to the initial rapid conversion of the amorphous to crystalline material. The deposition of the crystalline drug on the insoluble excipient MCC, which was used as filler in the formulation, formed a hard plug at the surface of the capsules thus inhibiting dissolution. The addition of fast dissolving or readily dispersible fillers should therefore improve the disintegration/initial dissolution rate, which was demonstrated by Fakes et al. by comparing the effect of lactose and MCC as fillers, clearly showing that the dissolution rate significantly improved for the lactose-containing formulation (Fakes et al. 2009).

The underlying physical processes that resulted in poor dissolution performance of an encapsulated amorphous solid dispersion consisting of amorphous celecoxib, polyvinyl pyrrolidone (PVP), and meglumine was investigated by Puri et al. (2011). They concluded that rapid hydration of the capsule in aqueous media leads to leaching out of meglumine; resulting in decreased ratio of amorphous celecoxib to PVP and the interaction in the solid dispersion causing hydrophobization of PVP. The water-mediated H-bond interlinked in the amorphous solid dispersion promoted interparticle cohesivity and formation of a nondispersible plug (Puri et al. 2011). In

order to circumvent undesired interfacial interactions, they proposed surface modification by particle coating, reduction in exposed surface area, and use of high-specific surface area and/or surface-adsorptive excipients as spacers in the formulation blend as effective measures to improve the dissolution behavior. In order to improve the wettability of the spray-dried material, surfactants can be integrated into the spray-dried solid dispersions. This approach needs careful consideration as the presence of surfactants in spray-dried amorphous solid dispersions can significantly affect the compressibility of the material, resulting in decreased tablet strengths, increased elastic deformation, and capping (Roberts et al. 2011).

Effect of Compaction/Compression: The effect of compression on the phase behavior of amorphous solid dispersion was first investigated in detail by Ayenew et al. They showed that compression can result in amorphous–amorphous phase separation in solid dispersions, and that this effect is more pronounced in metastable compositions of solid dispersions (Ayenew et al. 2012a). Further evidence that compression can lead to increased crystallinity upon storage can be found by Leane et al. (2013). They compared the crystallinity of tablets prepared from roller-compacted granules, tablets prepared by direct compression and blends filled into capsules without compression under accelerated stability testing. The degree of crystallinity increased with increasing number of compression steps (Leane et al. 2013).

In this connection, the effect of fillers on the physical stability of the compressed tablets was investigated by several research groups. Leane et al. compared the effect of MCC, mannitol, and lactose, and showed that greater physical stability was observed for formulations containing MCC, which is attributed to the fact that MCC deforms primarily by plastic deformation, whereas lactose and mannitol deform by brittle fracture (Leane et al. 2013). Based on the investigations done by Schmidt et al. (2003), carrageenan has the potential of protecting drugs from polymorphic transformation during tablet compression. Dhumal et al. (2007) also investigated the effect of carrageenan (Gelcarin® GP-379) on the physical stability of amorphous spray-dried dispersions upon compression and storage. Physical stability of the tablets improved when carrageenan was co-precipitated with the solid dispersion in the SD process compared to a physical mixture (PM) with carrageenan or to the solid dispersion alone. This effect may be attributed to the cushioning action provided by carrageenan, which releases mechanical stress by expansion and stores less stress in the tablet. It is assumed that the better stability of the co-precipitate is related to the close proximity of carrageenan, celecoxib, and PVP in the co-precipitate compared to the PM (Dhumal et al. 2007).

13.3.2 Fluid Bed Coating/Layering and Spray Granulation

The low bulk density and the bad flowability associated with spray-dried powders can be circumvented by manufacturing the amorphous solid dispersion either by fluid bed coating/layering or granulation, in particular spray granulation. In both

cases an organic solution, consisting of the drug substance, the polymer and potential other excipients, is applied on a filler which could either be a spherical pellet (fluid bed layering) or a conventional excipient. The development of barrier coated drug layered particles is described by Puri et al. After applying a methanolic solution containing celecoxib, PVP and meglumine (solid content: 10 % w/v) onto MCC in a Wurster process, a film coat is applied to the particles in order to avoid formation of an agglomerated capsule-shaped mass upon dissolution, and to improve the physical stability of the system. The authors investigated three different materials for the film coat, namely inulin, polyvinyl alcohol (PVA) and polyvinyl acetate phthalate (PVAP), and finally selected PVA for the accelerated stability study (Puri et al. 2012). Oshima et al. applied an organic solution of ITZ, polysorbate 80 and either hypromellose or hypromellose phthalate onto a powder blend consisting mainly of Ceolus RC® (a colloidal grade of MCC, the surface of which is covered with carmellose sodium) in a fluid bed coating process. The flowability of the obtained granules was optimized by adding 0.1 % of light anhydrous silicic acid as surface modifier. The amount of disintegrant was optimized and 2 % of croscarmellose sodium was finally selected (Oshima et al. 2007). A similar approach was tested by Chowdary and Rao who applied an organic ITZ solution onto three different superdisintegrants, or lactose or MCC and investigated the dissolution behavior (Chowdary and Rao 2000). The solid dispersions in superdisintegrants gave much higher rates of dissolution than the dispersions in other excipients (Ac-Di-Sol > Kollidon CL > Primojel > MCC > lactose).

13.3.3 Film Coating

The moisture uptake during an aqueous film coating process can lead to increased level of crystallinity as shown during stability testing. There was no difference observed between a moisture-barrier-containing formulation (Opadry® amb) and an Opadry® II system (Leane et al. 2013). However, reduced moisture uptake and improved physical stability was observed when a hygroscopic, amorphous solid dispersion-containing tablet was coated with hydroxypropyl methylcellulose phthalate (HPMCP) using organic solvents (Reven et al. 2013).

13.4 Downstream Process of MBP

MBP are usually free-flowing powders. MBP exhibit a certain porosity and surface roughness as compared to particles prepared by HME (Dong et al. 2008). A comparison of the specific surface area (BET) showed that the MBP particles had 47 times larger specific surface area, even so the true density was comparable (1.33 and 1.30 g/cm^3 for the MBP and the HME product, respectively) (Dong et al. 2008). In case of vemurafenib, the MBP is described as spongy network having pores in the

range of 50–200 nm and some bigger bubbles in the range of 3–10 μm (Shah et al. 2013). The properties of MBP particles are dependent on and can be tracked back to the process parameters used for precipitation. Especially, the amount of API and polymer dissolved in the organic phase as well as the solvent to anti-solvent ratio are critical process parameters in the MBP processes (Shah et al. 2012) and have a direct impact on the porosity, surface roughness, size, and bulk density of the particles.

A comparison of two different capsule formulations containing 40 mg of vemurafenib as MBP, one obtained by dry blending and the other one by a wet-mixing process, showed that the mean values of AUC_{0-inf} (86.2 ± 52.1 μMh and 79.8 ± 42.8 μMh) and the C_{max} were comparable with each other in a single 160 mg dose human bioavailability study. The AUC and C_{max} in each case were greater than that for the crystalline reference formulation (Shah et al. 2013).

13.4.1 Powder Blend, Dry Granulation and Compression

Milling of MBP: Depending on the particle size of the MBP, a milling step might be recommended prior to any downstream processing of the material. Milling could be done using different kinds of mills, like jet mills, pin mills, hammer mills, and so on. The selection of the type of mill as well as the process parameters used will have an impact on the final particle size obtained. The particle size itself will not only have an effect on the dissolution behavior (Shah et al. 2013), but might also effect the entire downstream processing as the flowability of jet-milled material might not be adequate for robust downstream manufacturing later on.

The selection of the downstream processing itself strongly depends on the bulk density of the obtained material. In case of sufficiently high bulk density, a direct compression approach could be used, otherwise it is recommended to increase the bulk density using a roller compaction process.

Effect of Excipients: Depending on the wetting behavior of the MBP particles, which strongly depends on the drug to polymer ratio, the lipophilicity of the compound as well as the hydrophilicity of the polymer used (Shah et al. 2012), additional excipients need to be added during downstream processing. Functional excipients like wetting agents, glidants, fillers, and disintegrants can be added intra- or extragranular to improve the wettability of the MBP, to improve the flowability of the powder blend, as well as to avoid sticking of the material onto the rolls/punches and enable a fast disintegration/dissolution behavior of the granules/tablets. The type and amount of the different excipients need to be carefully adjusted.

Effect of Compaction/Compression: Process parameters like compaction force, gap width, and screen size used for breaking the ribbons can have an impact on the properties of the granules and tablets. Compaction force and gap width should be selected in a way that the granules have a sufficiently high bulk density, but could still be compressed to tablets. In other words, overcompaction should be avoided as this leads to tablets with insufficient hardness.

The screen size used in the granulator unit needs to be selected based on the width of the anticipated tablet size of the lowest dose strengths. The granules should be characterized thoroughly in order to gain a good process understanding. Dissolution tests of the granules provide additional information on the process and help to link the measured attributes of the pure MBP with those of the final tablet. It is strongly recommended to investigate the effect of the roller compaction force, gap width, compression force, and other potential critical process parameters (pCPP) on the tablet properties like hardness, disintegration time, abrasion, dissolution, and so on. The selected process parameters should enable a robust manufacturing of MBP tablets at the end.

13.4.2 Film Coating

Depending on the desired product profile, a film coating may be applied to the tablets. The film coating parameters need to be selected carefully in order to avoid an uptake of water by the tablet kernels and exposure of the tablets to high temperatures. Both, water and temperature, might otherwise lead to increased molecular mobility in the amorphous system and the drug substance could recrystallize from the amorphous solid dispersion.

13.5 Downstream Processing of Mesoporous Silica-Based Systems

Mesoporous silica drug delivery systems are characterized by a unique pore structure in which the drug substance is entrapped at a molecular level. Upon contact with liquids, the drug substance is released from the pores at a certain rate, which depends among other factors on the pore size of the mesoporous silica and the degree of loading (Mellaerts et al. 2007). The rate limiting step for drug release seems to be the time needed for diffusion out of the internal pores, which is a function of the silica particle size and pore diameter, as shown by investigations of the drug release of ten physicochemically different drug molecules (Speybroeck et al. 2009). This indicates that the pore structure needs to be maintained during the downstream processing. Critical material attributes of mesoporous silica particles are the low bulk density (below 0.1 g/cm^3), poor compressibility, and flowability (Vialpando et al. 2011), which is a challenge for the development of tablets. Dry granulation or direct compression has primarily been investigated as downstream processing methods, but one reference mentions wet granulation as well.

13.5.1 Powder Blends, Dry Granulation and Direct Compression

Mesoporous Silica Loading Process: Mesoporous silica particles can be loaded with a broad range of different drug substances using different loading methods. Investigations showed that the loading method had an impact on the degree of loading, the degree of residual crystallinity, as well as bulk density (Limnell et al. 2011) therefore affecting the final drug product performance.

Effect of Excipients: The dissolution kinetic can be altered by adding additional excipients as shown by Limnell et al., who observed an increase in the amount of IMC released when mesoporous silica particles were blended with excipients. The increase in the release was attributed to PVP K30 in the excipient blend, which functioned as a precipitation inhibitor (Limnell et al. 2011). A systematic investigation on the addition of precipitation inhibitors was done by Speybroeck et al. (2010) by evaluating the in vitro and in vivo behavior of formulations consisting of ordered mesoporous silica SBA-15 loaded with ITZ and HMPC or HPMCAS, respectively. Due to the pH dependent solubility, HPMCAS was not able to prevent precipitation of ITZ in vitro at low pH and even upon transfer to FaSSIF, where rapid precipitation of ITZ occurred despite minimal or no HPMCAS being dissolved. Contrary to HPMCAS, HPMC was able to maintain the supersaturation in vitro and led to more than 60 % increase in absorption compared to ITZ-loaded SBA-15 particles in a rat pharmacokinetic (PK) study. The PM of the ITZ-loaded SBA-15 particles and HPMC (1:4:6) achieved 88 % of the AUC relative to Sporanox®, which was used as reference in this study (Speybroeck et al. 2010). Similar bioavailability of ITZ-loaded SBA-15 and Sporanox® was obtained in a PK study in rabbits and dogs. In this study, the loaded mesoporous silica system (49 %) was blended with croscarmellose (25 %), lactose (25 %), and sodium lauryl sulphate (SLS; 1 %) ensuring fast disintegration and good dispersion of the loaded ordered mesoporous silica system (Mellaerts et al. 2008).

The effect of adding disintegrants, low-hydroxypropylcellulose (L-HPC) or pregelatinized starch (PCS), to the tablet formulation was investigated by Takeuchi et al. The dissolution rate of IMC from the tablets was significantly improved and similar to the solid dispersion particles itself when an L-HPC was present in the formulation. Formulations containing PCS were also able to improve the dissolution and tableting properties, but the dissolution rate of IMC slightly decreased and the compaction property was slightly lower than that in the case of L-HPC (Takeuchi et al. 2005).

Ratio Between Drug-loaded Silica Particles and Excipients: Besides the influence of certain excipients on the drug release, several authors investigated the effect of the ratio between drug-loaded silica particles and excipients in the formulation. Limnell et al. (2011) used 25 % of IMC-loaded MCM-41 in their tablet formulations and obtained tablets with a fast release. Tahvanainen et al. further increased the amount of drug-loaded silica particles to 25, 30, and 35 % using IMC-loaded thermally oxidized mesoporous silicon microparticles (TOPSi-IMC), and observed a decrease

in dissolution rate and permeability as a result of loss of unique pore structure due to deformation of the particles under compression (Tahvanainen et al. 2012).

Effect of Compression: Increasing the compression force applied to the PM of TOPSi-IMC and excipients leads to a decrease in the release of IMC (Tahvanainen et al. 2012). Further investigations linking the effect of compression force on the drug release were conducted (Limnell et al. 2011; Vialpando et al. 2011; Kiekens et al. 2012). Limnell et al. observed a slight decrease in the amount of drug released from tablets compared to capsules containing IMC-loaded MCM-41 particles. Nevertheless, the tablets retained their ability for fast release of IMC as no major alteration in the porous structures of the particles after tablet compression was observed (Limnell et al. 2011). Vialpando et al. investigated the effect of compression force on ITZ-loaded ordered mesoporous silica (SBA-15 and COK-12), and observed a decrease in the amount of drug released with increasing pressure. This was related to a reduction in the pore size and volume. A comparison of both silica materials showed that SBA-15 is more sensitive towards compression than COK-12. This was related to the slightly thicker walls and higher condensation degree of the silica framework of COK-12 (Vialpando et al. 2011). The addition of plastic deforming materials, such as MCC, was helpful in protecting the silica and improving the release rate following compression as shown by Vialpando et al. who added 30, 50, or 70 % of MCC to the drug-loaded SBA-15 and COK-12, compressed tablets at 120 MPa, and investigated their release profile. The dissolution profile of the tablets clearly improved, but was still slower in comparison to the PM (approx. 80 % of ITZ after 60 min). Addition of 4.8–5.1 % croscarmellose sodium further enhanced the drug release following compression (Vialpando et al. 2011). The effect of compression was also investigated by Kiekens et al. comparing a 5 and 10 mg tablets and a 5 mg capsule containing ezetimibe-loaded ordered mesoporous silica (OMS) with a 10 mg Ezetrol tablet (reference formulation) in vitro and in vivo. In vitro, both OMS tablets showed comparable, but improved dissolution behavior compared to the reference. This was not reflected in vivo (PK study in Beagle dogs), where the area under the curve (AUC) for the OMS tablets and Ezetrol tablet was comparable, and more than two times increase in AUC was observed for the 5 mg OMS capsule compared to the reference. As the 5 mg capsule and tablet had an identical composition, this result showed reduced bioavailability due to compression (Kiekens et al. 2012).

13.5.2 Wet Granulation as Alternative Granulation Technique

Wet granulation was investigated as an alternative downstream process for ordered mesoporous silica by Vialpando et al. (2012). COK-12 was used as model ordered mesoporous silica due to its thicker walls and higher degree of silica condensation, which results in higher resistance towards compression. The authors successfully demonstrated that wet granulation can improve powder flow and compactibility by increasing the particle size, bulk density, and smoothing of the surface of the

ITZ-loaded COK-12 particles. In order to achieve this, process parameters such as binder concentration, binder addition rate, and granulation temperature need to be carefully selected avoiding overwetting of the material and therefore premature drug release on one hand, and ensuring agglomeration on the other hand. The decrease in the release profile upon compression was compensated by extragranular addition of croscarmellose sodium (2.4 %). Overall, the amount of "drug-loaded silica particles" in the tablet could be increased by wet granulation compared to the dry processes. In addition to the investigations of process parameters, the application of the wet granulation process to COK-12-loaded silica particles loaded with ITZ, fenofibrate, naproxen, or ibuprofen revealed that the risk of premature drug release during wet granulation is primarily compound dependent (Vialpando et al. 2012).

13.5.3 Modification of the Release Profile

The drug release from tablets containing drug-loaded mesoporous silica systems can be modified by applying a functional coat on top of the tablets. A pH-dependent drug release systems for intestinal drug release were achieved by using Eudragit S100 (Xu et al. 2011) or HPMCP (Xu et al. 2009). The concentration in the coating solution, the coating thickness, and the drying temperature had an effect on the amount of drug released at pH 1.2, whereas the drug release kinetic at pH 7.4 was unchanged (Xu et al. 2009, 2011).

Modification of the release rate of the loaded mesoporous silica can for instance be achieved by surface functionalization of the mesoporous silica (Song et al. 2005). This can be achieved either by applying polyelectrolyte multilayer coatings (Zhu et al. 2005), or by ionic interaction of oppositely charged polycations and anionic SBA-15 (Yang et al. 2005) or by anchoring suitable polyamines on the external surface to obtain a pH and anion-controlled nano-supramolecular gate-like ensemble (Bernardos et al. 2008).

13.6 Summary and Conclusion

The usual downstream processing of amorphous solid dispersion involves generation of granules either directly through milling or via granulation. This is followed by blending, capsule filling or tablet compression, and film coating. Due to the fact that solid dispersions contain substantial amounts of a stabilizing polymer, the properties of the polymer will have an impact on disintegration behavior as well as compactibility. As a consequence, one important aspect of formulation development is the selection of suitable excipients especially fillers and disintegrants. Especially, the selection of fillers is quite controversial in the literature. Fast dissolving fillers like lactose or mannitol are preferred from a disintegration and dissolution perspective, but these can induce brittle fracture, whereas plastic deformable fillers like MCC or

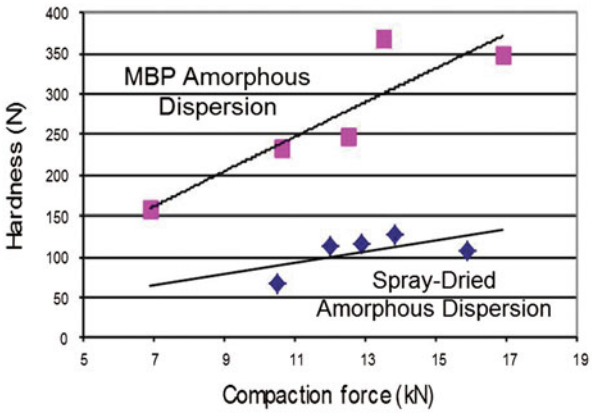

Fig. 13.2 Hardness–compression force profiles of MBP and spray-dried amorphous dispersions of vemurafenib

carrageen improve the physical stability of the system by protecting the amorphous solid dispersion during roller compaction/ tablet compression.

The value of proper compaction characterization, i.e., assessment of the tensile strength, compression pressure, solid fraction relationships leading to the compactability, tabletability, and compressibility (CTC) profiles, provides basic mechanical property information (Tye et al. 2005). Along with tensile strength, compression pressure and solid fraction, the elastic modulus, permanent deformation pressure, and brittleness of compacts are additional important properties (Hiestand and Smith 1984a, b) pharmaceutical scientists used to quantify the mechanical nature of materials. For example, mechanical properties of a compact are very much influenced by solid fraction, and even a change of 0.01 can influence mechanical property as much as 10–20 % (Amidon et al. 2009). These properties, therefore, are of significant interest in supporting tablet development in a scientific manner.

Hancock et al. reported (Hancock et al. 2002) a dynamic indentation hardness, 30 % higher for the amorphous form of a drug (178.4 MPa) compared to a crystalline form of a drug (230.3 MPa). Aggregation and fusion of compacted amorphous particles could form a harder surface that resists indentation, compared to crystalline particles. However, even among amorphous dispersions of similar composition, the techniques used to prepare these dispersions can impact the deformation attributes of the resulting product. At similar compression force levels, tablets of a given composition prepared by co-precipitation (containing amorphous MBP) had a significantly higher hardness than that of similar composition prepared by spray drying, as seen from Fig. 13.2.

In addition, tensile strength of compacts of amorphous solid dispersions is impacted by the level of polymers, the level of inclusion in the dispersion, and particularly dependent on the processing technique. Amorphous solid dispersion generated by HME process is quite different than amorphous solid dispersions prepared by other techniques. Powders processed by HME are subjected to elevated processing temperatures as well as high pressure. The reduced free volume retards molecular mobility and prevents further densification during tableting (Zhu et al. 2002; Young et al. 2005), which could adversely impact the product performance

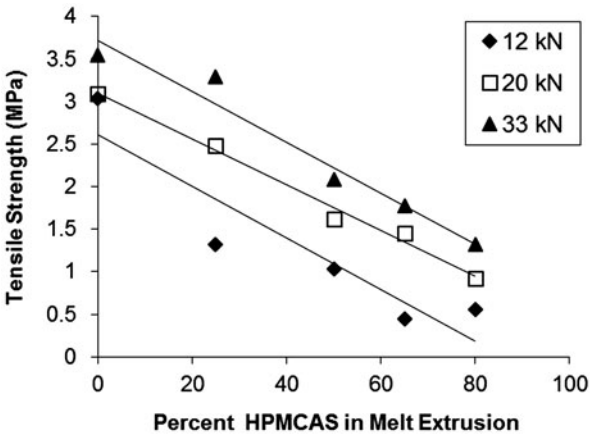

Fig. 13.3 Effect of HPMCAS level in melt-extruded solid dispersion on tablet tensile strength

such as drug dissolution. For example, solid dispersions containing HPMCAS prepared by melt extrusion exhibit decreasing tablet tensile strength with increasing level of HPMCAS, as shown in Fig. 13.3. The tensile strength was observed to decrease three- to fourfold when HPMCAS level was present at 80 % in the dispersion.

In addition, material properties such as dynamic hardness and tensile strength of amorphous solid dispersions are also governed by polymers and technologies used to prepare such dispersions (Iyer et al. 2013). The dynamic hardness of melt-extruded HPMCAS was greater than that of "as is" materials. However, both spray-dried HPMCAS and melt-extruded copovidone did not exhibit a significant change in dynamic hardness from that of "as is" materials, respectively, as seen from Fig. 13.4. The tensile strength of melt-extruded HPMCAS and copovidone decreased significantly compared to their respective native materials, as seen from Fig. 13.5 indicating that tablet development of melt-extruded solid dispersions could be challenging.

During each step of the downstreaming process, energy is applied to the system which can lead to amorphous–amorphous phase separation and can trigger recrystallization. In addition, a reduction in surface area occurs which might affect the dissolution behavior when the formulation is not adequately designed. Therefore, it is recommended to characterize each intermediate product as well as the final drug product. Figure 13.6 presents a schematic depiction of downstream process together with proposed analytical tests after each step as well as the critical quality attributes and critical process parameters. Especially the dissolution behavior and physical stability should be tested not only for the final drug product but also at the immediate level allowing identification of potential adverse effects earlier in the development chain. Several analytical methods, or combinations thereof, can help to gain a mechanistic insight into the dissolution behavior of tablets containing amorphous solid dispersions. Langham et al. combined the ultraviolet (UV) absorbance measurement of the re-circulating dissolution media from a flow cell with simultaneous acquisition of magnetic resonance images. The MR images showed the fundamental difference in the dissolution behavior of the investigated solid dispersions, and could thus explain the difference observed in the drug release (Langham et al. 2012).

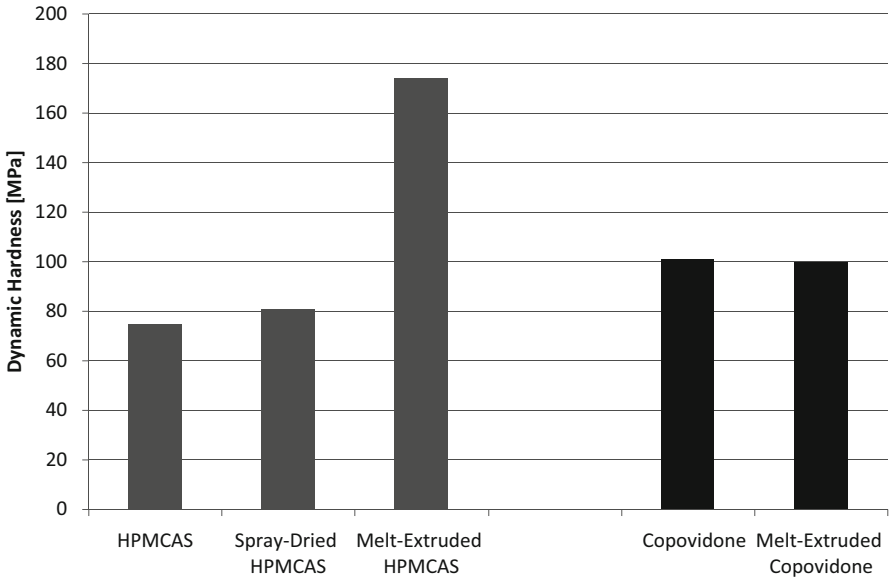

Fig. 13.4 Dynamic hardness of "as is" and processed HPMCAS and copovidone

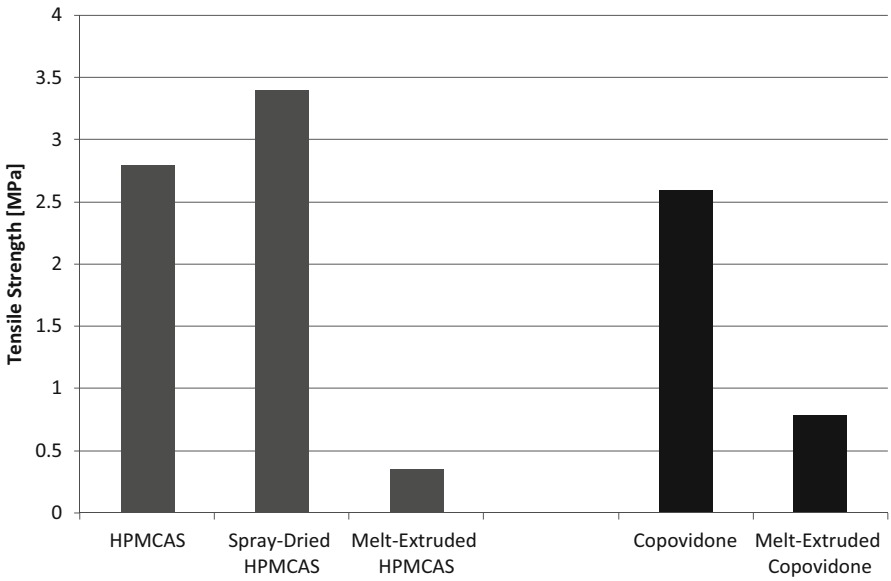

Fig. 13.5 Tensile strength of "as is" and processed HMPCAS and copovidone

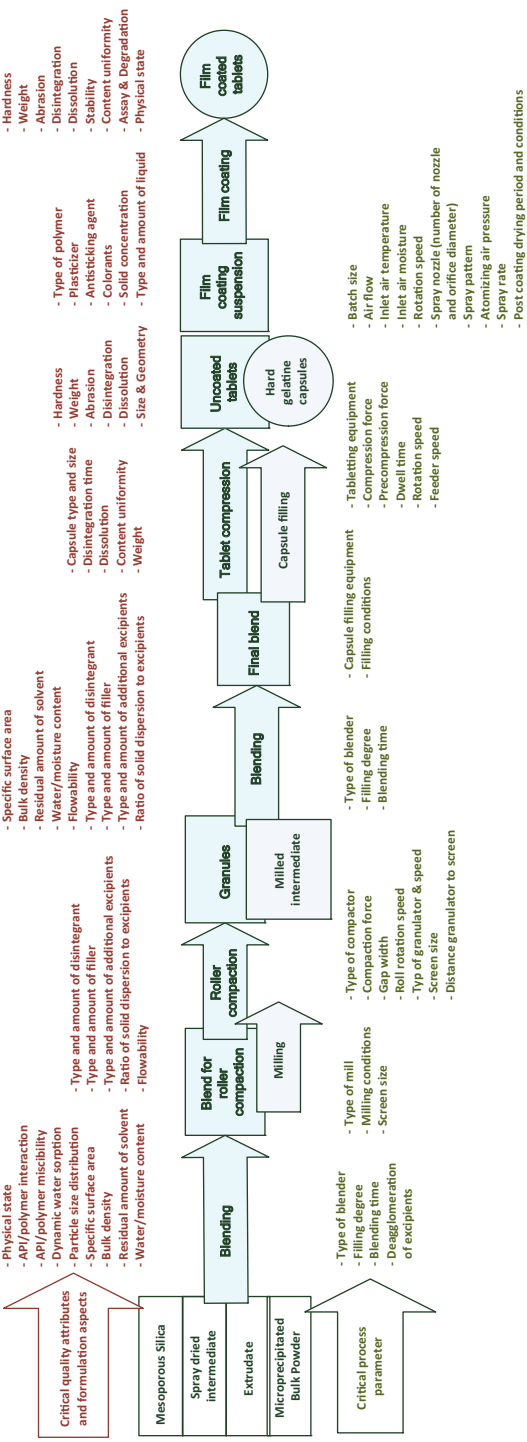

Fig. 13.6 Flow chart: amorphous solid dispersion downstream processing

In addition to the dissolution testing, analytical methods need to be established and validated in order to detect low amounts of crystalline material in the amorphous solid dispersion and/or the final drug product. Xie et al. described the development of such a method, and established a reliable multivariate curve resolution (MCR) method based on the second derivative Raman measurements for quantitative determination of the solid state forms of the drug substance and tablets (Xie et al. 2008).

Amorphous solid dispersions can be successfully transformed into an appropriate solid form like a tablet or a hard gelatin capsule by judiciously selecting the processing technologies. Critical process parameters must be identified and excipients carefully selected in order to obtain a final drug product with the desired quality attributes. Each of these factors plays a critical role in developing a successful commercial product from a solid amorphous dispersion.

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