Chapter 12
Pharmaceutical Development of MBP Solid Dispersions: Case Studies

Raman Iyer, Navnit Shah, Harpreet Sandhu, Duk Soon Choi, Hitesh Chokshi and A. Waseem Malick

12.1 Introduction

The biopharmaceutical classification system (BCS) was first introduced in 1995 to facilitate the drug development, and it is based on two independent variables that influence bioavailability, viz., aqueous solubility and intestinal permeability (Amidon et al. 1995; FDA 2000). Compounds that belong to BCS class II or IV are of primary interests from a formulation perspective and, therefore, solubility enhancement using formulation intervention is the key driver for improving the bioavailability of poorly soluble drugs. From a conceptual perspective, the dissolution rate can be expressed by the following equation (Noyes and Whitney 1897):

$$\frac{M}{t} = KAC_s \tag{12.1}$$

where *M/t,* the amount of drug dissolved at a given time *t,* is a function of the permeability coefficient (K), saturation solubility C_s, and surface area A of the dissolving particles. The saturation solubility refers to the thermodynamic or equilibrium solubility which is attained quickly for highly soluble drugs. In case of poorly soluble

R. Iyer (✉)
Novartis, East Hanover, NJ, USA
e-mail: raman.iyer@novartis.com

N. Shah · D. S. Choi
Kashiv Pharma LLC, Bridgewater, NJ, USA

H. Sandhu
Merck & Co., Inc., Summit, 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

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drugs, it may also refer to kinetic solubility $C_s f(t)$, which changes over time during the course of dissolution to the thermodynamic value.

A major thrust of the formulation intervention effort involves not only maximizing the kinetic solubility C_s but also modulating the rate of change of kinetic solubility to the thermodynamic value. The solubility C_s can be enhanced by using conventional solubilizers such as surfactants, micellar systems such as self-emulsifying drug delivery systems, and complexing agents such as cyclodextrins (Loftsson and Brewster 1996; Liu 2008; Williams et al. 2010, 2013). An approach to increase rate of dissolution is to increase the surface area by milling or micronization and, where feasible, to develop stabilized nanoparticulate systems using nanomilling or nanocrystallization techniques (Rabinow 2004; Keck and Muller 2006).

Over the past two decades, amorphous solid dispersion systems (ASD) where the drug is embedded in polymeric matrices as crystalline or amorphous form (solid dispersions) and/or drug–polymer solutions (solid solutions) have been studied extensively as a means of improving the bioavailability of poorly soluble drugs (Kai et al. 1996; Okimoto et al. 1997; Shin and Cho 1997; Kohri et al. 1999; Serajuddin 1999; Leuner and Dressman 2000). Despite their successes in improving bioavailability, the major concern is the reduced physical stability of these systems. Substantial efforts are required to achieve an optimal balance between the solubility gain and the risk of reversion to more stable form. Approaches to improve the stability of these high-energy amorphous systems rely on the use of polymers that help to stabilize the system by means of physical as well as chemical interactions. The physical stabilization is ascribed to the restricted molecular mobility and diffusional barriers that physically limit the motion of molecules, and the chemical stabilization is ascribed to Van der Waal's forces, hydrogen bonding, and electrostatic interactions between the drug and the polymer (Hancock et al. 1995; Rolfes et al. 2001; Faure et al. 2013). Due to the nature of processing, these interactions are maximized in microprecipitated bulk powder (MBP) process in contrast to other processing methods such as:

- Melt extrusion: solution-state interactions in MBP process may be more favorable than molten state
- Spray drying: solvent extraction with aqueous fluid in MBP process renders the particles more hydrophilic and porous, thereby providing superior compaction and wetting

These interactions increase the kinetic solubility of the drug, $C_s f(t)$, and help maintain the extent and duration of supersaturation which leads to enhanced bioavailability. Since only disolved drug can be absorbed, enhanced absorption can only occur in the "supersaturation maintenance window," the time during which the kinetic solubility $C_s(ft)$ is maintained at a high level. Beyond this window, the solubility reverts to the thermodynamic value via precipitation or crystallization resulting in lower solubility, and therefore loss of bioavailability. The stabilizing polymer in ASD is thus a critical component of the ASD that governs the drug's solubility and bioavailability. Several techniques are available to create a stabilized drug-carrier solid dispersion where the drug may exist in partial states of crystallinity or in an

amorphous state (Williams et al. 2010). Non-polymer-based amorphous conversion such as co-milling/co-grinding with inorganic silicates has also been used for some drugs (Bahl et al. 2008).

Polymer-based techniques of solid dispersion can be simple, moderately difficult, or complex. Co-melting and melt quenching are simple approaches, while examples of moderate ones are solvent evaporation under vacuum, fluid bed granulation or layering, spray drying, and lyophilization (El-Badry and Fathy 2006; Kim et al. 2006; Moser et al. 2008; Bley et al. 2010). Solvent–anti-solvent precipitation and hot-melt extrusion are examples of more complex techniques where solubility characteristics and thermal stability have to be considered in preparation of solid dispersion (Sertsou et al. 2002a, b; Wu et al. 2009; Evonik 2014). This chapter presents the case studies of ASD manufacture of highly crystalline compounds using MBP technology, the experiences gained during ASD development, galenical processing, and dosage form development. The details of MBP technology can be found in prior literature (Albano et al. 2002; Shah et al. 2012).

12.2 Factors to Consider in MBP Development

In a typical ASD, the drug (solute phase) is dispersed in an inert carrier (e.g., a polymeric continuous phase) with molecular level distribution being the most desirable. Depending on the interactions between drug and polymer and the method of preparation, the ASD may exist as a one-phase, two-phase, or mixed-phase system. In the one-phase system, the drug is immobilized within the polymer matrix at a molecular level such that it

- Prevents nucleation (and crystallization)
- Protects from moisture initiated mobility
- Maintains supersaturation (higher kinetic solubility)

Polymer-based amorphous dispersions attain their stability when the polymer molecules disrupt the self-assembly of drug molecules via positive drug–polymer interaction, for example, hydrogen bonding to form a stable matrix at the molecular level, akin to the concept of crystallization poisoning. Therefore, the selection of polymer and technologies of processing are critical in the development of ASDs with long-term stability. A polymer with a high glass transition temperature and several hydrogen-bonding sites is preferred. On the other hand, a polymer with high hygroscopicity and degradation potential is undesirable. Table 12.1 shows the factors that need to be considered in selection of polymer and technology.

The suitability of MBP technology depends on the physicochemical properties of drug or API active pharmaceutical ingredients (API) and polymer. As mentioned earlier, the stabilization of amorphous form in the ASD is attained by the physical and chemical interactions between drug and polymer. The strength of various interactions is ranked as electrostatic interactions > hydrogen bonding > Van der Waal's dispersion forces. The fact that MBP process uses ionic polymers helps to

Table 12.1 Factors in the selection of polymer and technologies for ASD

Factors to consider	Technologies
Glass transition temperatures (T_g) and melting points of API and polymer	Microprecipitation
Degree of lowering of T_g by water or residual solvent(s)	Hot-melt extrusion
MW and viscosity of the polymers	Fluid bed granulation/drying
Compatibility of API and the polymer (solubility parameters)	Spray drying/spray coating
Solubility of drug and polymer in solvents	Supercritical fluid extraction

API active pharmaceutical ingredients, *MW* molecular weight

maximize these interactions. Based on the assessment of more than 20 development compounds, the following characteristics of API are considered to be preferred for the MBP process (Hu et al. 2013):

1. *Non-covalent interaction:* Since the process involves water as anti-solvent, based on hydrophobicity of the compound, drug–polymer interactions are favored over the drug–water or polymer–water interactions. Therefore, compounds with log *P* greater than 3 and polymers having hydrophobic functional groups provide the best prospect for interactions.
2. *High molecular weight*: APIs with molecular weight greater than 500 tend to perform better. Although scientific literature in this regard is not definitive, the heuristic knowledge suggests that it may be more difficult for high molecular weight compounds to achieve the desired orientation for nucleation irrespective of the ASD-manufacturing technique.
3. *Hydrogen bond accepting group* > 8 preferred to enhance hydrogen bond interactions.
4. *Miscibility with polymer*: estimated by Flory Huggins interaction parameter and negative Gibbs free energy.

The crystallization inhibitory effect of polymer seems to play an important role in the stabilization of ASD (Miller et al. 2012). Additional criteria such as crystallization tendency determined by thermal cycling and polymer miscibility may also contribute to the overall performance. In addition to the API properties and the ASD stability considerations, the manufacturing process dictates that the drug and polymer should have good solubility in the solvent. The most suitable solvents include dimethylacetamide (DMA), dimethylformamide (DMF), dimethylsulfoxide (DMSO), terahydrofuran (THF), and N-methyl pyrrolidone (NMP). Also, the anti-solvent should have least solubility for drug and polymer to ensure maximum recovery and yield. By selecting appropriate solvent, polymer, and processing conditions, a high-quality ASD can be produced by MBP technology.

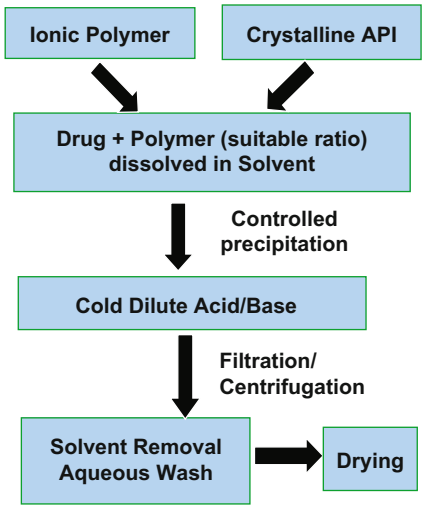


Fig. 12.1 Flowchart of MBP microprecipitation process (Shah et al. 2012)

12.3 MBP Preparation and Characterization

The flowchart of MBP microprecipitation process is shown in Fig. 12.1. In a typical run, the drug and an ionic polymer are dissolved in a suitable solvent. The solution is introduced into an anti-solvent under conditions that prevent nucleation and crystallization. Since solvent and anti-solvent are miscible, under the precipitation conditions, the solvent exchange occurs rapidly preserving the drug–polymer interactions. These interactions are further maintained during subsequent processing by maintaining a low temperature as well as avoiding conditions where either drug or polymer could dissolve. The resulting precipitate is washed, filtered, and dried at a relatively low temperature. Under appropriate processing conditions, the amorphous drug is precipitated as uniformly embedded in the polymer. Although precipitation conditions can also be generated by using organic anti-solvent, aqueous fluids are commonly used as anti-solvents. The MBP process is applicable to ionic polymers that have pH-dependent solubility and favor the use of aqueous acidic or basic anti-solvents. This helps in coprecipitation and also provides the added advantage of ionic interactions between the polymer and the API. Typically, enteric polymers that dissolve at physiological pH are more suitable for MBP process as they facilitate release of drug in an enteric environment resulting in a larger window of absorption.

Specific application of MBP lies in improving the bioavailability of poorly soluble crystalline drugs with high melting point or thermal liability that are not amenable to melt extrusion or spray drying (Shah et al. 2012). Further, it is more suitable for drugs that are prone to recrystallization since the MBP process is a relatively low energy process requiring relatively low temperature for processing as compared to extrusion or spray drying.

Since the biopharmaceutical performance of MBP is directly linked to the integrity of the amorphous form, suitable analytical methods are needed during development

of the MBP to ensure quality of the product. Characterization of an MBP product with respect to the physical state of the drug, dissolution, and stability follows similar protocols as other ASDs. Because water is used in processing, control of water content in ASD throughout the processing is critical to maintain stability of MBP.

Tools most commonly used for ASD characterization include powder x-ray diffraction (pXRD), thermal analysis (differential scanning calorimetry—DSC, thermogravimetric analysis—TGA), microscopy (atomic force microscopy, scanning electron microscopy, transmission electron microscopy), and hygroscopicity. In addition, spectroscopic tools can be employed to gain deeper insights into the nature of molecular interactions such as near-IR imaging, Raman mapping, solid-state NMR spectroscopy, dielectric spectroscopy, thermally simulated current, etc. The particulate properties including bulk and mechanical properties are relevant from a downstream processing perspective as well as dissolution performance of the final dosage form.

12.4 Pharmaceutical Development of MBP

In order to realize the benefits of MBP technology, the process needs to be scaled up beyond the laboratory into the manufacturing plant where large quantities can be prepared using a robust process. Further, the MBP ASD needs to be formulated into a dosage form that can be mass produced, packaged, stored, and transported to the distribution centers (pharmacy, hospitals, etc.). It is critical that the MBP ASD retains its integrity, stability, and bioavailability characteristics all through these phases of development, commercial manufacturing, packaging, and distribution.

The formulation of MBP ASD into a solid dosage form requires an integrated understanding of its stability profile, mechanical properties, interactions with the environment during storage (moisture, heat, light), and patient needs (dosage form size, convenience of administration, patient compliance). The factors that can affect the processability of MBP product during scale-up and its impact on the product quality are outlined in Fig. 12.2. The general prerequisites for amorphous stability of MBP material at the commercial manufacturing stage are: (a) that the aqueous MBP suspension remains amorphous at 5 °C for more than 48 h and (b) the final dried MBP powder remains amorphous for more than 2 years at ambient temperature of storage.

Several factors impact the performance of MBP. These include:

- Polymer type
- Drug loading
- Microprecipitation parameters (MBP manufacturing)
- Galenical processing/additives
- Packaging and storage

Impact of these factors on the ability to manufacture MBP and subsequent impact on its performance is presented in the following section with several case studies.

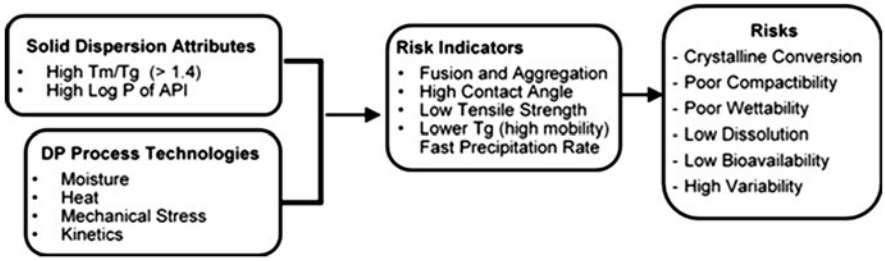


Fig. 12.2 Factors affecting processability of MBP and the associated risk factors

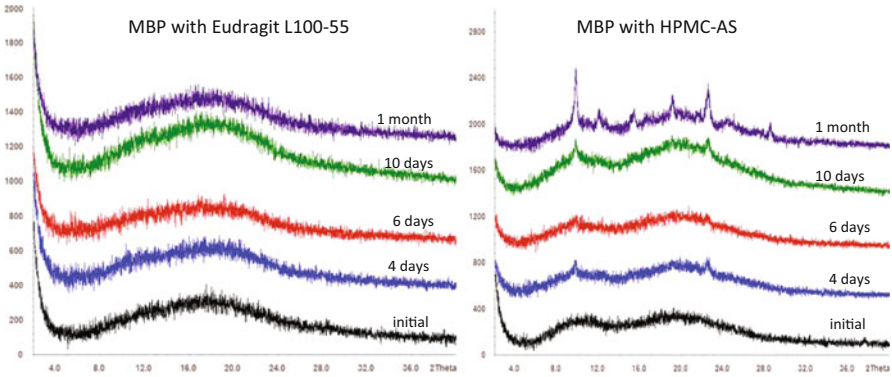


Fig. 12.3 Effect of polymer selection on stability of MBP of Compound "T"

12.4.1 Polymer Selection and Drug Loading

The MBP material contains amorphous drug dispersed in a polymeric carrier matrix either as molecular dispersion or as stabilized microdomains of drug. The matrix stabilizes the amorphous drug by various means such as vitrification of drug resulting in immobilized glass and drug–polymer-specific interactions. The dissolution characteristics of solid dispersions depend to a large extent on the physical state (amorphous), drug dispersivity (molecular dispersion), and particle size. The selection of polymer, drug loading, matrix composition, and preparation technique dictate the initial state of supersaturation (Urbanetz and Lippold 2005). The stability profile and ease of processing are dependent on the specific interactions between drug and polymer. Effect of API–polymer interaction on the MBP stability is shown in Fig. 12.3 for a poorly soluble Compound "T". The MBP was prepared using two different polymers, Eudrgait L100–55 and hypromellose acetate succinate (HPMC-AS). Both polymers provided amorphous material initially, but MBP with Eudragit L-100 55 exhibited greater stability than HPMC-AS when stored for 30 days at 40 °C/100 % RH, further proving the point that specific drug–polymer interactions between drug and polymer play a critical role in stabilization of amorphous state.

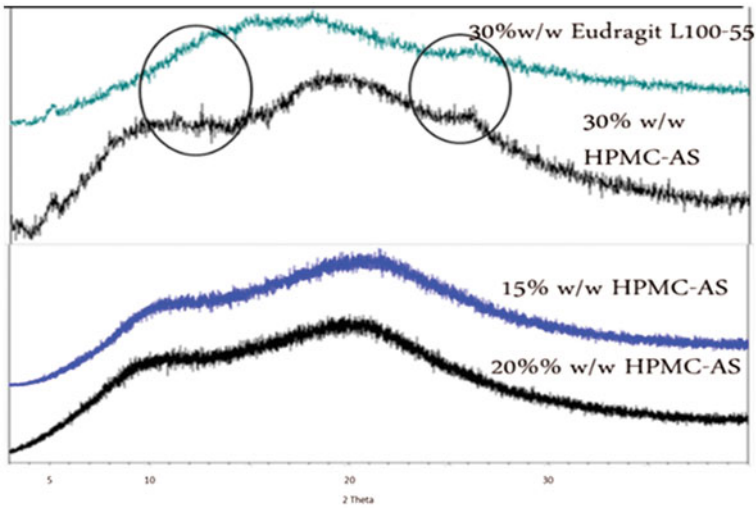


Fig. 12.4 MBP of Compound "X" showing effect of drug loading and polymer type

In the case of Compound "T," Eudragit L-100 55 provided stronger interaction, therefore better physical stability over HPMC-AS. However, a similar but opposite effect was observed with Compound "W." MBP with Eudragit L-100 55 did not yield completely amorphous material, whereas MBP prepared with HPMC-AS produced amorphous material that was stable for more than 2 years, further attesting that generation and stabilization of amorphous form are likely related to specific drug and polymer interaction.

In a study reported by Sertsou et al. (2002a, b) using the anti-solvent precipitation method, the impact of formulation and processing factors including drug loading, mixing speed, and anti-solvent pH was evaluated on the amorphous content of coprecipitated ASD. The effect of drug loading was found to be significant and the results were explained based on two competing phenomena influencing the amorphous content, i.e., crystallization inhibition by polymer and plasticization by solvent/anti-solvent. Similar results were obtained for MBP process as shown by application of MBP to Compound "X." As shown in Fig. 12.4, the drug loading up to 20 % provided a completely amorphous ASD, while drug loading above 30 % showed residual crystallinity for HPMC-AS.

12.4.2 Effect of Processing Technologies on MBP Stability

The handling of MBP requires consideration of heat, moisture, and shear stress that may destabilize the MBP. In a study of solid dispersion of Compound "Y," the MBP ASD prepared by MBP process provided a uniform and homogeneous solid solution of amorphous drug embedded in polymer while the same composition prepared by

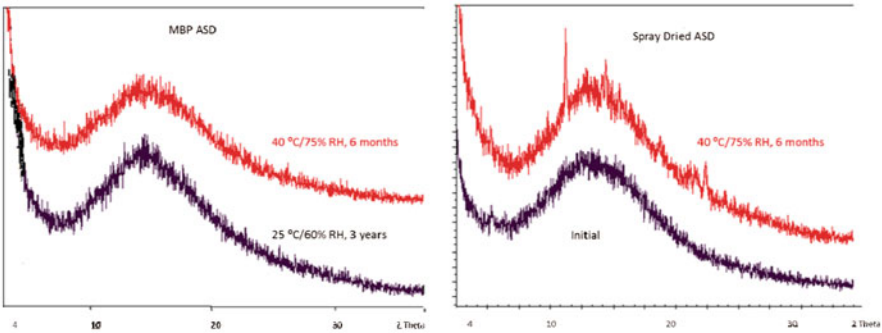


Fig. 12.5 Effect of processing technology on the crystallinity of ASD of Compound "Y" produced by MBP and spray drying with Eudragit L100 at 30 % drug loading

spray-drying process resulted in a two-phase dispersion that exhibited phase separation of drug and polymer. The particle size of the amorphous drug embedded in the ASD was determined by dissolving the polymer in an aqueous system, thereby separating the amorphous particles from the polymer matrix and leaving a suspension of amorphous API particles. Because of the destructive nature of the test, it is possible that some changes in the particle size could have occurred during the testing; regardless, the particle size of the recovered drug was found to be significantly different for the two processes. The $d_{90\%}$ of ASD from MBP process was found to be 0.9 μm, while that of spray-dried dispersion was 7.8 μm with a biphasic distribution, indicating that spray-dried dispersions may have a heterogeneous distribution of drug in the matrix resulting in higher variability during dissolution.

Further differentiation was observed in the stability of the ASD upon storage at accelerated stress conditions of temperature and humidity for 6 months. Crystalline peaks were observed for spray-dried dispersion, whereas ASD by MBP process remained amorphous as seen from Fig. 12.5 (Shah et al. 2012). Corresponding to this observation, the bioavailability of ASD by MBP was 100 %, while that of spray-dried ASD was 52 % when evaluated in a dog PK study.

As part of dosage form development, MBP ASD is often milled and densified for handling and filling operations. The densification is usually performed by either wet granulation or dry granulation processes. The aqueous wetting and massing of MBP granules can adversely affect its stability profile. As part of granulation process selection studies, the stability of wet granules of MBP in comparison with dry granules was studied. The adverse effect of wet granulation on physical stability was observed after long-term storage as shown in Fig. 12.6. Figure 12.6 shows the result of stress testing of tablets compressed from two types of granules, one by wet granulation and the other by dry granulation (roller compaction). Both tablets were shown to be amorphous at initially, but traces of crystalline peaks were observed from the wet granulated tablet after storage at accelerated conditions of 40 °C/75 % RH for 6 months.

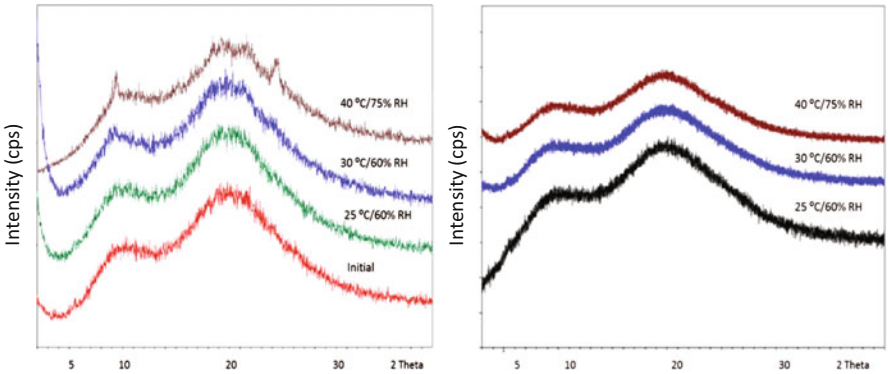


Fig. 12.6 pXRD profiles of wet and dry granulated MBP stored under various levels of stress (Compound Z)

Since the relaxation of amorphous state occurs over long periods of time, initial observations of amorphicity do not necessarily ensure long-term physical stability. Moreover, the relaxation may occur locally in microdomains instead of throughout the entire ASD during wet granulation. As such, multiple galenical technologies coupled with representative stability need to be evaluated to determine the robustness of the lead technology.

12.4.3 MBP Particulate Properties: Effect on Mechanical Properties, Downstream Processing, and Dissolution

The molecular state of API in the microstructural domains of MBP depends on the physicochemical properties of API, the polymer, and the specific interactions between API and polymer during precipitation. While the molecular state of API in ASD is important, the bulk particulate properties of MBP govern the critical galenical processes: material handling, flow properties, compaction behavior and performance, and dissolution. These particulate properties are closely related to the precipitation conditions such as shear, solvent–anti-solvent ratio, mode of addition, filtration efficiency, drying method, and milling. The final MBP powder is often milled and densified in order to minimize variability in the bulk particulate properties and to provide suitable flow and compactibility.

It is clear that the particle size of MBP can influence the downstream processing as well as performance of the final product. This is illustrated in Fig. 12.7 that shows the effect of MBP particle size on the particulate properties (bulk density and particle size) of the densified material, following the roller compaction process.

As discussed in Chap. 10 of this book, MBP particles are highly porous microstructures in general. This microporosity provides a number of benefits for enhanced

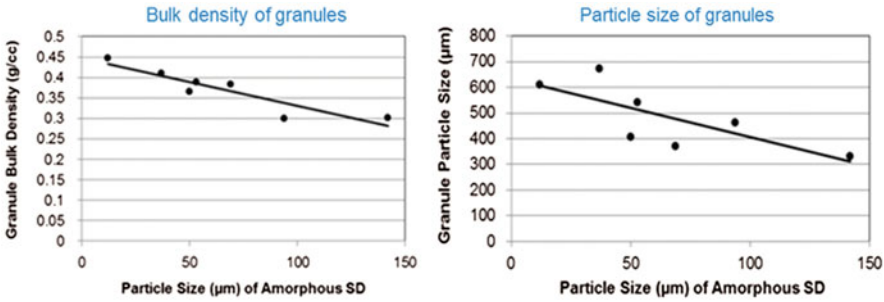


Fig. 12.7 Effect of primary particle size of MBP on bulk properties of roller compacted granules (Compound Z)

galenical processing, providing better compactibility, particle bonding, and densification. For example, the smaller particle sizes of the MBP powder, after roller compaction and milling, provided larger granules with high bulk density. Since MBP particles are porous, under compaction, they bond together efficiently, which results in densification. As expected, the extent of bonding between smaller particles is greater than larger ones. This occurs if, during roller compaction, the smaller MBP particles are compressed to the point of bonding, resulting in ribbons with high tensile strength. Such ribbons, upon milling, provide granules with a larger mean particle size and higher density or strength.

During product development, it is prudent to systematically evaluate the effect of MBP particulate properties on the properties of granules, tablet compaction, and dissolution preferably based on a statistically controlled experimental protocol to discern the interplay of the relevant interactions (Fig. 12.8). Due to the high polymeric content, the primary mode of compaction with amorphous materials is plastic deformation and as such the final compaction is sensitive to the dry granulation conditions (Herting and Kleinebudde 2008).

The impact of particle size on dissolution can be illustrated as follows: three different particle sizes of MBP powders were produced, in the range of 10–100 μm. The dissolution profile of these three MBP "as is" particles was monitored as shown in Fig. 12.9. As expected from the Noyes–Whitney equation, the dissolution of finer particles was faster than the dissolution of larger particles. Using these three particle sizes of MBP powders, tablets were prepared to the similar hardness value to 200 KN. The dissolution profile of these three tablets is shown in Fig. 12.10. Surprisingly, tablets made of smaller MBP particles dissolve slower than the tablet made of large particles.

The confounding effect of MBP particle size on the dissolution of tablet is attributed to the bonding of smaller particles during compression, particularly during roller compaction, where particle bonding is more pronounced with smaller particle sizes of MBP than larger particle sizes of MBP. These observations further support the hypothesis that particle size of MBP influences aggregation and bonding of the amorphous particles when subject to mechanical and/or thermal stress. The smaller

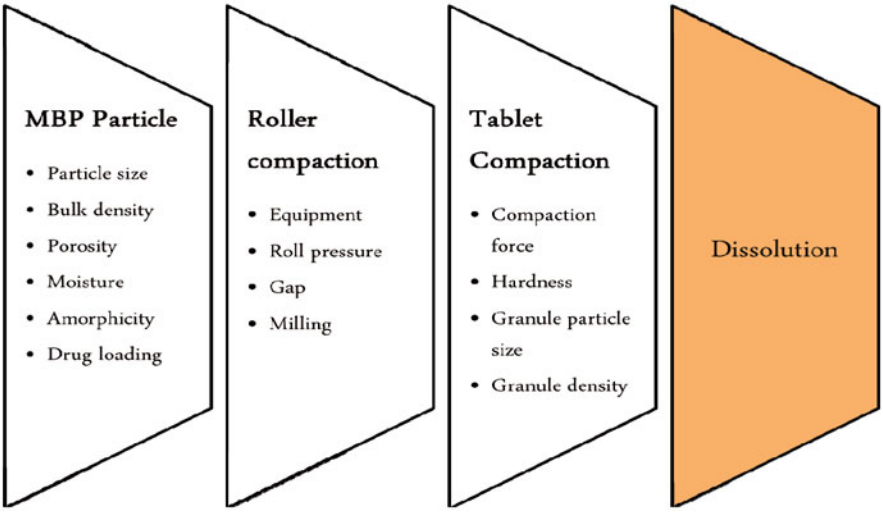


Fig. 12.8 Effect of MBP particulate properties on primary and secondary compression as well as dissolution

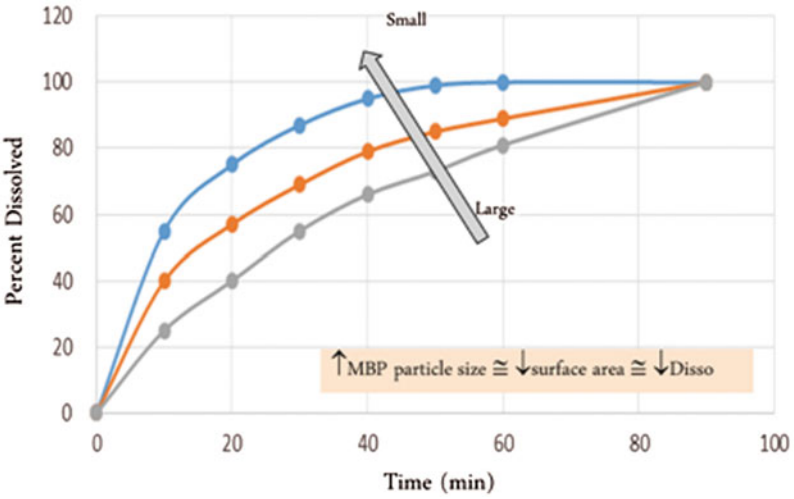


Fig. 12.9 An illustration of the effect of MBP particle size "as is" on dissolution

particles tend to exhibit a greater degree of sensitivity to external stress, resulting in comparably slower dissolution.

Both densification and compaction, being energy intensive processes, are sensitive to the physico-mechanical properties of the powders, more so in case of amorphous form. Bruno and colleagues showed that the dynamic indentation hardness of compacts of amorphous drug particles was approximately 30 % higher than that of

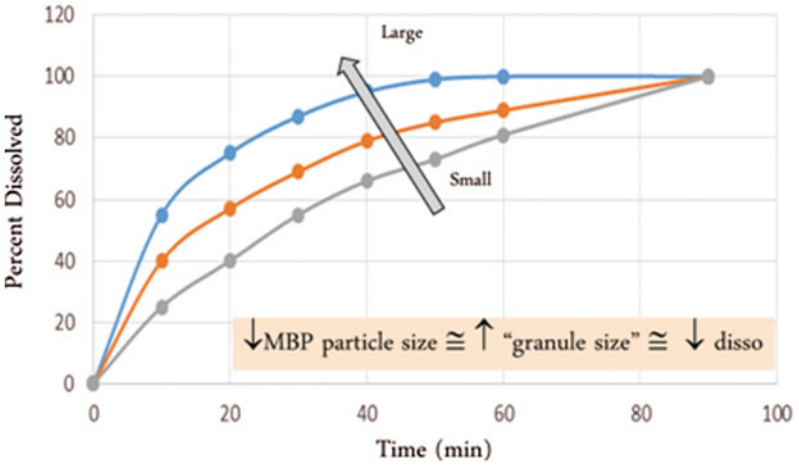


Fig. 12.10 An illustration of the effect of MBP particle size on dissolution of "Final Tablet"

crystalline particles of the same drug (Hancock et al. 2002). This suggests that the amorphous particles are prone to aggregation and fusion under mechanical stress. It may be hypothesized that when subjected to a high degree of compressive stress, the fused amorphous particles could form a hard surface that resists indentation. By the same token, it is possible that the ASD manufactured by different technologies can exhibit similar amorphous stability but behave differently under mechanical stress. The differences in the compactibility of ASD manufactured by spray drying versus melt extrusion have been recognized and studied extensively with a goal to improve the compaction properties of the melt-extruded products. Interestingly, similar results were observed when MBP was compared to spray-dried solid dispersions. In a compaction comparison study, two ASDs of an investigational compound were manufactured by MBP and by spray drying processes using the same polymer and drug loading. The tablets manufactured using MBP ASD exhibited several fold higher hardness than the tablets manufactured using spray-dried ASD. The difference in the mechanical properties can be attributed to the porosity of the MBP ASD.

12.4.4 Effect of Moisture Content and Crystallinity on Dissolution of MBP

The effect of moisture on the physical stability of ASD and its impact on dissolution is one of the most widely researched topics in the ASD literature (Simonelli et al. 1969; Hancock and Zografi 1994; Rumondor and Taylor 2010; Raina et al. 2013; Sarode et al. 2013). Reversion of amorphous systems to crystalline state occurs primarily as a function of temperature, water content, and storage time. Moisture can adversely impact stability of amorphous materials by lowering glass transition

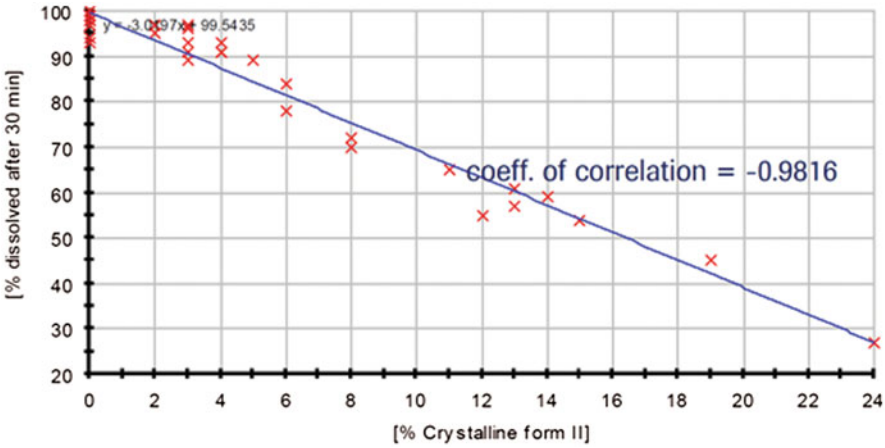


Fig. 12.11 Effect of crystalline content of Compound "Z" MBP on drug release (Shah et al. 2012)

temperature, thereby inducing mobility of the drug leading to phase separation, nucleation, and eventually crystallization. The moisture content in the MBP ASD is primarily controlled by its initial moisture content, the storage, and packaging conditions. Similar to the effect of aqueous wet granulation on product stability discussed in previous section, the MBP ASD also shows sensitivity to moisture during storage. A good correlation was observed between water content and the crystallinity in MBP ASD. In the authors' experience (unpublished work), the percent crystallinity of ASD was seen to increase with the moisture content up to a certain threshold value in a nonlinear fashion. Depending on the hygroscopicity and the crystallization tendency of the compound, the threshold moisture content above which MBP is significantly destabilized is generally between 3 and 10 %. The percent crystallinity in the ASD in turn is related to the dissolution performance of the product. For example, to investigate the effect of crystallinity, the percent drug dissolved at 30 min was plotted against percent crystallinity determined by pXRD (Fig. 12.11). As shown for Compound "Z," the percent dissolved was 90% or higher at crystallinity up to 4 %, but decreased linearly with percent increase in crystallinity beyond that level (Shah et al. 2013).

12.5 Case Studies of MBP of Poorly Soluble Drugs

The MBP process has been applied to numerous research compounds, enabling progression from preclinical to clinical stage. Examples of a few cases are presented in this section. The compounds were unsuitable for processing into ASD by spray drying or hot-melt extrusion due to either high melting point, thermal instability, or inadequate solubility in volatile solvents. The excerpts from these case studies

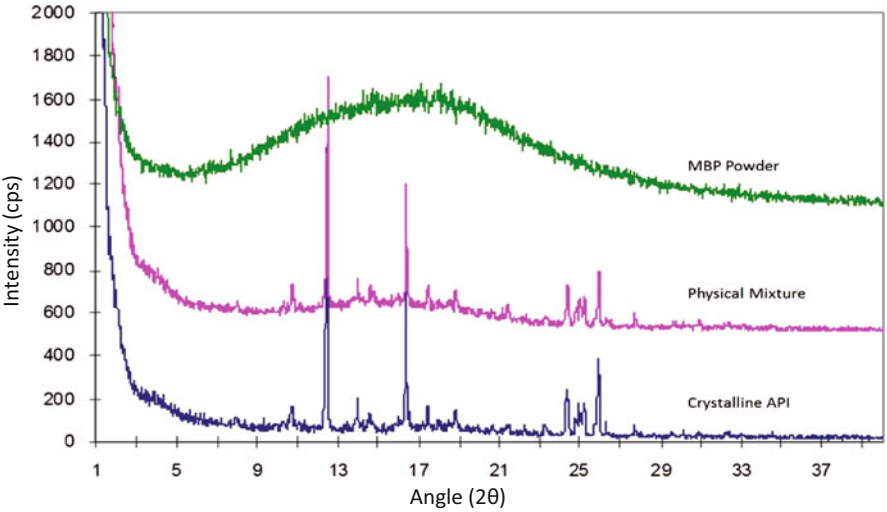


Fig. 12.12 pXRD of crystalline drug, physical mixture, and MBP of Drug A

are presented to demonstrate the application of MBP technology and highlight the relevance of various factors that ensure successful implementation of processes.

12.5.1 MBP Case A

Drug A has a high permeability but has very poor water solubility of < 1 μg/mL. Bioavailability in preclinical animal models was very low, 4 % in dogs and 9 % in rats. Nanomilling and lipid formulation did not provide acceptable exposures to move forward. Amorphous formulation approach using spray drying and hot-melt extrusion turned out not to be readily amenable to these processes, owing to poor solubility and thermal instability. Microprecipitation technology was employed to make amorphous solid dispersion of Drug A. MBP prescreening with polymers identified Eudragit L-100 as the best match for the physicochemical properties of the drug. Amorphicity by pXRD of MBP ASD is shown in Fig. 12.12 together with crystalline API and physical mixture of the same composition for comparison (Fig. 12.12). A drug load of up to 50 % was achieved, which was quite remarkable (Shah et al. 2012). Ability to achieve high drug loading was attributed to good miscibility of drug with Eudragit L-100 polymer, enhanced drug–polymer interaction, and the inherent versatility of the MBP process.

As Drug A was relatively non-hygroscopic compared to the polymer, the moisture sorption behavior of the MBP was in between that of pure drug and polymer as seen in Fig. 12.13.

The drug release profile of MBP ASD was compared to that of crystalline form using the United States Pharmacopoeia (USP) dissolution apparatus at a pH of 6.8.

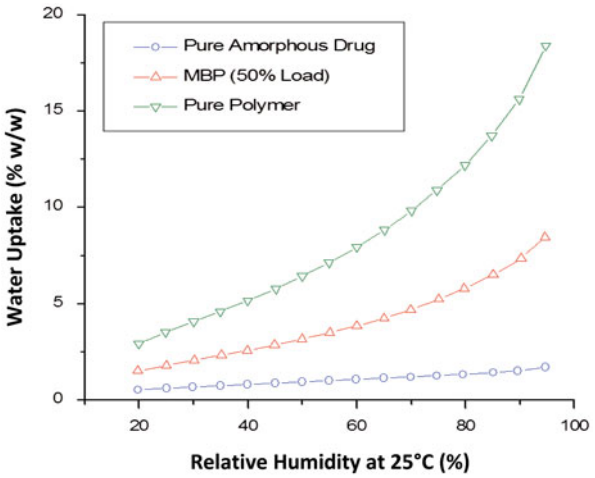


Fig. 12.13 Sorption Isotherm of MBP, polymer, and free form of Drug A. (Shah et al. 2012)

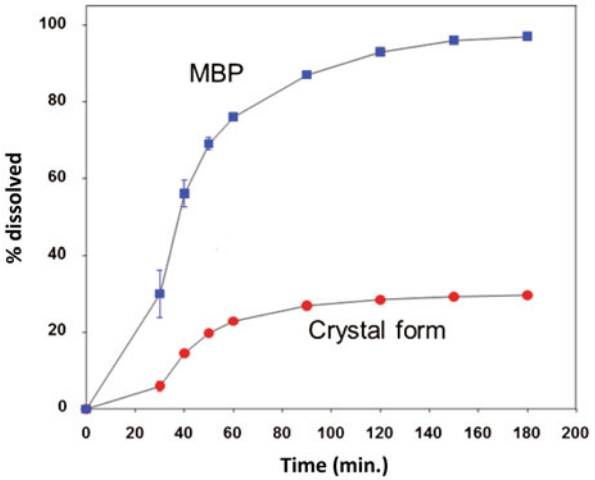
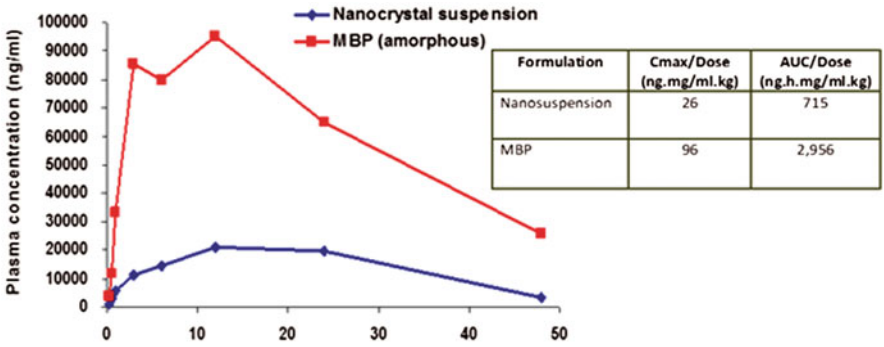


Fig. 12.14 Dissolution profile of crystalline form and MBP of Drug A. (Shah et al. 2012)

More than 80 % of drug was released from MBP ASD in 30 min, whereas about 30 % of drug was released from crystalline drug in the same time period. Moreover, MBP ASD maintained supersaturation for more than 3 h as demonstrated in Fig. 12.14.

In a dog PK study, the MBP provided 85 % bioavailability compared to 10 % for a crystalline nanosuspension formulation at an oral dose of 10 mg/kg (Shah et al. 2012). This product was evaluated in several clinical studies and was shown to provide a prolonged plasma release profile with MBP resulting in improved tolerability (Salazar et al. 2004), suggesting that the slow release of drug from the enteric polymeric matrix provides sustained release.



Formulation	Cmax/Dose (ng.mg/ml.kg)	AUC/Dose (ng.h.mg/ml.kg)
Nanosuspension	26	715
MBP	96	2,956

Fig. 12.15 Rat PK profile of nanocrystal formulation and MBP of Drug B

12.5.2 MBP Case B

Drug B has an aqueous solubility in the range of 3–10 μg/mL and provided inadequate exposures during preclinical studies. MBP was developed with an enteric polymer and compared against a nanocrystal suspension formulation in a rat PK study at 1000 mg/kg. A higher than fourfold increase in absorption was observed with MBP as compared to the crystalline form (Fig. 12.15).

12.5.3 MBP Case C

The dosage form development of drug C was very challenging because not only was the solubility poor with resultant poor bioavailability but also the plasma exposure levels of drug were very sensitive to the dosage regimen and frequency of dosing. An MBP formulation was developed and compared against a nanocrystalline suspension at a dose of 30 mg/kg in rat. The area under the curve (AUC) of MBP was about tenfold higher than crystalline form and was comparable to that of a cyclodextrin-based solution formulation.

Interestingly, MBP ASD prepared with Eudragit L-100 55 provided threefold higher AUC than that of MBP ASD prepared with HPMC-AS under similar dosing levels as shown in Fig. 12.16. This can be attributed to the specific drug and polymer interaction amongst other factors.

12.5.4 MBP Case D

Drug D had a high log P resulting in good lipophilicity for absorption; however, its solubility was extremely low at $<<1$ μg/mL resulting in the need for formulation

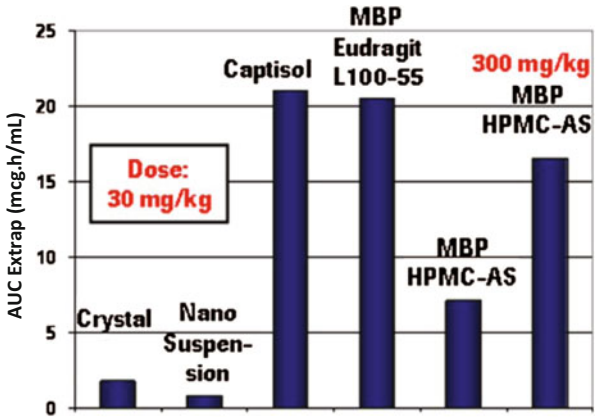


Fig. 12.16 Rat PK data of crystalline formulations and MBP of Drug C

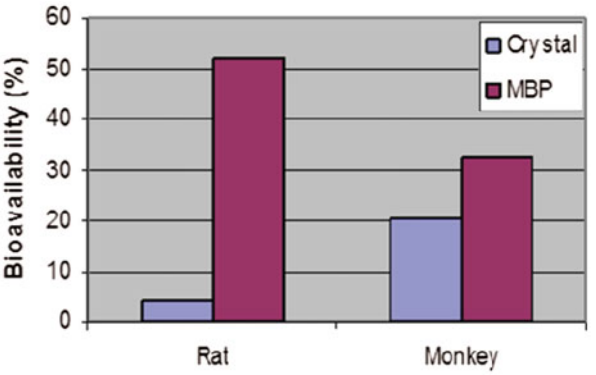


Fig. 12.17 Bioavailability of crystalline form and MBP of Drug D in rats and monkey

intervention. An MBP ASD was developed using HPMC-AS as the stabilizing polymer and it was evaluated in rat and monkey. The bioavailability was increased in the rat by more than tenfold and in the monkeys by more than 1.5 times compared to the crystalline form as shown in Fig. 12.17.

12.5.5 MBP Case E

Drug E is practically water insoluble ($<<1$ μg/mL) with a melting point above 270 °C. The solubility in common organic solvents such as acetone, alcohol, and acetonitrile was poor < 5 mg/mL at 25 °C, but in DMA the solubility was exceptionally high > 500 mg/mL. The development of MBP and its impact on bioavailability has been published elsewhere (Shah et al. 2013).

Amorphous solid dispersion using spray drying and hot-melt extrusion was not readily applicable due to the poor organic solubility and high melting point. MBP technology was applied to make the ASD. MBP prescreening identified HPMC-AS

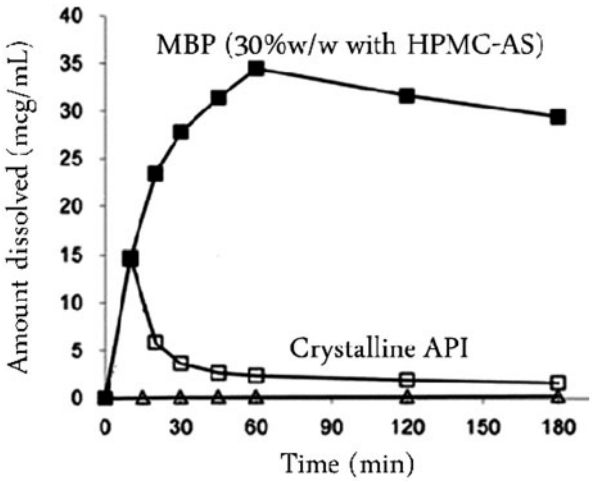


Fig. 12.18 Dissolution profile of crystalline form and MBP of Drug E (redrawn from Shah et al. 2013)

as a suitable polymer for Drug E. Further, miscibility study identified operable drug loading in the range of 30–40 %. ASDs with HPMC-AS were prepared using MBP technology and the resulting products were found to be pXRD amorphous upon preparation and storage under accelerated stress stability conditions of 40 °C/75 % RH for up to 6 months. The T_g values of amorphous Drug E and HPMCAS were 107 and 119 °C, respectively, while MBP ASD of 30 % Drug E exhibited a single T_g in the range of 100–110 °C, depending on residual moisture content in ASD (Shah et al. 2013).

The drug release profile from MBP ASD was compared against crystalline form (unstable crystalline form 1) using the USP dissolution apparatus and 900 mL of a pH 6.8 phosphate buffer medium (Fig. 12.18). A concentration of 35 μg/mL was achieved within 60 min and a supersaturation concentration of 30 μg/mL was maintained up to 3 h. The crystalline form (unstable crystalline form 1), on the other hand, exhibited an initial spike in concentration, which was immediately followed by a drop in concentration to the stable value of 1 μg/mL. Thus, about 20- to 30-fold increase in solubility (compared to unstable form 1) and maintenance of saturation levels was achieved with MBP (Shah et al. 2013).

In a relative bioavailability study comparing MBP formulations of Drug E against crystalline form (unstable crystalline form 1), the MBP formulations exhibited much higher exposures after a single dose of MBP compared to crystalline formulation, as seen in Fig. 12.19 (Shah et al. 2013). The relative bioavailability of the MBP formulations was four to fivefold higher than the crystalline formulation (capsule formulation). Furthermore, unlike the crystalline capsule formulation that reached a plateau at 600 mg dose, the exposure for MBP was dose-linear from up to 1200 mg.

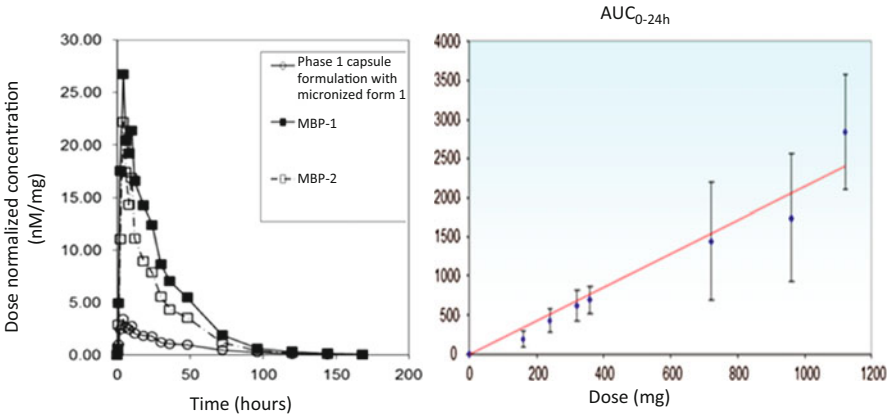


Fig. 12.19 Pharmacokinetic profile and dose-dependent increase in exposure observed with crystalline and MBP formulations of Drug E (Shah et al. 2013)

12.6 Summary and Conclusions

The MBP technology is well suited for compounds with poor solubility and high melting point, particularly when alternate ASD technologies such as spray drying and hot-melt extrusion are not readily applicable. This MBP technology has been employed to manufacture ASD of a number of poorly soluble drugs using stabilizing ionic polymers, mainly Eudragit L-100, L-100 55, and HPMC-AS. Drugs with high molecular weight, high melting point, low solubility (< 10 mcg/mL), and log P of greater than 3 seem to be highly suitable for MBP process. In all cases of MBP ASDs, the higher dissolution rate of the drug in MBP was translated into higher bioavailability and exposure in preclinical and clinical studies.

Application of MBP technique to diverse compounds has demonstrated the utility and the versatility of this technique. The MBP technique is highly adaptable to various manufacturing scales, from milligram quantities during preclinical research to hundreds of kilogram quantities in production phase with > 90 % recovery. As discussed in previous chapters, it is a material-sparing tool that can provide reproducible ASDs with superior performance, in some sense, compared to other ASD technologies for certain type of compounds. The material-sparing aspect is very important in the early stages of drug development to support animal studies when the drug supply is limited. Several research compounds have been scaled up from few milligrams to 100–1000 kg demonstrating that it is a scalable and robust process. The MBP technology can present a remarkable opportunity to advance certain poorly soluble compounds that otherwise would be considered undevelopable.

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