Chapter 9
Design and Development of HPMCAS-Based Spray-Dried Dispersions

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9.1 Introduction

Poor oral bioavailability due to the low aqueous solubility of potential drug candidates is an increasingly common challenge facing the pharmaceutical industry (Friesen et al. 2008). Nearly one third of compounds in early development have poor bioavailability due to low solubility, representing a significant loss in economic and therapeutic opportunity (Government Accounting Office (GAO) 2006). Although they may not fit Lipinski's "rule of five," many of these low-solubility compounds, which fall into classes II and IV of the biopharmaceutics classification system (BCS), have the potential to be safe and efficacious, so it is critical that their development is not halted by solubility limitations (Amidon et al. 1995). To address low active pharmaceutical ingredient (API) solubility, multiple drug delivery technologies have been advanced in an attempt to solubilize these molecules and enhance their oral bioavailability. Solubilization technologies can improve oral absorption of BCS class II compounds by:

1. Increasing solubilized drug levels (i.e., increasing the concentration of dissolved drug above the equilibrium concentration of the solubility of bulk crystalline drug)
2. Increasing dissolution rate
3. Sustaining the enhanced dissolved drug concentration in the intestinal milieu for a physiologically relevant time.

This chapter presents an overview of amorphous spray-dried dispersions (SDDs), which have been successfully used as a platform technology to enhance the oral bioavailability of hundreds of compounds with low aqueous solubility. SDDs can be prepared with several nonionic polymers, such as polyvinylpyrrolidone (PVP) and cellulosic polymers, as well as with ionic polymers, such as hydroxypropyl

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methylcellulose acetate succinate (HPMCAS-based and methacrylic-acid-, methyl–methacrylate-, and ethyl-acrylate-based copolymers. However, SDDs based on HPMCAS are highlighted, since this polymer has been found to have widespread utility for low-solubility compounds.[1]

We provide background information on past solubilization technologies and describe the attributes of HPMCAS that make it ideal for use as a dispersion polymer for SDD platform technology. Speciation theory, formulation and process selection methodology, and performance of amorphous HPMCAS-based SDDs are then described.

9.2 Background: Efforts to Enhance the Solubility of Pharmaceutical Compounds

Typically, solubilization technologies are used to achieve rapid dissolution and enhance drug concentrations in two ways: (1) By formulating the drug as a solution in which the drug is predissolved (e.g., lipid systems or self-emulsifying drug delivery systems, SEDDS) or (2) by formulating the drug as a high energy solid form (e.g., crystals formed by attrition, crystals formed by bottom-up nucleation and controlled growth, or amorphous forms formed by melting or solvent removal).

To improve the dissolution rate and solubility of a compound relative to its lowest energy crystal form, one general approach is the generation of an amorphous form, usually stabilized as an amorphous dispersion of the drug in a polymeric material. The major challenge for this approach is selecting the appropriate formulation and process to develop a high energy amorphous form that has adequate physical stability, and achieves and maintains an in vivo drug concentration that is well above the crystalline solubility.

In the 1960s and 1970s, a variety of reports described the use of solid solutions and dispersions of drugs with polymers and with small molecules to improve drug dissolution rate and bioavailability. In an early report, Sekiguchi and Obi (1961) presented data for a single human subject indicating that a eutectic mixture of sulfathiazole and urea resulted in higher blood levels than sulfathiazole alone. Goldberg et al. (1965) described the use of solid solutions of sulfathiazole with urea and chloramphenicol with urea that offered improved dissolution rate. In another study, Goldberg et al. reported the use of eutectic mixtures for this purpose (1966). Stoll et al. (1969, 1973) reported dissolution and bioavailability improvements using coprecipitates with bile acids.

Early reports on dispersions and coprecipitates with polymers were focused on the use of PVP (Chiou and Riegelman 1969, 1971; Simonelli et al. 1976). However, the mechanism of solubility enhancement with PVP was somewhat unclear, and in

[1] HPMCAS is also known as hypromellose acetate succinate and is commercially available from Shin-Etsu Chemical Company and The Dow Chemical Company.

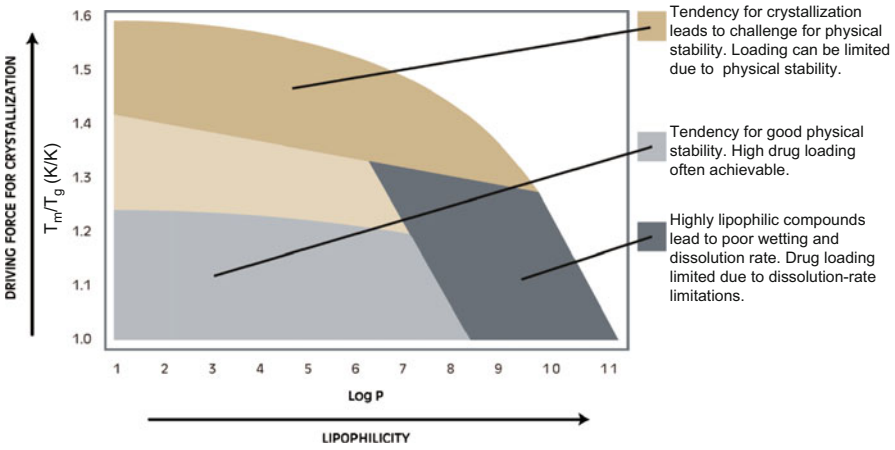

Fig. 9.1 SDD formulation guidance plot, showing the ratio of melting temperature (T_m) to glass-transition temperature (T_g) as a function of log P

fact, other reports described specific drug/PVP complexes designed to slow drug release in solution (Higuchi and Kuramoto 1954; Horn and Ditter 1982).

In other work, Chiou and Riegelman (1970) demonstrated enhanced canine oral absorption of griseofulvin in drug/polymer dispersions prepared by melting using polyethylene glycol (PEG) 6000. Many subsequent reports of drug/polymer dispersions have been published, and some have been summarized in excellent reviews by Serajuddin (1999), and Leuner and Dressman (2000).

9.3 SDD Formulation Selection and Manufacture

The selection of SDD formulations and manufacturing conditions can be conducted based on a rational methodology that relies on extensive experience with a wide variety of low-solubility compounds. The process for selecting the type of SDD formulation, polymer, and active loading is based on the product concept (dose and type, size, and number of dosage forms) and the properties of the compound. Guidance maps based on historical experience, such as the plot shown in Fig. 9.1, can be leveraged to formulate compounds of interest (Friesen et al. 2008). For example, experience has shown that compounds with a high tendency to crystallize (i.e., those with a T_m/T_g ratio > 1.4) will likely require higher dilution (lower active loading) in the polymer dispersion to achieve appropriate physical stability. Based on this information, formulation efforts should focus on lower active loadings, e.g., SDD containing 10 wt% active compound and 90 wt% polymer.

Once a formulation or formulations have been selected, manufacturing of homogeneous dispersions becomes the critical factor. Spray drying is a well-established and widely used industrial process for transforming solutions, emulsions, and suspensions of materials into dry powdered forms (Morgen et al. 2013). A general process configuration is shown in Fig. 9.2.

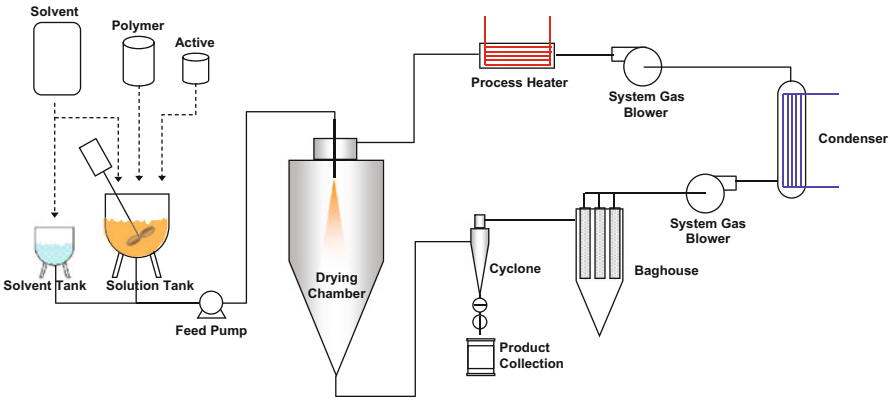

Fig. 9.2 General spray-drying process configuration

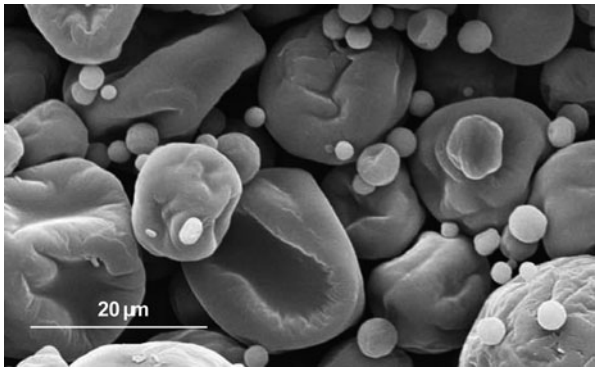

Fig. 9.3 SEM image of an HPMCAS-M SDD at 1500-fold magnification (Friesen et al. 2008)

In this process, a feed solution is prepared by dissolving drug and polymer (e.g., HPMCAS) in a volatile solvent and then pumping the solution to an atomizer inside a drying chamber. The atomizer breaks the solution into a plume of small droplets (typically, less than 100 µm in diameter). In the drying chamber, the droplets are mixed with a hot drying gas stream (typically, nitrogen for organic solvents). Heat is transferred from the hot drying gas to the droplets to provide the latent heat of vaporization required for rapid evaporation of the solvent from the droplets. As the solvent is removed from a droplet containing film-forming ingredients, a high-viscosity gel or "skin" forms on the outside of the droplet. Typically, at this stage of drying, the skin is sufficiently plasticized (due to the high solvent-to-solids ratio) that the particle skin collapses on itself as the solvent evaporates from the core, yielding particles with the "shriveled raisin" morphology shown in the scanning electron micrography (SEM) image in Fig. 9.3.

By controlling the temperature at the inlet and outlet of the spray dryer, along with the rate at which spray solution and drying gas are introduced to the spray dryer, the morphology, particle size, and density of the resulting SDD powder can

be controlled. The solid powder is typically collected from the gas stream using a cyclone or filter system.

Based on an evaluation of the physicochemical properties of the active compound, several initial formulations (generally, four to six) are selected and screened in this step (Dobry et al. 2009). A small-scale spray dryer designed for maximizing yields from SDD batches of less than 100 mg is used. This dryer is not designed to replicate optimized bulk powder properties (e.g., particle size, density) of larger scale spray dryers, but rather is used to guide formulation decisions based on physicochemical properties and fast, efficient formulation-screening studies.

Process and formulation selection flowcharts, which refer predictive physical stability models, rapid chemical stability screens, and biorelevant in vitro performance tests, are used to select a lead SDD formulation (including the drug/polymer ratio) and process parameters (Dobry et al. 2009).

Additional formulation information is gathered during this stage of product development, including preferred spray solvents and spray solution solids content. At the end of this step, a robust formulation has been selected based on fundamental physicochemical properties. Typically, the entire formulation-screening step can be completed with 200–400 mg, and sometimes as little as 100 mg of active compound. The formulation and process development flowchart methodology uses time and resources similar to those required for conventional immediate-release crystalline formulations. The methodology, which is based on fundamental engineering models and state-of-the-art process characterization tools, is an alternative to traditional empirical spray-drying process development methods, and results in streamlined and robust process development.

Using a quality-by-design (QbD) approach, formulation and process are linked through identification of critical quality attributes (CQAs) and key quality attributes (KQAs), which are related to critical process parameters (CPPs) and key process parameters (KPPs). CQAs, KQAs, and CPPs are defined in criticality and risk assessment (Babcock et al. 2009). Using this methodology, process development is focused on the selection of spray-drying process parameters that result in the desired KQAs (e.g., particle size and density) and process performance (e.g., yield) with minimal impact on the CQAs of bioperformance and stability. This model-based process development represents a QbD approach that lays the groundwork for continuous improvement and eventual design space process regulatory filings. This approach is in alignment with the FDA's current guidance on pharmaceutical development (US Food and Drug 2008; Pharmaceutical Development Q8, Revision 1).

9.4 HPMCAS Attributes for Use in SDD Platform Technology

HPMCAS has been identified as a particularly effective polymer for preparing SDDs of low-solubility drugs. HPMCAS-based SDDs have proven broadly applicable at improving the oral exposure of low-solubility compounds by (1) enhancing aqueous solubility compared with bulk crystalline drug, (2) enhancing the dissolution rate

relative to bulk crystalline drug, and (3) sustaining the enhanced solubility in the intestinal milieu for a physiologically relevant time.

SDDs are often formed using HPMCAS in its unionized (protonated) form which is quite soluble in volatile organic solvents, such as methanol and acetone. Since many drug candidates are soluble in these solvents, they can be processed into HPMCAS-based SDDs readily and economically using spray drying.

Curatolo et al. (2009) described a large study in which HPMCAS was compared to other common dispersion polymers using in vitro solution performance. This work showed that among the dispersion polymers studied, HPMCAS was the most effective in achieving and maintaining drug supersaturation. HPMCAS-based SDDs achieved and maintained drug supersaturation in vitro more consistently and effectively than SDDs prepared with other polymers. In addition, dispersions prepared by spray drying (i.e., SDDs) had better homogeneity and better performance than dispersions prepared by a rotary evaporation process, presumably due to the significantly faster drying kinetics in the spray dryer.

HPMCAS has unique attributes that make it ideal for use in SDDs, as described by Friesen et al. (2008). These attributes include the following:

(1) A high T_g in its unionized state. This high T_g results in low drug mobility, which is responsible for the excellent physical stability of HPMCAS SDDs. The T_g also remains relatively high at elevated relative humidity (RH).
(2) Solubility in volatile organic solvents, such as acetone and methanol, allowing for economical and controllable processes for preparation of SDDs.
(3) When the polymer is at least partially ionized (as it is at any pH above approximately 5), the charge on it minimizes the formation of large polymer aggregates, stabilizing drug/polymer colloids (e.g., amorphous nanostructures).
(4) The amphiphilic nature of HPMCAS allows insoluble drug molecules to interact with the hydrophobic regions of the polymer, whereas the hydrophilic regions of the polymer ensure these structures will remain as stable colloids in aqueous solution.

HPMCAS is a cellulosic polymer with four types of substituents semi-randomly substituted at the saccharide hydroxyls:

- Methoxy, with a mass content of 12–28 wt%
- Hydroxypropoxy, with a mass content of 4–23 wt%
- Acetate, with a mass content of 2–16 wt%
- Succinate, with a mass content of 4 –28 wt% (National Formulary (NF) 2006).

The succinate groups of HPMCAS have a logarithmic acid dissociation constant (pKa) of about 5, so the polymer is less than 10 % ionized at pH values below approximately 4 and is at least 50 % ionized at pH values of approximately 5. Due to the presence of relatively hydrophobic methoxy and acetate substituents, HPMCAS is insoluble in water when unionized (i.e., at pH values < approximately 5) and remains predominantly colloidal at intestinal pH (i.e., at pH values of 6.0–7.5).

Traditionally, three grades of HPMCAS have been sold commercially, designated –L, -M, and –H, as illustrated in Fig. 9.4. The approximate pH values above which

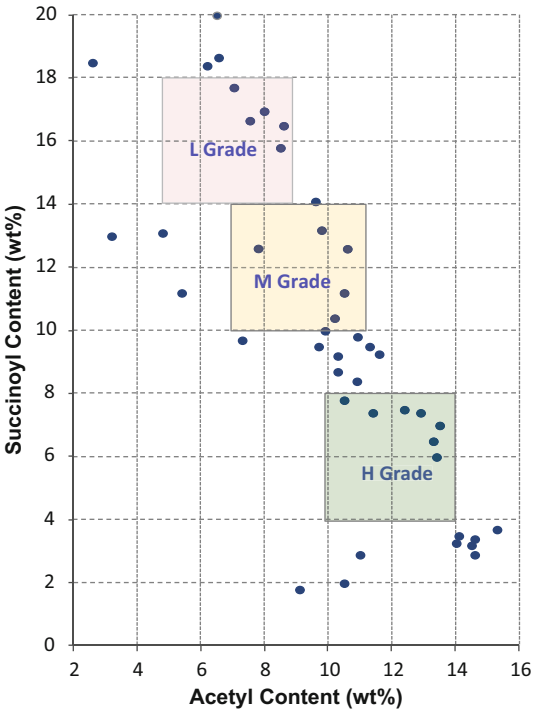

Fig. 9.4 Degree of substitution map for HPMCAS, showing the three commercially available grades of HPMCAS and other substitutions sampled in an R & D setting that fall within the US Pharmacopeia (USP) specification for HPMCAS, but outside the supplier specifications for the individual grades

each grade becomes aqueous dispersible or soluble are 6.8 (-H grade), 6 (-M grade), and 5.5 (-L grade).

HPMCAS contains several hydrophobic substituents. As a result, even when HPMCAS is ionized, as it is at intestinal pH, the polymer is only sparingly soluble, and exists predominantly as colloidal polymer aggregates in aqueous solutions. The negative charge of the ionized succinate groups ensures the colloids will remain stable, avoiding large hydrophobic aggregates of the polymer in aqueous solution.

This colloidal nature of HPMCAS when ionized, combined with the hydrophobic nature of the substituents on the polymer, allows insoluble drug molecules to interact with the polymer to form amorphous drug/polymer nanostructures in solution. These drug/polymer nanostructures constitute a high energy ("high solubility") form of amorphous drug that is quite stable for hours or days and, in selected cases, for weeks in aqueous suspensions. In vitro measurements have shown that drug in these nanostructures can rapidly dissolve to provide a high free drug concentration that is supersaturated relative to bulk crystalline drug.

In vivo, drug partitions into bile salt micelles and is absorbed from the intestine into systemic circulation. Additional drug can subsequently be rapidly sourced from these nanostructures to maintain a supersaturated free drug concentration. These properties ultimately lead to the enhanced absorption observed when HPMCAS-based SDDs are dosed orally.

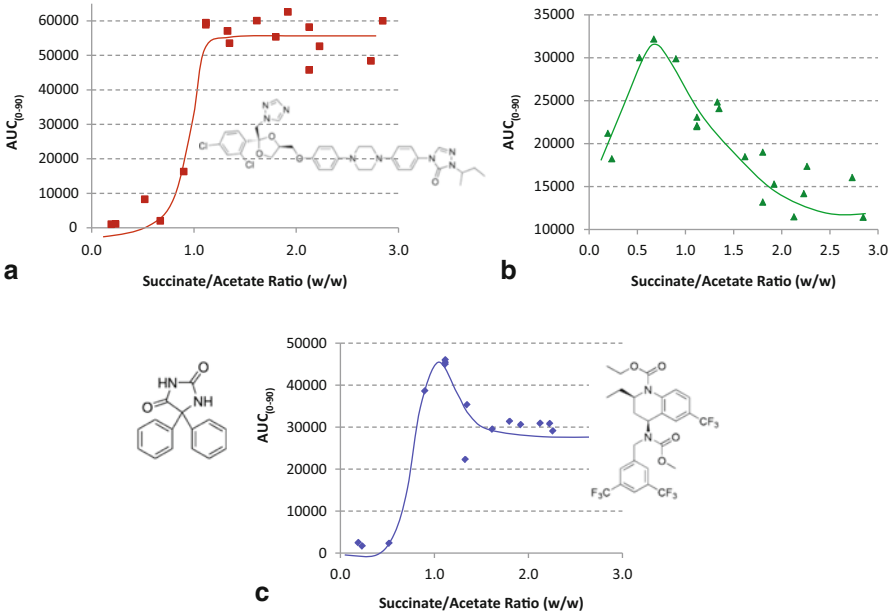

Fig. 9.5 Effect of succinate/acetate ratio on the HPMC backbone on the in vitro performance of SDDs prepared for three model compounds: itraconazole (**a**), phenytoin (**b**), and torcetrapib (**c**)[2]

Recent work has shown that the in vitro performance of SDDs can be optimized by altering the succinate/acetate ratio on the hydroxypropoxy methylcellulose (HPMC) backbone (Morgen et al. 2013). Figure 9.5 shows how small changes in the hydrophilic to hydrophobic substitution profiles, i.e., the succinate/acetate ratio, can be used to maximize in vitro performance for three low-solubility-model compounds, and illustrates that a specific optimal ratio can be identified for an individual active compound. This work illustrates the rich opportunity that exists to develop new functional excipients that are optimized for the performance of specific classes of molecules (Vodak 2013).

9.5 Speciation of HPMCAS-Based SDDs

When added to an aqueous solution simulating the environment of the small intestine, SDDs rapidly dissolve and/or disperse to produce a wide variety of species that facilitate absorption. To enhance the bioavailability of poorly soluble drugs, fundamental understanding of the drug species formed and the mechanism of action of SDDs is essential. Two general routes of HPMCAS SDD dissolution and drug speciation have been observed, which seem to bracket the behavior for most SDDs that have been studied. The two mechanisms of action—referred to as nanoparticle formation and erosion, respectively—are illustrated in Fig. 9.6a and 9.6b, respectively, and

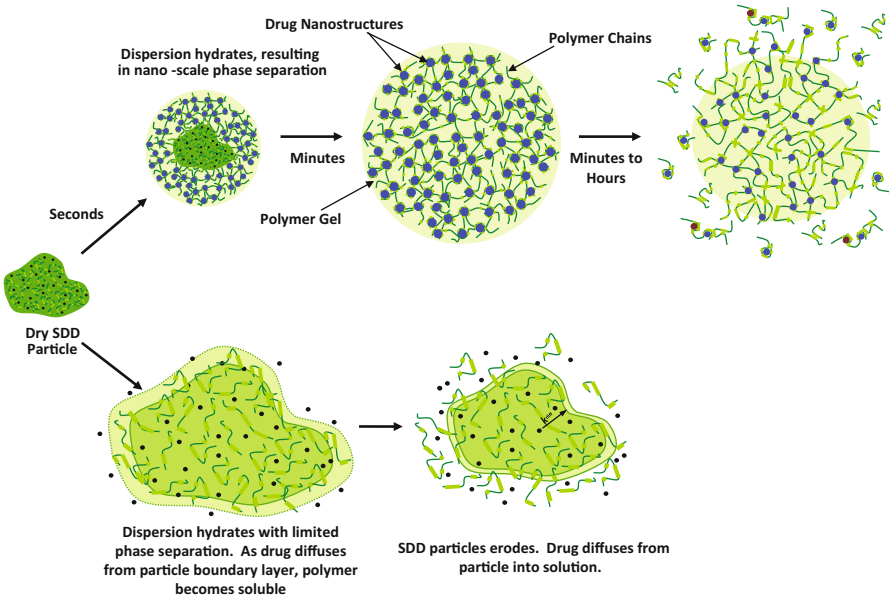

Fig. 9.6 Illustration of two SDD dissolution mechanisms and formation of drug–containing species critical to in vivo performance: nanoparticle formation (**a**) and erosion (**b**)

are described below. We also describe the species present during these dissolution mechanisms and test methods used to determine their presence.

9.5.1 Nanoparticle Formation Mechanism

In the first dissolution mechanism, the drug has limited solubility in the polymer and the solubility decreases upon absorption of water in biorelevant media. As the water enters the SDD particle, two factors, decreased drug solubility in the polymer and increased overall mobility of the components in the dispersion, lead to spinodal phase separation. The drug phase separates into drug-rich nanodomains that break off from the larger SDD particle and produce high energy amorphous nanoparticles. HPMCAS in its ionized state can then act as a surface stabilizer to the drug-rich nanoparticles. The same effect can be achieved using nonionic polymers with the addition of a surfactant in the formulation. Due to their small size (20–300 nm), these nanoparticles can rapidly source free drug that crosses the intestinal epithelial wall or partitions into bile salt micelles. It is believed that these nanoparticles also have a stabilizing influence in inhibiting rapid precipitation of drug from the supersaturated state in the intestine. This mechanism is illustrated in Fig. 9.7 with images that show the different stages of dissolution.

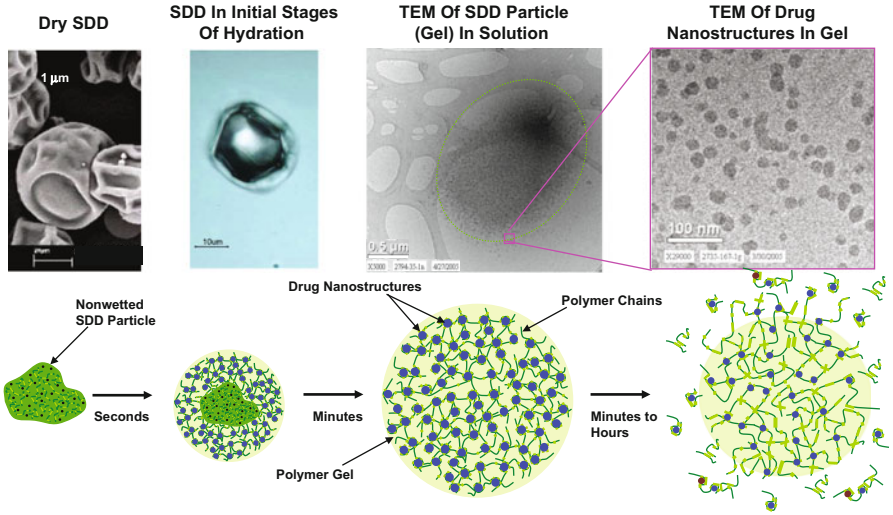

Fig. 9.7 SDD dissolution via the nanoparticle formation and dissolution mechanism

9.5.2 Erosion Dissolution Mechanism

In the erosion mechanism, the SDD particle does not disintegrate, but rather erodes from the surface to generate supersaturated free drug species and dissolved polymer chains. Typically, no nanoparticles are formed when this mechanism occurs, and performance usually is tied to the size and surface area of the particles, since the mechanism is a surface phenomenon.

Generally, this type of dissolution mechanism is observed when (1) the formulation has a high drug loading (> 35 % active), (2) the drug has high solubility in the polymer, or (3) the drug solubility in the polymer increases as the water content of the SDD increases. This mechanism is illustrated in Fig. 9.8, with images that show the different stages of dissolution. Note in the SEM image, which was taken after the dissolution test, the "shriveled raisin" morphology of the original SDD particles remains.

9.5.3 Dissolution Species

For convenience in characterizing and comparing the species formed by SDDs under various conditions, we have divided these species, based on their size and composition, into the following seven classes: (1) free or solvated drug, (2) drug in bile-salt micelles, (3) free or solvated polymer, (4) polymer colloids, (5) amorphous drug/polymer nanoparticles, (6) large amorphous particles (i.e., "precipitate"), and (7) drug crystals, can be observed when things are improperly formulated.

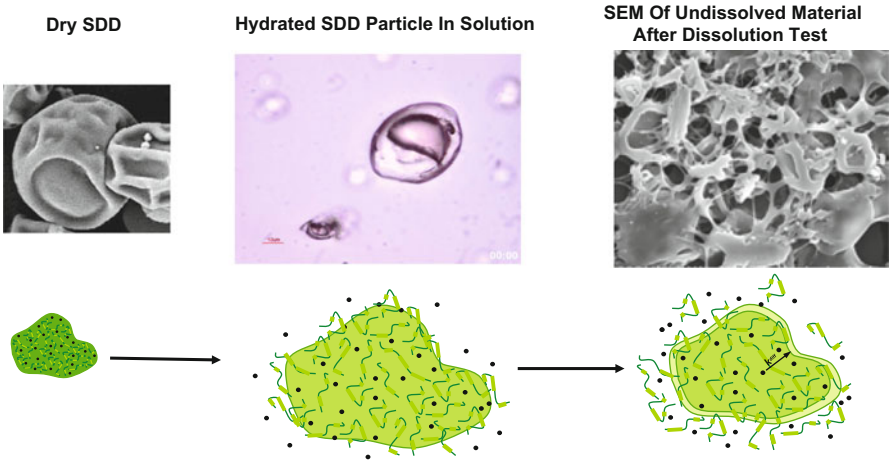

Fig. 9.8 SDD dissolution via the erosion mechanism

9.6 Testing Methods

To understand the performance of each SDD, a number of characterization tests have proven useful to measure and quantify individually the drug species that are present. In early development, bulk sparing methods are critical, due to the cost and limited quantities of drug compound available.

Two types of bulk sparing in vitro methods are described: (1) the centrifugal dissolution tests and (2) the membrane permeation test. These tests are used to identify the critical performance attributes of the system that are important to improve absorption and to rank the relative performance of SDD formulations.

9.6.1 Centrifugal Dissolution Tests

Centrifugal dissolution tests are used to measure the capability of SDDs to increase dissolution rate and levels of solubilized drug relative to crystalline drug. One key measure is the ability of SDDs to supply and sustain high energy, neutrally buoyant drug/polymer nanoparticles (Friesen et al. 2008; Curatolo et al. 2009). These nanoparticles are important because they can rapidly and continually source free drug during absorption.

The microcentrifuge dissolution test measures total drug arising from several species in solution, separated based on size and density: free drug ([D_{free}]), drug in bile-salt micelles ([$D_{micelles}$]), and drug in drug/polymer nanoparticles ([DPN]). The total drug ([D_{total}]) measured is:

$$[D_{total}] = \left[D_{free}\right] + [D_{micelles}] + [DPN]. \tag{9.1}$$

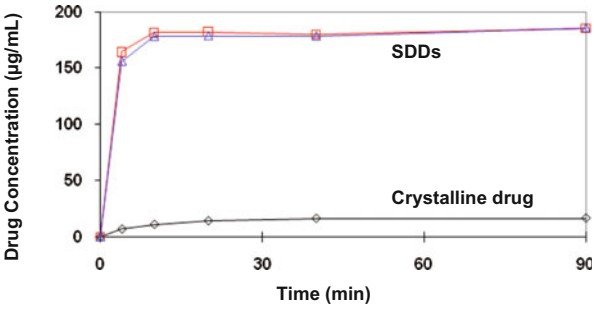

Fig. 9.9 Representative microcentrifuge dissolution results for a model compound comparing two HPMCAS-based SDDs and bulk crystalline drug

In this test, samples are dosed with suspension vehicle. Sample is weighed into a centrifuge tube, suspension vehicle is added, and the tube is vortexed to mix the sample with suspension vehicle. At each time point, the tubes are centrifuged at 13,000 g for 1 min. This step pellets any undissolved solids that are too dense to remain buoyant in the aqueous medium, predominantly undissolved SDD and API that precipitates or crystallizes. High-performance liquid chromatography (HPLC) is used to analyze aliquots of the supernatant for [D_{free}], [$D_{micelles}$], and [DPN].

These species often form rapidly when an SDD is added to simulated intestinal media. As illustrated in Fig. 9.9 for a model compound, the dissolution rate of SDD particles is at least two orders of magnitude faster than that of bulk crystalline drug. As the figure shows, the SDDs dissolve completely within 3 min, whereas the crystalline drug requires approximately 60 min to reach its equilibrium solubility.

The microcentrifuge test may also be used in conjunction with an ultracentrifuge test to generate additional size separation data, allowing separation of drug in nanoparticles from free drug and drug partitioned into bile salt micelles.

As Fig. 9.10 shows, the microcentrifuge test is also used (1) to quantify precipitation inhibition for compounds that rapidly crystallize and (2) to compare dissolution rates for SDDs of more lipophilic compounds, which tend to dissolve more slowly as particle size increases during process scale-up. A simulated gastric exposure step before dissolution in simulated intestinal media can also be added. This option is useful when evaluating weakly basic compounds that have pH-dependent solubility (Mathias et al. 2013).

9.6.2 Membrane Permeation Test

The membrane permeation test is another bulk sparing in vitro dissolution technique. It was developed at Bend Research and has been used for more than a decade (Babcock et al. 2009). This biphasic dissolution test is designed to assess the ability of a formulation to rapidly establish a high free drug concentration and then sustain that concentration for a physiologically relevant time period.

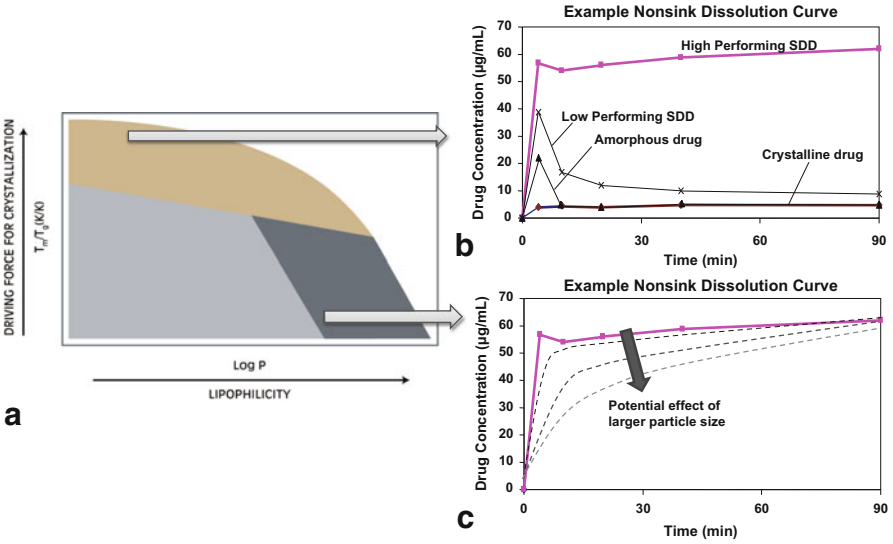

Fig. 9.10 Representative drug properties and data for a wide range of SDD formulations from a solubilization technology map (**a**), showing how the microcentrifuge test can be used to quantify precipitation inhibition (**b**), and to show negative impacts on dissolution rate for properties such as increased particle size (**c**)

The membrane permeation test measures the flux of drug across a synthetic membrane into an organic sink (permeate). For the test, a synthetic semipermeable membrane is used to separate the feed solution (i.e., simulated intestinal medium) and permeate (sink) solution (e.g., 80 % decanol and 20 % decane, by weight). Aliquots of permeate are taken at specific time points and the concentration of drug is measured by HPLC. High flux indicates a formulation's ability to rapidly dissolve and source a high concentration of free drug.

In the membrane permeation test, only free drug molecules from the feed solution can diffuse into the sink permeate. The test is intended to simulate the in vivo situation in which rapid passive diffusion of lipophilic molecules across the intestinal membrane occurs. In this situation, the ability of a formulation to establish a high level of free drug and its ability to maintain that level of free drug are critical formulation attributes for improved absorption. While the membrane permeation test does not enable the correlation of in vitro/in vivo performance, this test is useful in ranking the relative performance of SDDs. Representative results for the membrane permeation test is shown in Fig. 9.11, which compares results for an HPMCAS-based SDD formulation to that of bulk crystalline drug for a model compound. When combined with data from other in vitro dissolution tests (e.g., the microcentrifuge dissolution test), the results give mechanistic insight into relative formulation performance.

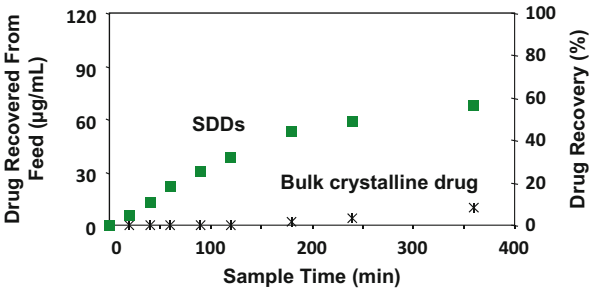

Fig. 9.11 Representative membrane permeation test results for a model compound comparing an HPMCAS-based SDD and bulk crystalline drug

9.7 Performance of the SDD Platform

SDDs have a proven track record for improving bioavailability for BCS II or IV compounds. Many in vivo studies have been performed in preclinical animal models and in human clinical studies demonstrating the enhancement. The following section describes some of these in vivo results, as well as an approach to understand the physical stability of these high energy formulations.

9.7.1 SDD Performance In Vivo

More than 500 different drugs have been formulated as SDDs at Bend Research and tested in various animal models.[2] Absorption enhancement relative to crystalline drug ranges from around 1.5-fold to nearly 100–fold, but varies widely based on the dose and drug properties. Figure 9.12 shows representative preclinical in vivo data for BCS class II compounds.

In addition, SDDs of 65 different drugs have been successfully tested in humans.[4] In all cases, the fraction of dose absorbed was at least twofold higher for the SDD than for the poorly absorbed control formulation. Figure 9.13 shows representative results from human clinical studies for BCS class II compounds.

As the data in Figs. 9.12 and 9.13 show, in cases where the crystalline drug (or comparison formulation) is poorly absorbed, the average AUC enhancement is approximately tenfold higher for SDDs dosed orally.[3]

[2] Numbers are much higher for global testing experience.
[3] The enhancement over bulk crystalline drug is lower in cases where the crystalline drug control is moderately well absorbed.

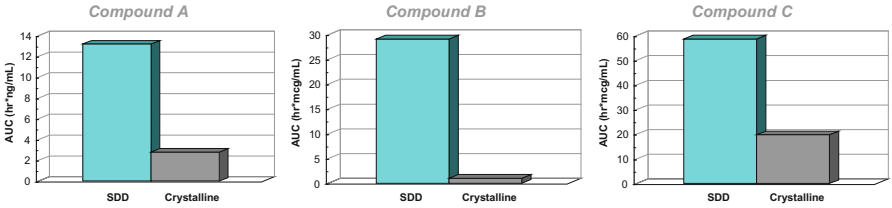

Fig. 9.12 Representative preclinical in vivo data, illustrating enhanced bioavailability of BCS class II compounds for SDDs relative to bulk crystalline drug

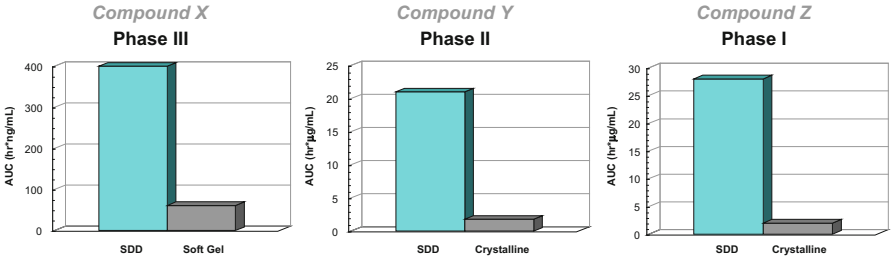

Fig. 9.13 Representative clinical data illustrating enhanced bioavailability of BCS class II compounds for SDDs relative to bulk crystalline drug or soft-gel formulations

9.7.2 Stability

HPMCAS SDDs have demonstrated long-term kinetic physical stability, routinely demonstrating shelf lives of more than 2 years under standard storage conditions. This is due, in part, to the high T_g of the polymer, and the resulting high T_g of the HPMCAS-based SDDs. As described below, T_g is a primary indicator of SDD physical stability.

In its unionized state (as it is in the solid SDD before dissolution), HPMCAS has a high T_g, even when exposed to high RH. Figure 9.14a shows the T_g for three commercially available grades of HPMCAS that had been equilibrated with air having varying RH.[6,7] Under dry conditions, the T_g is on the order of 120 °C. Like all amorphous materials, when exposed to humid air HPMCAS absorbs water, which plasticizes the polymer, increasing its mobility. This is reflected in the decrease in its T_g. However, the relative hydrophobicity of HPMCAS results in absorption of much less water than for typical water soluble polymers. Figure 9.14b shows dynamic vapor sorption (DVS) data taken at 25 °C for selected polymers. At 75 % RH, PVP and HPMC absorbed approximately 23 wt% and 10 wt% water, respectively, whereas HPMCAS absorbed only about 6 wt% water. As a result, the T_g value of HPMCAS remained above about 70 °C, even when equilibrated with 75 % RH air (Friesen et al. 2008). The low mobility of drug molecules dispersed in such high T_g glassy polymers leads to the excellent physical stability observed for HPMCAS-based SDDs.

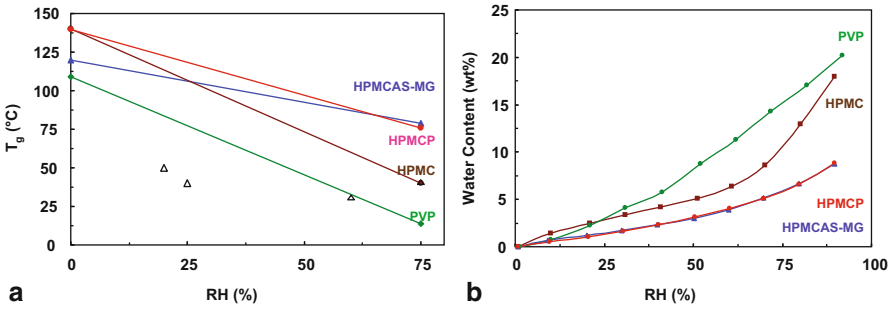

Fig. 9.14 Effect of RH on HPMCAS, PVP, HPMC, and hydroxypropyl methylcellulose phthalate (HPMCP): T_g versus the RH to which samples were equilibrated at ambient temperature for representative polymers (**a**), and equilibrium water absorption versus RH measured at 25 °C (**b**)

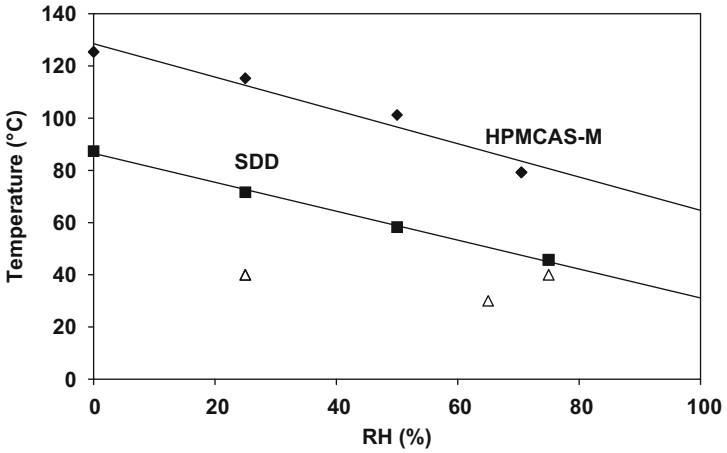

Fig. 9.15 Tg of a 25wt%-HPMCAS-based SDD and HPMCAS alone as a function of RH at 25 °C. Key: lines are least-square fits to the data and triangle data points show typical storage conditions

Figure 9.15 shows the T_g for a 25-wt%-drug-loaded HPMCAS-M SDD as a function of the RH of air to which it was equilibrated (at ambient temperature, about 22 °C). As the figure shows, the T_g of the SDD is high, well above the typical storage temperatures for RH values, up to about 60 % RH. As a result, drug mobility within the SDD (that is, the diffusion coefficient of drug in the SDD) is low even at temperatures of 40 °C and at water contents associated with RH values up to 60 %. This low rate of diffusion of drug in an SDD at or below the T_g of the SDD results in the diffusion of drug being the rate-limiting step for drug to phase separate and crystallize. For such homogeneous fluids near their T_g, the diffusion coefficient of a solute with a size of about 1 nm decreases by about tenfold for every 10°C decrease in temperature (Friesen et al. 2008; Angell 1985; Wang et al. 2002).

Using the approach introduced by Angell (1985), the temperature dependence of the viscosity of glasses can be presented in a T_g scaled Arrhenius plot. The minimum slope of the log10 viscosity versus T_g/T occurs for so-called strong liquids. For all organic glass forming materials, the slope at temperatures near T_g (0.9 to 1.1 with the T_g/T measured in Kelvin) is at least two- to threefold this minimum value (Wang et al. 2002). This slope is a measure of the "fragility" of the amorphous material. Taking a conservative estimate of fragility to be two- to threefold that of the strong fluid limit, for a 10 °C decrease in temperature from a T_g value of 60 °C (333 K), viscosity increases between 10-fold and 20-fold. Assuming that the diffusion coefficient of drug in the SDD decreases in inverse proportion to the viscosity, the diffusion coefficient of drug in an HPMCAS dispersion with a T_g near 60 °C would be expected to decrease 10-fold to 20-fold for every 10 °C decrease in temperature.

This suggests that a drug molecule dispersed in a polymer matrix is essentially immobilized and unable to migrate in the powder, in order to find other drug molecules and crystallize. This is defined as kinetic stabilization of the high energy form. Kinetic stabilization in tandem with the rapid quenching kinetics of the spray drying process enables higher drug loadings in SDD formulations, and also allows for predictive models to be developed based on the mobility (T_g) of the dispersion.

As a result, for the regime where (1) the temperature is between 30 °C below and 20 °C above the T_g, (2) there is a homogeneous dispersion, and (3) the drug concentration is above its solubility in HPMCAS but below about 70 wt%, the diffusion of drug is sufficiently slow that it is the rate-limiting step for crystallization.

The time to 5 % phase separation for an SDD increases by about tenfold for every 10 °C increase in the value of T_g–$T_{storage}$ (T_g is the T_g of the SDD at the storage conditions and $T_{storage}$ is the storage temperature). As a result, as long as the value of T_g–$T_{storage}$ is greater than about 5 °C to 30 °C and the SDD is initially homogeneous, less than 5 % phase separation is expected over a period of 2 years.[4]

The theory described above can be assessed by analysis of data from SDDs of more than 500 compounds that have been evaluated for physical stability. The data are summarized in the histogram presented in Fig. 9.16, which shows the fraction of stable SDDs (i.e., no phase separation) after storage for 6–13 weeks in stability challenges. Based on these data, physical stability estimates can be made using only the SDD T_g versus RH data. For example, as shown in this Fig. 9.16, 95 % of SDDs having a T_g more than 20 °C above $T_{storage}$ show no phase separation during the stability challenge, suggesting the rule of thumb that SDDs stored at 20 °C or more below their T_g are very likely to be physically stable for an extended period of time.

The physical stability of SDDs is further illustrated by the data in Table 9.1, which show that SDDs can be stored for long periods of time with no change in the

[4] The actual rate of phase separation and the corresponding time to 5 % phase separation has been measured for 17 different SDDs over a wide range of storage temperatures—both above and below the T_g of the SDD. Based on linear extrapolation of the data for temperatures near or above the T_g (plotted as the $\log_{10}$ of the time to 5 % phase separation versus $T_g/T_{storage}$), SDDs should be stable for at least 2 years if stored at temperatures from 5 °C to 33 °C below the T_g of the SDD. This prediction is based on data from HPMCAS SDDs for seven different active compounds.

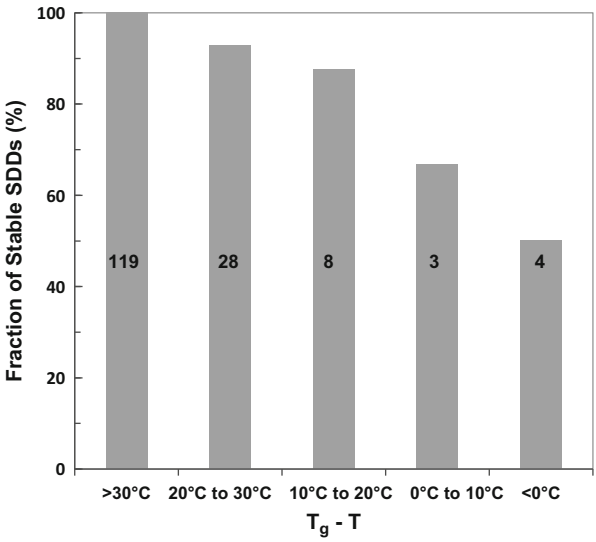

Fig. 9.16 Histogram summarizing selected bend research experience in formulating stable SDDs after 6- to 13-week stability challenges for given T_g–$T_{storage}$. Key: bold numerals on the bars represent the number of formulations used to generate the percentages

Table 9.1 Physical stability of HPMCAS-based SDDs aged at ambient conditions

SDD formulation	Aging time (year)	Observations
25-wt% compound 1:HPMCAS-M	3.0	No change in T_g, appearance, or dissolution performance
66-wt% compound 2:HPMCAS-M	2.2	No change in appearance or dissolution performance
10-wt% compound 7:HPMCAS-H	2.0	No change in appearance or dissolution performance
33-wt% compound 8:HPMCAS-L	0.7	No change in appearance or dissolution performance
33-wt% compound 9:HPMCAS-M	0.7	No change in appearance or dissolution performance

amorphous nature of the drug in the SDD. This is corroborated by the similarity of the SDD appearance in SEM images taken before and after storage. SEM images have been shown to be a sensitive measure of crystallinity, down to 1 wt% or less, allowing more sensitive detection than by powder X-ray diffraction (PXRD). Even more importantly, the dissolution properties of the SDDs, as reflected in their AUC values, show no significant changes over the time of storage. Based on the model above, these HPMCAS-based SDDs are expected to remain physically stable for even longer storage times than those used in this study.

9.8 Conclusions

HPMCAS SDDs are a particularly effective platform for enhancing the oral bioavailability of poorly aqueous-soluble pharmaceutical compounds, and have been successfully used for drug candidates having a wide range of physicochemical properties.

These SDDs provide significant enhancements in oral absorption of compounds with low aqueous solubility by (1) rapidly providing a free drug concentration well in excess of their crystalline solubilities and (2) maintaining these enhanced concentrations for long times. The composition and resulting physicochemical properties of HPMCAS are responsible for the formation of bioavailability-enhancing colloidal structures. Furthermore, the high T_g of the HPMCAS-based SDDs, combined with the homogeneous, single phase amorphous nature of the SDD, the result of the spray-drying process used to form the SDDs, produces physically stable formulations that have shelf lives of more than 2 years under standard storage conditions.

Spray drying has proven to be a robust and scalable method to manufacture SDDs from early formulation screening through commercial manufacture. Spray drying from an organic solution enables rapid drying kinetics, which is critical for preparing homogeneous amorphous dispersions of drug and HPMCAS.

The advantageous features of SDDs described above make them an attractive and broadly applicable platform technology for formulating poorly aqueous-soluble (BCS classes II and IV) compounds in a robust, scalable manner from very early development through commercial manufacture.

References

Amidon GL, Lennernas H, Shah VP, Crison JR (1995) A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res 12:413–420

Angell CA (1985) Strong and fragile liquids in relaxations in complex systems. In: Nagai K, Wright GB (eds) National Technical Information Service, US Department of Commerce, p 1

Babcock WC, Friesen DT, McCray SB (2009) Method and device for evaluation of pharmaceutical compositions. U.S. Patent No.7,611,630 B2

Chiou WL, Riegelman S (1969) Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. J Pharm Sci 58:1505–1510

Chiou WL, Riegelman S (1970) Oral absorption of griseofulvin in dogs: increased absorption via solid dispersion in polyethyleneglycol 6000. J Pharm Sci 59:937–942

Chiou WL, Riegelman S (1971) Pharmaceutical applications of solid dispersion systems. J Pharm Sci 60:1281–1302

Curatolo W, Nightingale J, Herbig S (2009) Utility of hydroxypropyl methylcellulose acetate succinate (HPMCAS) for initiation and maintenance of drug supersaturation in the GI milieu. Pharm Res 26(6):1419–1431

Dobry DE, Settell DM, Baumann JM, Ray RJ, Graham LJ, Beyerinck RA (2009) A model-based methodology for spray-drying process development. J Pharm Innov 4(3):133–142

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

Goldberg AH, Gibaldi M, Kanig JL (1965) Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures I–theoretical considerations and discussions of the literature. J Pharm Sci 54:1145–1148

Goldberg AH, Gibaldi M, Kanig JL (1966) Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II– experimental evaluation of a eutectic mixture: urea-acetaminophen system. J Pharm Sci 55:482–487

Government Accounting Office (GAO) (2006) Report to congress, new drug development, GAO-07-49

Higuchi T, Kuramoto R (1954) Study of possible complex formation between macromolecules and certain pharmaceuticals. J Amer Pharm Assn Sci Ed 47:393–397

Horn D, Ditter W (1982) Chromatographic study of interactions between polyvinylpyrrolidone and drugs. J Pharm Sci 71:1021–1026

Leuner C, Dressman J (2000) Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm 50:47–60

Morgen M, Lyon D, Schmitt R, Brackhagen M, Petermann O (2013) New excipients for solubilizing APIs: expansion of the HPMCAS chemistry space. Tablets Capsul 11(5):10–16

Mathias NR, Xu Y, Patel D, Grass M, Caldwell B, Jager C, Mullin J, Hansen L, Crison J, Saari A, Gesenberg C, Morrison J, Vig B, Raghavan K (2013) Assessing the risk of pH-Dependent absorption for new molecular entities: a novel in vitro dissolution test, physicochemical analysis, and risk assessment strategy. Mol Pharm 10(11):4063–4073. doi: 10.1021/mp400426f

National Formulary (NF) (2006) Official monograph for hypromellose acetate succinate, NF 25, pp 1136–1138

Sekiguchi K, Obi N (1961) Studies on absorption of eutectic mixtures. I. A comparison of the behavior of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man. Clin Pharm Bull 9:866–872

Serajuddin A (1999) Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. J Pharm Sci 88:1058–1066

Simonelli AP, Mehta SC, Higuchi WI (1976). Dissolution rates of high energy sulfathiazole-povidone coprecipitates II–characterization of form of drug controlling its dissolution rate via solubility studies. J Pharm Sci 65:355–361

Stoll RT, Bates TR, Nieforth KA, Swarbrick J (1969) Some physical factors affecting the enhanced blepharoptotic activity of orally administered reserpine-cholanic acid coprecipitates. J Pharm Sci 58:1457–1459

Stoll R, Bates T, Swarbrick J (1973) In vitro dissolution and in vivo absorption of nitrofurantoin from deoxycholic acid coprecipitates. J Pharm Sci 62:65–68

US Food and Drug Administration (2008) International conference on harmonisation (ICH)–draft guidance: Q8(R1) pharmaceutical development revision 1. US FDA; Rockville, Maryland

Vodak DT (2013) Development of amorphous solid dispersions using the spray-drying process. Presentation at the 15th international workshop on physical characterization of pharmaceutical solids (IWPCPS®-15), Philadelphia, Pennsylvania, 24–27 June 2013

Wang L, Velikov V, Angell CA (2002) Direct determination of kinetic fragility indices of glass-forming liquids by differential scanning calorimetry. J Chem Phys 117(22):10184–10192