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Review Article

Theme: Next Generation Formulation Design: Innovations in Material Selection and Functionality
Guest Editors: Otilia M. Koo, Panayiotis P. Constantinides, Lavinia M. Lewis, and Joseph Reo

Use of Spray-Dried Dispersions in Early Pharmaceutical Development: Theoretical and Practical Challenges

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Abstract. Spray-dried dispersions (SDDs) have become an important formulation technology for the pharmaceutical product development of poorly water-soluble (PWS) compounds. Although this technology is now widely used in the industry, especially in the early-phase development, the lack of mechanistic understanding still causes difficulty in selecting excipients and predicting stability of SDD-based drug products. In this review, the authors aim to discuss several principles of polymer science pertaining to the development of SDDs, in terms of selecting polymers and solvents, optimizing drug loading, as well as assessing physical stability on storage and supersaturation maintenance after dissolution, from both thermodynamic and kinetic considerations. In order to choose compatible solvents with both polymers and active pharmaceutical ingredients (APIs), a symmetric Flory-Huggins interaction ($\Delta\chi \sim 0$) approach was introduced. Regarding spray drying of polymer-API solutions, low critical solution temperature (LCST) was discussed for setting the inlet temperature for drying. In addition, after being exposed to moisture, SDDs are practically converted to ternary systems with asymmetric Flory-Huggins interactions, which are thermodynamically not favored. In this case, the kinetics of phase separation plays a significant role during the storage and dissolution of SDD-based drug products. The impact of polymers on the supersaturation maintenance of APIs in dissolution media was also discussed. Moreover, the nature of SDDs, with reference to solid solution and the notion of solid solubility, was examined in the context of pharmaceutical application. Finally, the importance of robust analytical techniques to characterize the SDD-based drug products was emphasized, considering their complexity.

KEYWORDS: Flory-Huggins interaction parameter; physical stability; polymer and solvent selection; spray-dried dispersion; spray drying manufacturing.

INTRODUCTION

As a large proportion (~60%) of new chemical entities are poorly water-soluble (PWS), it is a common practice in the pharmaceutical industry to develop amorphous dispersions (ADs), either by spray drying or an extrusion process, to increase the dissolution and, in turn, the bioavailability of these compounds (1–5). Particularly for the early phases of clinical development, it is often necessary to combine spray drying technology with polymers such as hydroxypropyl methyl cellulose acetate succinate (HPMCAS) to prepare spray-dried dispersions (SDDs) (6–10). This is evident by the fact that formulations containing ADs have been commonly used in first-in-human (FIH) trials and about a dozen of pharmaceutical products with amorphous dispersions have been marketed, and as shown in Table I, 7 of 14 drugs used in manufacturing processes involved solvent evaporation (11). Although only four of commercially marked drugs are manufactured based on spray drying technology, in the early pharmaceutical development process, spray drying is widely used to prepare ADs to enhance bioavailability. While ADs can be generated by both spray drying and hot melt extrusion (HME), in this review, we will concentrate on the issues associated with SDD.

The use of AD technology to formulate PWS compounds can be historically dated back to the time when the dispersion of β-carotene with polyvinylpyrrolidone (PVP) was prepared in 1965 by Tachibana and Nakamura (12), where β-carotene

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Table I. Selected Marketed Drug Products Containing Amorphous Dispersions

Trade name	Manufacturer	Drug	Processing technology	Polymer	Dosage form	FDA approval
Isoptin® ER-E	Abbott	Verapamil	HME	HPC/HPMC	Tablet	1981
Cesamet®	Valeant	Nabilone	Solvent evaporation	PVP	Tablet	1985
Sporanox®	Janssen	Itraconazole	Fluid-bed bead layering	HPMC	Capsule	1992
Nivadil®	Fujisawa	Nilvadipine		HPMC	Tablet	1989
Prograf®	Fujisawa	Tacrolimus	Solvent evaporation	HPMC	Capsule	1994
Kaletra®	Abbott	Ritonavir/lopinavir	HME	PVPVA 64	Tablet	2007
Intelence®	Janssen	Etravirine	Spray drying	HPMC	Tablet	2008
Zortress®	Novartis	Everolimus	Spray drying	HPMC	Tablet	2010
Norvir®	Abbott	Ritonavir	HME	PVPVA 64	Tablet	2010
Onmel®	Stiefel	Itraconazole	HME	HPMC	Tablet	2010
Zelboraf®	Roche	Vemurafenib	Solvent-controlled precipitation	HPMCAS	Tablet	2011
Incivek®	Vertex	Telaprevir	Spray drying	HPMCAS	Tablet	2011
Kalydeco®	Vertex	Ivacaftor	Spray drying	HPMCAS	Tablet	2012
Noxafil	Merck	Posaconazole	HME	HPMCAS	Tablet	2013

HME hot melt extrusion, *HPMC* hydroxypropyl methyl cellulose, *PVPVA* polyvinylpyrrolidone vinyl acetate, *HPMCAS* hydroxypropyl methyl cellulose acetate succinate

and PVP were dissolved in methanol followed by drying. However, the systematic investigation of the amorphous systems in relation to their pharmaceutical usage was not initiated until the 1990s when George Zografi and his associates, from the University of Wisconsin at Madison, started to examine these systems at molecular level (12,13). During this period, the principles of polymer physics, such as rules for molecular mixing, as formulated in the Flory-Huggins (F-H) theory, were applied (14). These scientific endeavors resulted in an industry-wide interest in pharmaceutical amorphous systems for drug delivery.

It is a common practice to combine spray drying technology with polymers such as HPMCAS to achieve reasonable shelf life and biorelevant dissolution (6–10). Since polymeric excipients typically account for about 50–75% (*w*/*w*) of the composition of the formulation, their properties significantly influence the physical properties of SDDs and the performance of SDD-based dosage forms, including properties such as interaction with water, physical stability, dissolution, and even compressibility. As HPMCAS becomes the polymer of choice for preparing drug-polymer dispersions due to its capability of maintaining supersaturation of active pharmaceutical ingredients (APIs), thus improving their physical stability, it is increasingly being used for supporting toxicological investigations and early clinical studies (15). Although the SDD approach is promising, there are still many challenges to develop oral solid dosage forms with SDDs including selecting appropriate polymers and solvents, optimizing spray drying processes, and preserving the physical stability of dispersions, along with maintaining supersaturation after dissolution. In this review, we will discuss some of these challenges related to the development of SDD-based drug products.

THEORETICAL CHALLENGES

Thermodynamics

SDDs developed in the pharmaceutical industry frequently contain more than two components, which create a significant complexity for investigation. For instance, SDDs are typically prepared by spray drying drug-polymer solutions with either a single solvent or a mixture of solvents. Additionally, SDDs absorb water during storage, which changes the binary drug-polymer dispersions into a three-component system—water-API-polymer. To describe these systems thermodynamically, a three-component F-H equation is shown below:

$$\frac{\Delta G_m}{mRT} = \left[\phi_1 ln\phi_1 + \phi_2 ln\phi_2 + \frac{\phi_3}{n} ln\phi_3 + \chi_{12}\phi_1\phi_2 + \chi_{23}\phi_2\phi_3 + \chi_{13}\phi_1\phi_3\right] \quad (1)$$

where m, R, and T are the total number of lattice sites, the gas constant, and temperature, respectively. ϕ_1, ϕ_2, and ϕ_3 are the volume fractions of components 1, 2, and 3, respectively, along with n as the degree of polymerization. χ_{12}, χ_{23}, and χ_{13} are the F-H interaction parameters for components 1 and 2, 2 and 3, as well as 1 and 3, separately (16). For the polymer solutions used in spray drying, components 1, 2, and 3 represent a solvent, an API, and a polymer, individually. Correspondingly, they represent water, an API, and a polymer for SDDs with moisture. Thermodynamically, $\phi_1 \ln \phi_1 + \phi_2 \ln \phi_2 + \phi_3/n \ln \phi_3$ represents the entropy of mixing of three components in a combinatorial fashion, which typically favors small molecules—an increase of entropy with mixing. However, $\chi_{12}\phi_1\phi_2 + \chi_{23}\phi_2\phi_3 + \chi_{13}\phi_1\phi_3$ stands for the enthalpy due to the interactions among components in pairwise manner such as hydrogen bonding and van der Waals interaction. For systems with two solvents (small molecules 1 and 2) and one polymer (3), their ternary phase behavior was investigated by Tompa (17) and Scott (18). Specifically, if $\chi_{12} \cong \chi_{13} = \chi$ and $\chi_{23} = 0$, the system is very much compatible throughout for a very small value of χ ($\chi << 2$). However, as χ increases, the propensity for phase separation grows—especially when χ is beyond 2 and significant phase separation would occur (Fig. 1). As pointed out by Scott, generally when $\chi_{12} \neq \chi_{13} \neq \chi$ and $\chi_{23} = 0$, a good miscibility among three components can still be achieved if χ is very small. A symmetric balance in χ value, such as $\chi_{12} = \chi_{13} = \chi$, would substantially enhance the miscibility of the system. As shown by Zeman and Patterson, even for noncompatible polymer-polymer pairs-$\chi_{23} \neq 0$, their miscibility can be

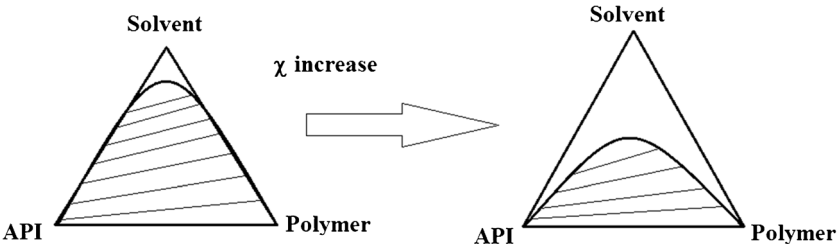

Fig. 1. Three-component phase diagram

attained by selecting a solvent having an equal interaction with both components, $\chi_{12} = \chi_{13}$ (19). Hence, it is critical to choose a solvent that have an equivalent or similar χ value with both polymers ($|\Delta\chi| \sim 0$) to prepare miscible polymer blends. This principle can serve as a guide for solvent selection when spray drying SDDs. To prepare a miscible blend of indomethacin (IND) with polyvinylpyrrolidone vinyl acetate (PVPVA) copolymer, a compatible solvent with both the drug and the polymer ($|\Delta\chi| \sim 0$) is preferred even though, hypothetically, IND-PVPVA does not have to be compatible. Therefore, finding a solvent with χ equally close to that of both the drug and the polymer is critical.

After being exposed to moisture during storage, a binary SDD can be converted into a three-component system (water-API-polymer). Since the interaction between water and polymer is significantly different from that of water with API, an asymmetric interaction is expected. Therefore, $|\Delta\chi|$ is typically high (probably >2) for SDDs with moisture, and thermodynamically high $\Delta\chi$ drives phase separation. In summary, most of SDDs would exhibit instability after sorbing water, and essentially kinetic stabilization plays a significant role to maintain their stability.

Regarding χ which was only concerned with endothermic mixing originally-the energy difference prior and after mixing, *it* is not only related to enthalpy but also connected with entropy. χ can be determined by the following methods: constructing phase diagram, measuring osmotic pressure, or determining interaction energy between stationary phases, and probing molecular interactions using inverse gas chromatography (IGC) (20). One of the most convenient methods is to derive χ from a solubility parameter based on the following equation:

$$\chi_{12} = 0.6\frac{V}{RT}\left[(\delta_{d1}-\delta_{d2})^2 + 0.25(\delta_{p1}-\delta_{p2})^2 + 0.25(\delta_{h1}-\delta_{h2})^2\right] + 0.34 \quad (2)$$

where V, R, and T are the molar volume, gas constant, and temperature, respectively, and δ_d, δ_p, and δ_h represent the solubility parameters contributed by dispersive force, polar interaction, and hydrogen bonding of two materials (1 and 2), respectively (21). If dispersive force is dominant, neglecting the last two terms, the above equation can be simplified to Hildebrand expression (22).

$$\chi_{12} = \frac{V}{RT}(\delta_1-\delta_2)^2 + 0.35 \quad (3)$$

Experimentally, the solubility parameter can be determined using IGC. Additionally, the solubility parameter can also be calculated based on a group contribution method (23). In the following sections, χ calculated from Eqs. 2 and 3 will be used in analyzing the compatibility between components of SDDs.

Solid Dispersions *Versus* Solid Solutions

Although solid solution systems are commonly found in alloy systems, it is very rare for organic molecules to form solid solutions due to constrains in terms of matching the same/similar size and shape (22). Because polymers are much larger than drugs (small molecule-API), dispersions such as SDDs are inherently heterogeneous even though they are occasionally misnamed as solid solutions. The microstructure of polymer chains in solution ranges from a few nanometers to over 10 nm, which depends on both the properties of polymers (chemical structure and size of molecules and degree of polymerization) and solvents used (24). The size of a polymer expands in a good solvent and shrinks in a poor solvent (25). For a linear homopolymer with a flexible chain, its size in solution (theta condition) is generally expressed as the radius of gyration:

$$\langle R_g{}^2 \rangle = \frac{nl^2}{6} \quad (4)$$

where n and l are the degree of polymerization and the size of a monomer, respectively (25). For PVP (K29/32), its degree of polymerization is about 400 (MW = 40,000), and based on Eq. 4, its theoretical radius of gyration is calculated to be about 1.25 nm (26,27). Experimentally, as reported in the literature, the measured R_g for polyvinyl polymers is found to be proportional to $M^{1/2}$ with a coefficient of about 0.03. According to the prediction using this formula, the experimental radius of gyration for PVP K29/32 should be around 6 nm (28). In comparison, the size of a drug molecule, such as indomethacin, is usually less than a nanometer—very small relative to a polymer. Hence, SDDs are inherently heterogeneous where drug molecules are dispersed either among chains of polymers of much larger size and various structures or along polymer chains, depending on solvent conditions.

Dynamically, drug-polymer dispersions also exhibit significant heterogeneity in terms of relaxation—thus molecular mobility (29). Since drugs (small molecules) tend to have higher mobility compared to polymeric molecules, representing faster rotation and transport coefficient, the heterogeneity in relaxation can drive phase separation (30). When the mobility of drug molecules reaches certain threshold, they will move around a polymer matrix to phase separate, which increases the propensity for crystallization.

Solid solubility has been used in the pharmaceutical industry to indicate the maximum accommodated concentration of APIs in amorphous dispersions at equilibrium (30–33). However, given that drug-polymer systems are heterogeneous, the concept of solid solution of APIs in polymers is not adequate to describe SDD systems. Therefore, SDDs need to be treated as dispersions in which drugs are dynamically stabilized by polymers. For the majority of miscible SDDs in which no separate distinct T_g is detected by differential scanning calorimetry (DSC), they are made miscible by selecting appropriate polymers, processing solvents, and spray drying conditions (10,34–36). Particularly, for high drug loading SDDs (25% and above, *w*/*w*), they are mostly miscible (not phase separated) at the time of manufacturing, with an expectation that these SDDs remain stable through product shelf life. In summary, SDDs are amorphous systems where drug molecules are mostly kinetically stabilized, possibly by reducing molecular mobility. In addition, analytically it is very hard to confirm that SDDs are actually solid solution or to meaningfully measure solid solubility, and so it is confusing to use these terms loosely in the development.

DEVELOPMENT CHALLENGES

Manufacturing-Spray Drying

Polymer Selection

Polymer selection for forming stable drug-polymer amorphous dispersions is frequently discussed in the literature. Many interesting approaches have been taken including *in silico* solubility calculation, F-H interaction parameter calculation, phase diagram prediction, and crystallization inhibition (37–39). To enhance the bioavailability of APIs and to maintain their physical stability against crystallization, certain properties of polymers are preferred such as having high enough T_g to maintain the physical stability of APIs even when being exposed to humidity. Alternatively, the polymers with a right balance between hygroscopicity and hydrophobicity, in which the final T_g values of the resultant SDDs are not significantly impacted by moisture, are preferable. Additionally, the selected polymers should exhibit good dissolution in aqueous media while maintaining supersaturation through strong API-polymer interactions. Because of these constrains, only a few of polymers that are used to prepare SDDs are included in the drug products made to market, as shown in Table II. In this section, we only focus on the role of polymer selection in spray drying preparation besides its impact on physical stability upon storage and dissolution.

For spray drying, interactions between polymers and APIs are very critical to maintain a homogeneous system. As discussed before, a small $\Delta\chi$ between an API and a polymer usually warrants a good miscibility. However, it is difficult to find polymers that can satisfy this condition as well as others. For indomethacin, its χ values with four polymers (Table II) can be estimated based on the Hildebrand equation: PVP (0.94), PVPVA (0.38), HPMC (0.78), and HPMCAS (1.13). According to χ_{12} values above, all polymers have χ_{12} less than 2—a critical value for phase separation. In particular, PVPVA is the polymer with the least χ_{12}, which suggests that it is the most compatible polymer with indomethacin. However, in preparation of indomethacin SDDs, HPMCAS might be selected when considering

Table II. Physical Properties of Some Common Polymers Used in the SDD Preparation

Polymer	Chemical category and classification	T_g (°C)	Molecular weight (MW) (g/mol)	Water solubility	Hygroscopicity	Solubility parameter
Polyvinylpyrrolidone (povidone)	Polyvinyllactam polymers; nonionic	150–180	50,000	Soluble	High	19.4
Copovidone (Kollidon® VA64/Plasdone™ S-630)	Polyvinyllactam polymers; nonionic	101	45,000–70,000	Soluble	High	21.2
Polyvinyl acetate phthalate (PVAP) (Opaseal®, Sureteric®)	Polyvinyllactam polymer; anionic	42.5	47,000–60,700	Soluble in solvents	Nonhygroscopic	25
Poly(butylmethacrylate-co-(2-dimethylaminoethylmethacrylate-co-methyl methacrylate) 1:2:1 (Eudragit® EPO)	Methacrylate copolymer; cationic	~48	~47,000	Soluble in gastric fluid up to pH 5.0	Low	19.6
Hypromellose (HPMC)	Cellulose ethers; nonionic	190	85,000–150,000	Soluble	High	23.7
Hypromellose acetate succinate (HPMCAS)	Cellulose ethers; anionic	130	50,000	Above pH 5.0	Low	29.1
Eudragit® S100	Methacrylic acid copolymer; anionic	>130	125,000	Above pH 7.0	Low	–
Hydroxypropyl cellulose (HPC)	Cellulose ethers; nonionic	100	40,000–115,000	Water soluble	High	26.4

the following factors: glass transition, hygroscopicity, and supersaturation effect. Additionally, solvent selection became critical when a polymer is chosen since solvent can determine the miscibility of SDDs. Furthermore, viscosity or rheological properties of a polymer in a solvent can affect the dynamics of spray drying. A further discussion on solvent effect will be discussed in the "Solvent Selection" section.

In terms of the effect of polymers on the physical stability of SDDs during storage, both glass transition temperature of polymers (including glass dynamics) and their interaction with water are the principal factors to consider. Polymers with high T_g are required to reduce the molecular mobility of APIs and increase their stability against crystallization. Interaction with water can have two opposite effects: lowering the final T_g of SDD-reducing physical stability and increasing polymer solubility, maintaining an adequate dissolution of drugs. For the five polymers listed in Table II, based on their T_g values, PVP is the best choice followed by HPMC. However, both PVP and HPMC are hygroscopic, which can significantly lower their final T_g values of SDDs after being exposed to moisture. Besides, hygroscopic polymers have less interaction with hydrophobic compounds. To further illustrate the impact of moisture sorption on T_g, we can compare PVP with HPMCAS. PVP has a T_g of about 160°C at dry state, and its T_g dropped to about room temperature at 75% relative humidity (RH) since PVP is very hygroscopic (it sorbs ~25% water at 75% RH). In contrast, HPMCAS has a T_g of about 119°C at dry state, but its T_g is only reduced to about 100°C at 75% RH due to the fact that HPMCAS only sorbs a few percents (3–4%, *w*/*w*) of water at this humidity. Therefore, synergistically, the effect of T_g on coupling with a hygroscopic property of a polymer determines its final T_g as an excipient. In addition to thermal glass transition, recently, relaxation time from dielectric relaxation time measurement has been demonstrated to be beneficial for evaluating the use of polymer in SDDs. It is shown that SDD stability can also be affected by β relaxations (6,36).

As denoted by Taylor and Hancock (13) and Wu *et al.* (40), polymers in SDDs also play a significant role in influencing both dissolution and subsequent supersaturation, which will be discussed later in detail. Highly hydrophilic polymers like PVP—which promotes fast dissolution—often yield an initial burst in the solution concentration of API. This is often followed by a decrease in API concentration (precipitation of API) because these polymers cannot maintain the supersaturation state of APIs in solution, which is due to the fact that they prefer to interact more with water than with hydrophobic APIs. However, even though polymers such as HPMCAS produce a slow dissolution initially, their dissolution prolongs over hours by sustaining the supersaturation state of APIs in solution through the API-polymer interaction, thus providing higher bioavailability. In general, although T_g, polymer relaxation, hygroscopicity, and API-polymer interactions are mentioned here, there are other factors to consider when selecting polymers for preparing SDDs.

Drug Loading

To support toxicological and early clinical studies, high doses are required to explore the therapeutic window for clinical candidates. However, one of concerns for SDDs is that the dosage form with SDD is limited for increasing drug loading (37). This is because the presence of large amount of polymers, typically around 75% (*w*/*w*) in SDDs, leaves a little room for increasing drug loading in the final dosage forms (9) Typically, SDDs of 25% drug loading are commonly used for pressing tablets which typically transforms to a drug loading of approximately 15% or less in tablets. However, the maximum drug loading for SDDs can differ depending the physical properties of compounds (41,42). The question is how to establish the maximum drug loading in SDDs. Fundamentally, there are a few parameters to consider when evaluating the impact of drug loading on SDDs given that SDDs are dispersions consisted of a drug molecule and a polymer. Drugs are small molecules with low glass transition temperatures. An increase of drug content in SDDs will often decrease the final T_g values of SDDs and therefore increase the molecular mobility of APIs, which potentially impacts both product stability and manufacturability (43). In addition, the miscibility between the API and the polymer may be reduced with an increase of drug loading, leading to phase separation (44). Furthermore, depending on the interactions between water and a polymer, higher drug loading can result in instability issue as water may preferably interact with the polymer. This may cause API phase separated from the polymer and crystallized out. Overall, to optimize the drug loading in SDD dosage forms, multiple factors are needed to be considered including the physical properties of API and polymer as well as the mechanical properties of SDD prepared.

Solvent Selection

As mentioned before, choosing a right solvent is just as important as selecting a suitable polymer for SDD preparation (30). In the pharmaceutical industry, solvents for spray drying are frequently selected based on the following criteria: the solubility of an API and a polymer in common solvents, drying efficiency of solvents, the acceptable level of residual solvents, desired shelf life stability, and their disposal. Because of these reasons, acetone, methanol, dimethylsulfoxide, dimethylacetamide, and *N*-methylpyrrolidone are commonly used as listed in Table III. However, in this review, only the solvent properties affecting the behavior of polymers and APIs have been focused on, especially the solution characteristics of polymers in these solvents (45–48). As shown in Fig. 1, the miscibility behavior of a ternary polymer solution is strongly influenced by solvent properties, where the miscibility is determined by F-H interactions among a solvent, a polymer, and an API. As discussed before, if the solvent has similar interactions with the API and the polymer ($\chi_{solvent\text{-}API} = \chi_{solvent\text{-}polymer} = \chi$ [χ is very small]), the polymer solution may not exhibit phase separation, given that the χ between the API and the polymer is zero (no interaction) or negative (attractive interactions) (16,17). As the incompatibility between the solvent and other two components (larger and asymmetric χ) grows, the immiscible region in the phase diagram expands, as shown in Fig. 1. Therefore, choosing a compatible solvent is essential for obtaining uniformed spray-dried product. If the chosen polymer is not completely compatible with API ($\chi_{23} > 0$) for other reasons such as chemical incompatibility and dissolution enhancement, it is important to select a solvent having similar interactions with the API and the polymer. Indeed, the immiscible region can be kept small if the difference between $\chi_{solvent\text{-}API}$ and $\chi_{solvent\text{-}polymer}$ is close to zero ($|\Delta\chi| \cong 0$) as shown by Zeman and Patterson (19). For instance, to prepare an indomethacin-

Table III. Drying-Related Properties of Some Commonly Used Solvents

Solvent	Molecular weight (g/mol)	Heat capacity (J/g/°C)	Boiling point (°C)	Heat energy required to evaporate 1 kg of the solvent (kJ)
Ethanol	46	2.44	78	983
Acetone	58	2.17	56	610
Methanol	32	1.96	65	1300
Dimethylsulfoxide	78	1.96	189	1009
Dimethylacetamide	87	2.0	165	828
N-Methylpyrrolidone	99	1.7	204	846

HPMCAS SDD in which HPMCAS is selected for improving physical stability and enhancing supersaturation, an appropriate common solvent with $\Delta\chi \approx 0$ should be chosen in principle. Given that both HPMCAS and indomethacin are soluble or partially soluble in methanol, ethanol, and acetone, they are all suitable as a solvent. Considering F-H interactions among three components, χ values were calculated, based on Eqs. 2 and 3, for both polymer-solvent and API-solvent pairs (Table IV) (49–51). According to the χ values in Table IV, methanol is the solvent providing the minimum $|\Delta\chi|$ value (0.02), so thermodynamically it has the best compatibility with both HPMCAS and indomethacin. However, as shown in Table IV, the three solvents all have relatively small $|\Delta\chi|$ values, suggesting that they can all provide good compatibility. For instance, the χ_{12} between acetone and HPMCAS is 0.3, and this indicates that acetone is not a bad solvent for the polymer although methanol and ethanol are better. Besides, the viscosity of HPMCAS in acetone solution is relatively lower compared with the other two. Therefore, overall acetone is preferred as a solvent for spray drying HPMCAS and indomethacin. When finding a common solvent for both the API and the polymer is difficult or impossible, mixed solvents are often used, which renders polymer solutions into a quaternary system. In this case, it is desirable for both solvents to have similar boiling points and miscibility throughout. Phase diagram is fairly complex for a quaternary system. To simplify this, the two solvents can be approximated as a single liquid. Again, the miscibility of a four-component system is influenced by the difference of F-H interaction parameters ($\Delta\chi$). Finally, given that mixed solvents are a complicated system, it should be avoided as much as possible. In summary, when selecting a solvent for spray drying, it is paramount to consider the phase behavior of polymer solutions in which F-H interaction parameters play a significant role. However, χ varies with temperature according to the following equation:

$$c = A + B/T \tag{5}$$

where A and B are constants and T is the temperature. As indicated by Eq. 5, χ decreases with drying temperature, and this can significantly impact the phase behavior of polymer solutions during spray drying.

Practically, disposal of solvent is of concern for spray drying operation in many companies. Currently, many pharmaceutical companies use Capsugel, Inc. (formerly Bend Research) as a contract partner for preparing SDDs. However, for a feasibility study, many corporations have acquired their own capability for producing SDDs. Mostly small laboratory spray dryers are used to prepare samples, and typical batch size is less than a kilogram. In addition, at production scale, since disposal of solvent is a challenge for many companies, most of them opt for outsourcing this activity. Because this paper focus on preparation of SDDs in the early development, we will not comment on some issues related to SDD production even though they are very critical for preparing SDD dosage forms.

Temperature-Induced Phase Separation. Rising temperature during spray drying can significantly impact SDD properties as a dryer is required to raise the temperature quickly from

Table IV. Calculated F-H Interaction Parameters and Their Differences Based on the Solubility Parameters

Component	δ_d	δ_p	δ_h	χ_{12}	Difference of χ between the polymer-solvent and drug-solvent ($\|\Delta\chi\|$)
Indomethacin	21.3	10.7			
HPMCAS	16.73	12.37	10.33		
Acetone	15.5	10.4	7.0		
Methanol	15.1	12.3	22.3		
Ethanol	15.8	8.8	19.4		
Indomethacin/HPMCAS				1.27	
HPMCAS/methanol				0.37	0.02
HPMCAS/acetone				0.11	0.30
HPMCAS/ethanol				0.27	0.17
Indomethacin/methanol				0.39	0.02
Indomethacin/acetone				0.41	0.30
Indomethacin/ethanol				0.44	0.17

HPMCAS hydroxypropyl methyl cellulose acetate succinate

the ambient condition to the desired drying temperature which is above the boiling point of solvents (52). This rapid increase in temperature can substantially change the phase behavior of polymer solutions as well as drying dynamics, thus impacting the physical characteristics of the final products (53). Practically, inlet temperatures are usually selected based on the boiling points of solvents to achieve the desired outlet temperatures: *e.g.*, the inlet temperatures for acetone and methanol are 60 and 75°C, respectively, resulting in outlet temperatures of 40 and 58°C (54,55). Thermodynamically, it is critical to understand the impact of temperature elevation on the phase behavior of polymer solutions. Based on the F-H theory, it is believed that the solubility of molecules increases with temperature, and thus, polymers only phase separate as solutions are cooled. The temperature at which a polymer solution phase separates when cooling is called upper critical solution temperature (UCST) as shown in Fig. 2 (56–58). According to the UCST, there is no phase separation risk for spray drying polymer solutions since the temperature is increased during the drying process. As reported in the literature, the UCST was only observed for polymer solutions which can be treated as a regular solution—no volume and heat change after mixing. Since 1960, a significant number of polymer solutions were observed to phase separate when temperature was raised, and this is commonly referred to as a lower critical solution temperature (LCST) behavior (59,60). To elucidate this phenomenon, the corresponding state theory was developed (61–63). In the new theory, χ is expressed as

$$\chi = -\left(\frac{U_1}{RT}\right)v^2 + \left(\frac{C_{p1}}{2R}\right)\tau^2 \tag{6}$$

In Eq. 6, the first term represents the energy interchange on forming contacts of the unlike types of molecules including the differences of size segments. U_1, R, T, and v^2 are the evaporation energy of a solvent, the gas constant, temperature, and the parameter characterizing a molecular difference between a polymer and a solvent, respectively. The second term reflects the structural contribution due to the free volume change after mixing in which C_{p1} and τ^2 are the heat capacity of the solvent and the parameter related to free volume, respectively. The change of χ as a function of temperature is illustrated in Fig. 3, where χ increases to above 0.5 (theta condition) when temperature is either increased or decreased. Clearly in this theory, the molecular compatibility between a solvent and a polymer is greatly affected by thermal expansion propensity of these molecules. For spray drying, LCST is more important than UCST as temperatures of polymer solutions are quickly brought up (inlet temperatures) to dry off solvents. Fortunately, for most of the polymer solutions undergoing spray drying to produce SDDs, their LCSTs are much higher than the inlet temperatures chosen. However, to ensure LCST is not reached, it is recommended that the cloudy points of polymer solutions as temperature need to be monitored. In addition to the impact of temperature on phase behavior, both concentration and temperature changes also affect the solution properties related to drying processes such as surface tension and viscosity.

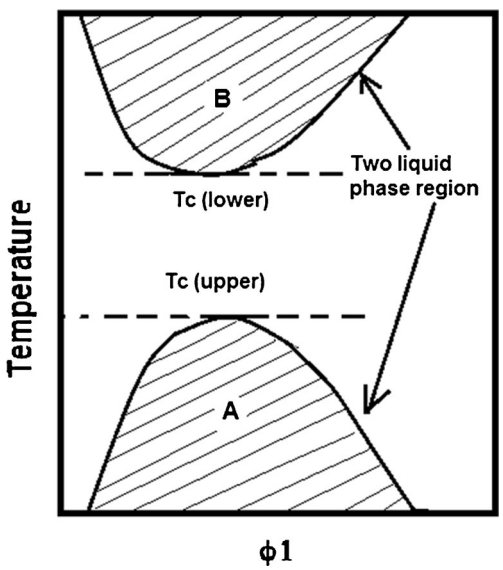

Fig. 2. A diagram displaying the low critical solution temperature and upper critical solution temperature

Process Development

To generate SDD dispersions with desired attributes such as controlled particle size, size distribution, and shape, the spray drying process needs to be controlled. For successful execution of a spray drying operation in large scale, optimization of operating parameters and the properties of polymer solutions is required. As a variety of spray dryers are used in the pharmaceutical industry, each with unique design, particularly nozzle and drying chamber design, optimization for processing parameter has to be based on the designs of equipments used. However, in this review, the focus is on the parameters related to solution properties. Generally, droplet formation and droplet characteristics—droplet size and size distribution—are strongly influenced by both nozzle design and solution properties such as viscosity and surface tension. When pressure nozzles are employed in lab scale, they typically yield a particle size range of 100–1000 μm, which is a broad range for size distribution. To control particle size and size distribution, the formation of droplets and droplet size needs to be controlled, which is strongly influenced by the viscosity and surface tension of solutions (64).

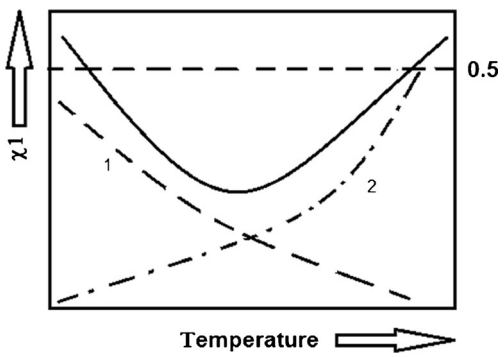

Fig. 3. F-H chi values change with temperature based on the equation of state theory

While increasing solution temperature in general tends to reduce the viscosity and surface tension of a solution, viscosity rises significantly with increasing concentration, especially for polymer solutions. For spray drying, viscosity is the key process parameter controlling spray pattern. In addition, the surface tension of polymer solutions also influences the formation of droplets. The surface tension values of polymer solutions depend on the polymers and the solvents used. Furthermore, polymers in a good solvent will tend to expand and yield higher viscosity values relative to those in a poor solvent. Solvents not only affect the viscosity of polymer solutions but also possibly impact the density of SDD particles after drying. The effect of solvent-induced expansion and contraction of polymers in solution on spray drying process and product attributes requires further investigation for SDDs.

Product Performance

Physical Stability

Moisture plays a significant role in influencing the physical instability of SDDs (65). After sorbed moisture, binary SDDs are changed to a three-component system: water, an API, and a polymer. Depending on the polymer used and the humidity level being exposed, the water content of SDDs can vary from a few percents in the SDDs made with HPMCAS to over 10% in PVP SDDs. In terms of Gibbs free energy, the introduction of a small molecule (water) into a binary system (SDDs) should enhance mixing according to the F-H theory (34). However, water often preferably interacts with polymers due to the formation of hydrogen bonding or hydration. This causes SDDs phase separated if mobility is allowed (66). These asymmetrical interactions can be described using F-H interaction parameters: $\chi_{\text{water-polymer}}$, $\chi_{\text{water-API}}$, and $\chi_{\text{API-polymer}}$. Note that $\chi_{\text{water-polymer}}$ is negative because most of polymers used are hydrophilic in nature. In contrast, $\chi_{\text{water-API}}$ is positive since water is typically a poor solvent for PWS compounds. $\chi_{\text{API-polymer}}$ values vary with compounds and polymers, but in general, they are positive and very small (67). Thermodynamically, the difference in χ ($\Delta\chi$) drives phase separation. The interaction of water with polymers excludes API and causes API to aggregate, which can lead to API crystallization if there is enough mobility for molecular diffusion. Therefore, SDD systems used in the pharmaceutical industry are mostly kinetically stabilized by reducing the system mobility.

Kinetic stabilization of SDDs depends on the physical state of SDDs. To maintain stability, the diffusion of drug molecules in polymer matrices needs to be reduced to negligible within the shelf life time of the product. Therefore, a rational approach for the product development of SDD-based dosage forms is to prolong relaxation time of drug molecules or to slow down their diffusion in polymer matrices. Within SDDs, diffusion of drug molecules is determined by the physical state of SDDs (viscosity) and the diffusion propensity of APIs (68). For small molecule drugs, their diffusion propensity remains similar due to a similar size. However, the physical state of SDDs often varies significantly with polymers. In addition, under supersaturation condition, the crystallization propensity of APIs differs substantially because of their variability in hydrophobic nature. Therefore, it is critical to understand the mobility of API molecules in SDDs relative to the physical state of SDDs. According to glass dynamics, as illustrated in Fig. 4, there are three regions when an amorphous material is cooled from a liquid state to form a glass state: the warm liquid zone (beyond 1.2 T_g; Arrhenius behavior), the cold liquid zone (from T_g to 1.2 T_g; α process, Vogel-Fulcher-Tammann (VFT) behavior), and the glass state (below T_g; β relaxation) (69). For APIs in SDDs, their crystallization most likely occurs in the warm and cold liquid zones where Arrhenius and VFT are the best models to predict their behavior. To predict the relaxation time of amorphous polymers as a function of temperature, the William-Landau-Ferry (WLF) equation similar to VFT is often used. Typically, a temperature of 50°C below T_g is treated as an immobile state in which the viscosity of a polymer is so high that its relaxation may approach infinity with negligible diffusion (70). Applying this rule to SDDs, it suggests that APIs in SDDs should be fairly stable if the storage temperature is 50°C or greater below T_g (14). However, the exposure of SDDs to moisture can significantly reduce T_g to close to storage temperature.

Chemical Instability

Drug molecules (APIs) in SDDs also encounter chemical instability issue since molecules in an amorphous state are highly reactive due to their high energetic states (71,72). Additionally, because hydrophilic polymers in SDDs absorb a fair amount of water, drug molecules in SDDs are subject to hydrolysis and other reactions initiated by water. The rate of degradation of drugs in SDDs is frequently increased because of high molecular mobility of API molecules in the amorphous state. Furthermore, the impurities from polymers such as peroxides can also cause unintended degradation. Moreover, the residual impurities from solvents used in spray drying (*i.e.*, peroxides) can also react with APIs, which can result in chemical instability. Overall, amorphous nature, water sorption, and residual impurities from organic solvents

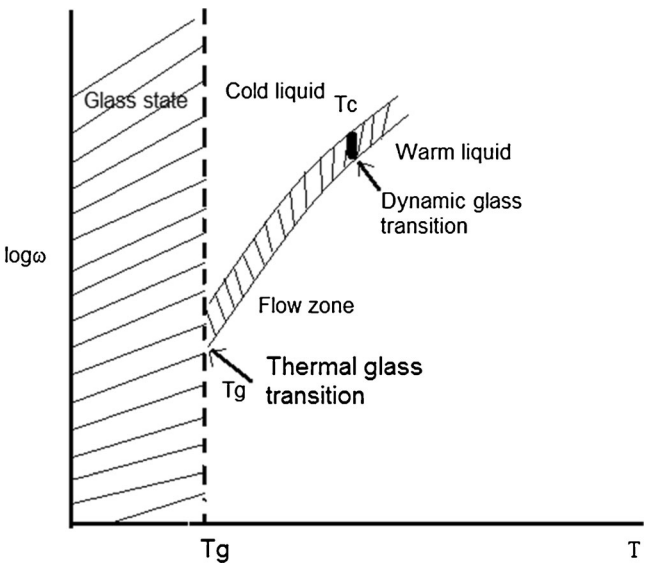

Fig. 4. A diagram showing three dynamic glass transition zones

are of major concerns for the chemical instability of APIs in SDDs.

Dissolution Rate Enhancement and Supersaturation Maintenance

Thermodynamically, the equilibrium solubility of an amorphous drug present in SDDs should be the same as that of the most stable crystalline form since molecules in an amorphous state will eventually revert to the most stable crystalline form due to their unstable nature (36). However, SDDs could provide significantly higher dissolution rate and kinetic solubility (or degree of supersaturation) due to several factors including (1) the high energy or amorphous form of the drug, (2) the supersaturation maintenance by precipitation inhibitors, and (3) smaller particle size of SDDs (1,73). Recently, the generation and maintenance of supersaturation by SDDs has recently been described by a "spring and parachute" approach. In this model, the higher energy form of drug molecules creating supersaturation is compared with the "spring" analogy whereas the precipitation inhibitors (PIs) such as polymers are equated to the "parachutes" that maintain supersaturation by inhibiting drug precipitation (74). If the supersaturation in the gastrointestinal (GI) tract is sustained throughout the absorption window—the time interval for complete GI absorption, it could enhance the oral bioavailability of a drug significantly. The bioavailability enhancement from SDDs depends on the degree of supersaturation and the extent of supersaturation maintenance (75).

With the aid of polymers, the amorphous form of the drug in SDDs can help in generating supersaturation once contacting dissolution media. However, the maintenance of supersaturation depends on the phase separation behavior of SDD interactions among drugs, polymers, and water as well as crystallization kinetics of the drug (76,77). The conditions in the GI tract including pH, amount of bile surfactant, and permeation rate vary significantly based on the location in the GI tract. Due to the continuous change in the local GI microenvironment and a high patient-to-patient variability in the local GI conditions, the aqueous solubility of drugs in the GI tract can vary by several orders of magnitude during GI transit. This may result in either local supersaturation or rapid precipitation of solubilized/dissolved drug, leading to high variability in oral bioavailability of PWS compounds. Specifically for the SDDs, it is essential to understand how the drug and the polymer react to the introduction of water. Several studies have shown that in aqueous media, SDDs could form colloidal structures such as nano-aggregates depending on the interactions between the drug and the polymer (78–80). These colloidal structures help create an environment in stabilizing the amorphous or high energy form of the drug during dissolution that results in generation of supersaturation (81). Currently, there is a significant gap in the literature in terms of mechanistic understanding of the properties and behavior of these colloidal structures. This is predominantly due to the challenges of assessing the behavior of SDDs *in vitro* during dissolution such as formation of colloidal structures, phase conversions, and the effect of precipitation inhibitors.

Additional impact of SDDs on bioavailability is influenced by the effect of nucleation inhibition of drug molecules relative to their retardation. Although the true supersaturated solution obtained by inhibiting primary nucleation would be desirable to achieve higher bioavailability, the inhibition or slowdown of crystal growth immediately after the nucleation event could also significantly enhance bioavailability (82). This could be attributed to the fact that the small particle size and, consequently, high surface area of the nuclei could eventually lead to higher dissolution rate and larger apparent solubility sufficient enough for desired bioavailability enhancement. As observed by Dai *et al.*, poor bioavailability was caused with fast precipitating formulations whereas for both the slow and no precipitating formulations, bioavailability remained similar (82). This clearly indicates that even after formation of primary nuclei, high bioavailability could be achieved by prolonging the crystal growth process when amorphous formulations were exposed to the GI environment. This suggests that the crystal growth inhibition of PWS drugs could also be significantly beneficial in terms of enhancing oral bioavailability.

Although achieving supersaturation mostly enhances the bioavailability of drugs, negative impact of supersaturation on the bioavailability has also been reported. It has been suggested that achieving very fast dissolution rate—thus a very high degree of supersaturation from SDDs—may not be sufficient to achieve higher oral bioavailability unless the degree of supersaturation is maintained through the absorption window (83). In addition, the higher dissolution rate could lead to a very high degree of supersaturation, which, in turn, could increase the driving force for precipitation. For example, when the *in vitro* dissolution behavior of several itraconazole amorphous solid dispersions was compared with their *in vivo* performances, an opposite correlation was observed. The solid dispersion of itraconazole with Eudragit E100 or Eudragit E100-PVPVA64 showed faster and higher *in vitro* dissolution as compared to the itraconazole dispersion with HPMC. However, the HPMC dispersion showed higher oral bioavailability as compared to that from the Eudragit E100 or Eudragit E100-PVPVA64 dispersions (84).

Overall, the optimal success of SDDs in terms of bioavailability enhancement depends on the maintenance or prolongation of supersaturation in the GI tract for a prolonged period of time. The success of SDDs in promoting higher and less variable oral bioavailability of PWS drugs has often been attributed to the generation and stabilization of supersaturated solutions in the GI tract. Knowledge of the fundamental relationships between the mechanisms of crystallization (*i.e.*, nucleation and crystal growth) and the variables that govern the crystallization rate including the crystallization tendency of drug, properties of colloidal structures, and pH would be essential for assessing the benefits or risks in utilizing SDDs to enhance the oral bioavailability of poorly water soluble drug.

Analytical and Regulatory Considerations

During drug development, SDDs can be used in various dosage forms, including suspensions, tablets, and capsules, to support different phases of clinical studies. Particularly, in phase 2 and 3 clinical studies, tablets or formulated capsules are generally preferred for the reason of patient compliance. To ensure their quality consistency, various analytical tests

against specifications are required for these dosage forms. These include characterizing the quality attributes of dosage forms to demonstrate the control of manufacturing process. To develop specifications, testing results reflecting the critical quality attributes of SDD dosage forms are collated from both developmental batches and stability studies for assessment throughout the analytical development cycle. If either the formulation compositions of SDDs or spray drying conditions—solvent, solution concentration, drying temperature, flow rate, etc.—are altered, a new specification is deemed necessary. The final dosage forms comprised of SDD material, intended for clinical uses, are required to have release-tested against and passed regulatory specifications. However, there is no such requirement for SDD material alone although in some cases, SDDs have been treated as product intermediates and been monitored correspondingly. SDD dosage forms are typically subjected to the conditions of conventional stability studies, including temperature, humidity, and light exposure for assigning storage conditions and use-period extension process where experimental conditions as well as test method are based on scientific justification. Nonetheless, since SDDs are amorphous, their physical and chemical stability is generally inferior to their crystalline form. Hence, the degradants from oxidation, hydrolysis, and other types of reactions involving API need to be closely monitored and controlled, and even more critical, they should be qualified before using in patients. Furthermore, prior to manufacturing stability batch, profiles of SDD materials are needed to be established during the product development. It is recommended that the stability batch be on station before the manufacture of the first clinical batch to facilitate the use-date and use-period extension process. In addition, the results from a stability study can also help in establishing the specification of the dosage form to be used in clinical studies. A typical specification for a product with a SDD includes dissolution, purity/impurity, and identity besides color and appearance. In addition, measurement for water content and other tests related to physical characteristics are also performed. Since spray drying involves using a large amount of volatile organic solvent (usually class 2 solvents) such as acetone, ethanol, methanol, tetrahydrofuran (THF), or dichloromethane, in which they are used to dissolve both APIs and polymers, the residual solvent content in the dosage forms of SDDs needs to be determined by gas chromatography (GC) with sufficient sensitivity and specificity. Regarding the control level of these solvents, the specification typically complies with the international conference on harmonization (ICH Q3C (R5)) guideline. Comparing with dosage forms of crystalline API, one of disadvantages of SDD dosage forms is their propensity to convert to crystalline forms during the spray drying process and storage, which can potentially impact their dissolution and bioavailability. Therefore, it is important to monitor crystalline content in SDDs, which is commonly included in the stability studies and specifications. In terms of techniques, both polarized light microscopy and powder X-ray diffraction (pXRD) are used to assess the crystallinity of SDDs. While pXRD is more commonly used to quantify the crystalline content of SDDs, it is limited for its sensitivity when the crystalline content is low. In comparison, polarized light microscopy is more sensitive in measuring a trace amount of crystalline API in SDDs although it is less quantitative (85). Furthermore, thermal analysis, including thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC and modulated DSC), can provide important information related to the thermal stability of SDDs and phase transition from amorphous to crystalline phase: loss of water, solvent or decomposition, glass transition, melting temperature, energy flow associated with phase transitions, and crystallinity.

In addition to attributes listed in the specifications, there are many other parameters to be monitored during product development such as the particle size and size distribution of SDDs. Commonly used techniques for determining particle size and size distribution include light or scanning electron microscopy, as well as light scattering techniques. Considering SDDs as product intermediates to be incorporated into the final dosage forms, their particle size and size distribution are often measured prior to preparation of the final dosage forms. Typically, SDD particles are spherical, and their size is described by their geometric diameters, which can be measured with ultramicroscopic image analysis. Other common techniques such as light scattering are also used to characterize particle sizes by deriving their responses to probe in the analysis. Besides the SDD particle size, morphology and density can also be tuned through control of spraying drying process and particle size engineering to help achieve the desired drug product performance. Morphology is frequently characterized using transmission electron microscopy (TEM), scanning electron microscopy (SEM), and atomic force microscopy (AFM) to qualitatively assess the crystalline states of drug active and phase separation. In terms of porosity, mercury porosity measurement is a quick analysis and often used to collect the information of pore size distribution and porosity of SDD materials. The density of SDD materials, as an important attribute, can be determined with a pycnometer.

To enhance a mechanistic understanding, a variety of other analytical techniques can be applied to measure the physical and chemical properties of SDD (86). X-ray microtomography was used to characterize the SDD particles with varying degrees of wall collapse which cannot be accurately measured with a cryogenic SEM method (86). Fourier transform infrared (FTIR) and FT Raman, both vibration spectroscopy techniques, are sensitive to molecular level interactions such as hydrogen bonding between API and its matrix. The *in vitro* dissolution test can be used to simulate the *in vivo* drug release profile, help in understanding the drug release mechanism, and therefore provide important information in guiding the development of the SDD and final dosage form.

Overall, many analytical tools have been used to characterize and monitor the stability of SDD materials. To successfully develop a solid dosage form with SDD materials, it requires an in-depth understanding of the physicochemical properties and its correlation with the product performance (87).

FUTURE DEVELOPMENT

As described in this review, SDDs provide an effective tool to improve the dissolution of PWS compounds and enable pharmaceutical companies to develop them as

potential drugs. Once the efficacy of a compound is confirmed, evaluation of other processing methods for developing the final dosage forms in amorphous dispersion such as hot melt extrusion needs to be performed. Based on the merits of each method, the most economical one is typically selected. Regarding the development of SDD dosage forms, there remain significant challenges as described in this review although amorphous dispersions have been successfully used in the pharmaceutical industry as demonstrated by marketed products. One of obstacles for successfully developing SDD dosage forms is a lack of suitable polymers. Currently, there are limited numbers of polymers available for selection, and HPMCAS is the one commonly used in preparing SDDs. One approach to circumvent this problem is to prepare ternary systems by choosing two polymers in which one polymer serves in stabilizing APIs while the other helps in maintaining supersaturation and improving dissolution (88). Nonetheless, there is an urgent need to synthesize or qualify more suitable polymers for this purpose. For preparing SDDs, polymers are required to have the right balance between hydrophilicity and hydrophobicity, because hydrophilic polymers sorb too much water and cause physical stability concern on storage in addition to a lack of capability to maintain supersaturation. On the contrary, hydrophobic polymers may have shown no dissolution and thus no bioavailability. As of today, it is encouraging to see that in both academia and industry, there is an increasing activity of producing suitable polymers for SDD preparation.

Besides selecting a right polymer, choosing a suitable solvent is also critical for SDD preparation. Presently, solvent selection and identification of spray drying conditions are based on the experience established from successful manufacturing processes. However, scientifically, this approach is inefficient particularly when polymers for preparing SDDs are changed. Therefore, it is desirable to establish the phase behavior before executing any spray drying operation, in which understanding phase behavior such as LCST will help both process development and control. At last, dryers, particularly nozzles used, can also substantially influence the drying process, in which many companies choose their own design. Hence, equipment selection is a critical factor to be considered for spray drying. To successfully develop SDD dosage forms, many factors including polymers, solvents, and equipment need to be evaluated. Most importantly, a mechanistic understanding of the relationship between component interactions and SDD performance, such as supersaturation *versus* drug-polymer interaction, will increase the effectiveness of dosage form development.

CONCLUSIONS

In this paper, challenges associated with developing SDD dosage forms for delivering PWS compounds are critically assessed and summarized. With regard to spray drying and physical instability, SDDs are ternary systems involving either a solvent or water, in which F-H interactions among components—especially $\Delta\chi$ between solvent-API and solvent-polymer—determine the phase behavior as well as their stability. Practically, to select a right solvent ($\Delta\chi \cong 0$) for spray drying is critical. In the case of SDDs strongly interacting with water, because $\Delta\chi$, due to a strong water-polymer interaction, is often much greater than zero, kinetic stabilization as well as dynamic stabilization are required. Additionally, to maintain supersaturation and enhance bioavailability after dissolution, a strong API-polymer interaction in an aqueous environment is preferred. Therefore, a mechanistic understanding of supersaturation maintenance is needed. Furthermore, a proper analytical assessment of the performance of SDD dosage forms will greatly expedite their development that challenges are not only associated with monitoring the dissolution of SDD alone or SDD dosage forms but also related to identification of physical/chemical attributes of SDDs and their dynamic implications. Finally, to increase the choice of selection for polymers, new polymers or modified polymers with the right balance of hydrophilicity and hydrophobicity need to be synthesized and approved for use. Without it, the industry will suffer the consequence of having a limited choice for polymer selection.

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