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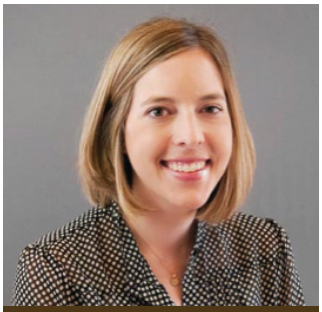
Fundamentals of Spray-Dried Dispersion Technology



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Introduction

A common problem statement in the pharmaceutical industry is low oral bioavailability of drug candidates with poor aqueous solubility. The literature suggests that a significant majority of new drug candidates are in the Biopharmaceutics Classification System (BCS) class II and IV space, which includes compounds that are dissolution rate, solubility or permeability limited to absorption, or all three. As portfolios across the industry are increasingly focused on these compounds, the need for enabling technologies continues to grow.

Many technologies exist to address issues of oral delivery of BCS II and IV active pharmaceutical ingredient (API), and selecting the right strategy depends on the physical chemical properties of the drug and the final product concept. Solid amorphous dispersion is one technology approach that has a broad range of applicability to BCS II compounds.

One process used to make amorphous dispersions is spray drying. Spray drying is a process in which the drug and excipients are dissolved in a common solvent and the resulting solution is atomized into a drying chamber **Figure 1**. Hot drying gas is introduced to the chamber that evaporates the solvent, ultimately reducing droplets to dried solid particles.

The amorphous powders improve bioavailability by producing a high-energy form of the drug that functions by dissolving to form a supersaturated concentration in the intestine. This supersaturation provides a high driving force for absorption. Ideally, this powder is homogenous, amorphous and stable. Spray-dried dispersions (SDDs) are usually amenable for incorporation into a variety of final oral dosage forms, including capsules, tablets and sachets.

One advantage of spray drying is how readily excipients can be incorporated into the process. As long as the excipient is soluble in a spray solvent, it can be included in the formulation. If the drug is not prone to degradation under acidic conditions, ionizable cellulosic polymers are often a good excipient choice because of their high glass transition temperature and low hygroscopicity in a solid state. At physiological pH of the intestine, the side chains on these polymers ionize and form amphiphilic coil structures that inhibit API crystallization and maintain supersaturation.

When acid-mediated degradation is a concern, non-ionizable polymers help avoid chemical stability issues. Other excipients such as surfactants can be added to the spray-dried formulation to help stabilize high-energy drug species in the intestine by preventing precipitation of the hydrophobic API in a supersaturated intestinal media.

While API properties drive the formulation and excipient choice, formulation guidance maps correlate physical and chemical compound properties to likely critical performance attributes. For example, a compound with a high Tm over Tg ratio is prone to crystallization.

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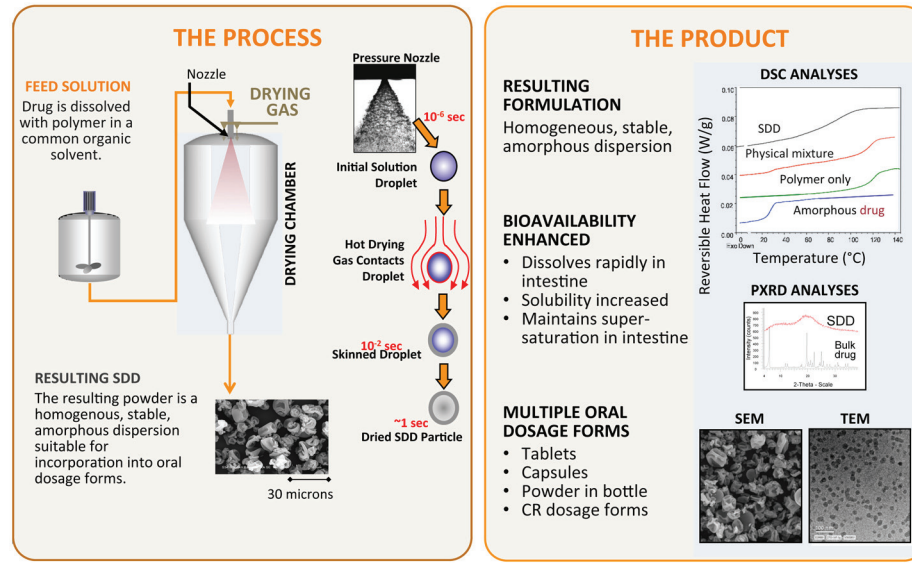
The SDD should be formulated with a high Tg stabilizing polymer at a low-drug loading to prevent nucleation and the growth of API crystals.

In summary, the cornerstones of a successful development program are performance, stability and manufacturability.

Figure 1: Spray-Dried Dispersion – What Is It?

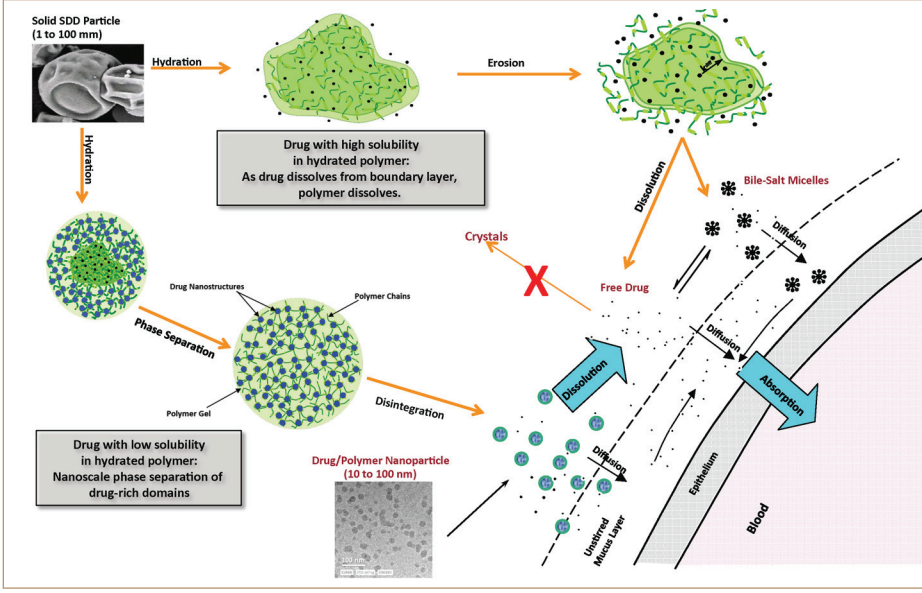


How SDDs Work

Appropriate in vitro tests can provide data to develop mechanistic models of how the SDD dissolves and enhances bioavailability. This mechanistic understanding uses a combination of predictive in silico PK biomodeling with specific in vitro tests. Identifying the state of the API molecule is used to design the formulation so that the API transits the intestinal tract, it dissolves and is absorbed.

The dissolution mechanism of SDDs is compound and formulation dependent, but usually falls somewhere on a spectrum between two extreme cases: a drug with either high or low solubility in the polymer matrix, as seen in **Figure 2**. In both mechanisms, water diffuses into the SDD particle and the polymer hydrates. If the drug is largely soluble in the hydrated polymer, the particle erodes at the edges and the drug dissolves and diffuses away from the particle at the boundary layer, similar to a classic dissolution from a crystal. However, if the drug is largely insoluble in the hydrated polymer – as is common for highly lipophilic compounds – drug-rich amorphous domains spontaneously phase separate from the particle. This leads to disintegration of the primary SDD particle and the formation of high-energy, high-surface area drug polymer nanoparticles from which the drug is sourced to the media.

Figure 2: SDDs Enhance Bioavailability by Increasing Solubility and Dissolution Rate



The key solution species for absorption are freely solvated drug and drug partitioned into bile salt micelles, which are in rapid equilibrium with the unbound molecules. In-vivo, These species diffuse rapidly across the unstirred mucus boundary layer and supply high free-drug concentrations at the epithelium, driving absorption.

The drug/polymer nanoparticles are too large for rapid diffusion across the mucus layer, but act as high-energy, high-surface area repositories for amorphous drug that maintain supersaturation and resupply free drug to the intestinal media as it is absorbed.

Determining Drug Species

There are many ways to measure dissolution in vitro, but the key is to correctly identify the dissolved solution species and gain an understanding of the dissolution mechanism of the

SDD. Centrifugation is commonly used to separate bulk solids from supernatant, which leaves free drug, drug bound into micelles and nanoparticles.

Other techniques which are used to probe the size and concentration of dissolved or neutrally buoyant drug-related species include light scattering to evaluate the size of suspended nanoparticles, UV-Vis, either by HPLC or real-time probes, and NMR for measuring dissolved drug concentration.

To illustrate how the physical properties of a compound impact the dissolution performance of an SDD, consider the examples in **Figure 3**. In the first scenario, on the top dissolution profile, the compound is prone to crystallization and the dissolution data reflect that. In one of the formulations, the drug dissolves rapidly, supersaturating the solution, and then precipitating as crystalline drug. The second formulation uses a colloid-forming polymer to sustain super-saturated concentrations of drug throughout the time course of the experiment.

In the second case, we consider a compound with high log P and a slow dissolution rate, which can lead to low in vivo exposure. Since sustainment of supersaturation is no longer the primary goal, formulations should be designed with excipients that maximize the dissolution rate (e.g., more hydrophilic polymers). In this compound space, the particle size of the SDD should be relatively small to increase surface area. Dissolution rate and drug loading might also be kept low to enhance the dissolution rate.

SDD Dosing Versatility

SDDs are versatile and, with good formulation and process understanding, can be incorporated into a wide variety of final dosage forms **Figure 4**. Common examples include immediate release (IR) and controlled release (CR) tablets.

For in vitro testing of dosage forms, USP type 2 dissolution equipment is typically used. Testing can be performed under sink or non-sink conditions, depending upon the problem statement. Running the test under non-sink conditions makes it possible to measure the concentrations and relative ratios of important free and micellar drug species relative to nanoparticles that might be sourced by the formulations. The data shown in **Figure 5** illustrates an example of dissolution of a SDD in an IR tablet.

SDDs may also be dosed in capsules. Much of the same testing and formulation requirements for IR tablets are also applicable for these dosage forms **Figure 6**. The graph shows that similar performance can be achieved using a tablet or a capsule dosage form. One advantage of using capsules is

Figure 3: Solubilization-Technology Applicability Maps –Know What Problem You are Solving

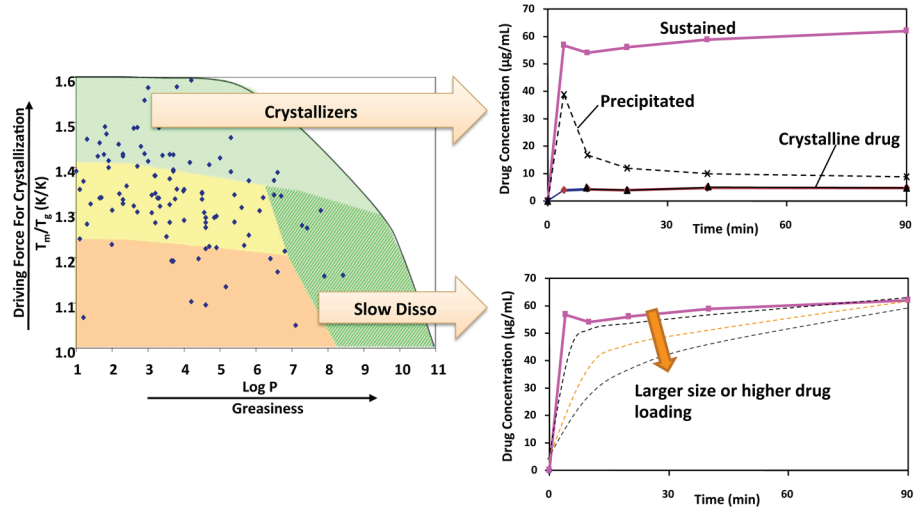
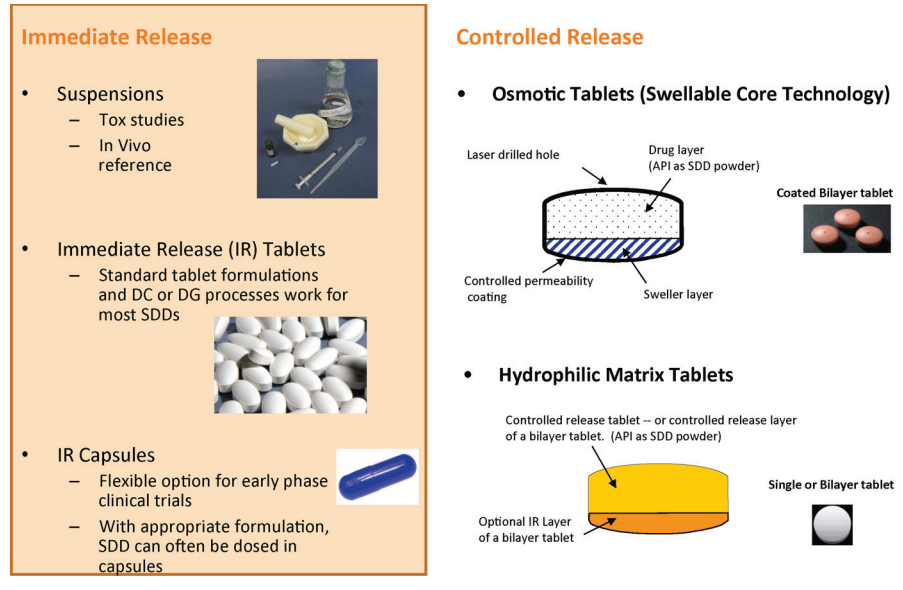


Figure 4: Common SDD Dosing Options



rapid dose titration for clinical trials.

Concepts and Approaches to Evaluating the Stability of Kinetically Stabilized Amorphous Dispersions

Amorphous dispersions can be formulated as thermodynamically stable systems, typically at low drug loading in the dispersion and/or in situations where the processing method utilizes slow quenching rates. Commonly though, amorphous dispersions are formulated as kinetically stabilized metastable dispersions. These dispersions begin as homogenous amorphous systems, but phase separate over time into pure amorphous or crystalline domains, in a polymer rich phase, thus presenting a risk to product performance. It is critical to formulate such that the thermodynamic end point is not realized during pharmaceutically relevant timeframes.

The key to forming homogenous metastable dispersions is to use a process that rapidly quenches the system. Long-term stability is realized by reducing the mobility of the system, by ensuring that the storage conditions are well below the glass transition temperature of the SDD.

To help understand these concepts, consider the Flory-Huggins model **Figure 7**. This is the same model used to predict similar solvent and polymer miscibility chemistry. While there are many assumptions that go into the model, it is a pragmatic way to think about mixtures of small-molecule API in a large-molecule polymer matrix.

At low drug loadings, the model predicts that it should be possible to make thermodynamically stable mixtures. However, it is possible to increase loading of the drug in the dispersion, such that the delta G of mixing is greater than 0, meaning that the mixture will spontaneously phase separate.

Finally, there is a range of active loadings above the thermodynamically favored miscibility limit, where it is still possible to make a homogenous system (delta G of mixing less than 0) if the quenching kinetics are sufficiently rapid. The resulting solid is a kinetically trapped super-saturated state that will persist as long as the mobility is limited. Therefore, the glass transition temperature of the dispersion, relative to storage conditions, is critical for physical stability.

Kinetic stabilization of an SDD in a metastable region in the Phase Diagram shown in **Figure 8** requires fast quenching rates. Spray drying is well-suited to this application due to extremely fast-drying kinetics. Droplets are converted from a single-phase liquid droplet to a dried particle in a fraction of a second. Keeping molecular mobility low, even in the drying process from the nozzle to the final product, is key to making homogenous drug particles.

As one example of a non-ideal case, the drug might precipitate in the droplet before the polymer gels. In this case, heterogeneous drug-rich domains are scattered throughout the final particle, which could negatively impact the long-term stability. On the other hand, if the process is designed such that the

Figure 5: *In Vitro* Dissolution Testing of Dosage Forms

- **Translation of dissolution methods from powder to dosage form: non-sink, biorelevant media, include gastric -> intestinal transfer steps**
- **Goal: ensure dosage forms and intermediates release SDD rapidly and in high-activity form**

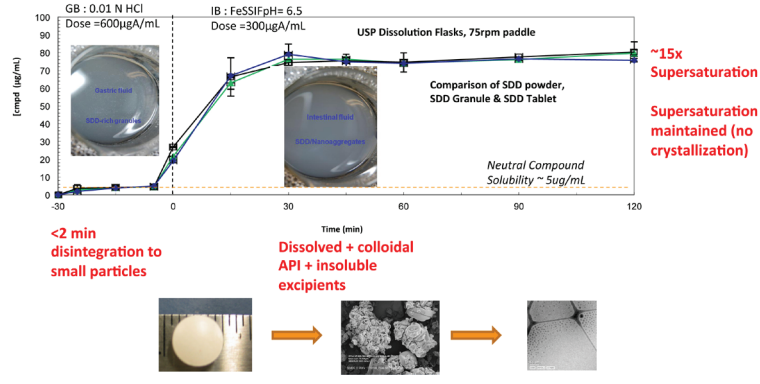
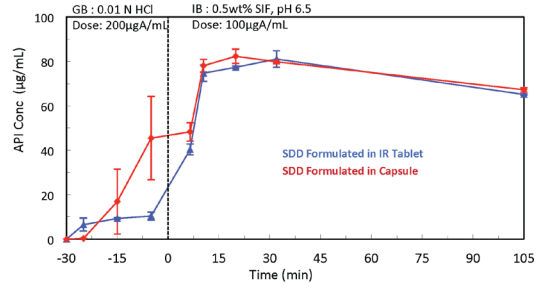


Figure 6: *In Vitro* Dissolution Testing of SDD in Capsules

Capsules and IR tablets can yield equivalent SDD dissolution performance when formulated properly.



Test Conditions (n=2):
- USPII w/ large paddles & 500mL vessels. 37.5°C, 75rpm.
- 50mgA in 250mL GB (0.01N HCl) for 30 minutes.
- Transfer to 500mL IB (0.5wt% SIF from Phares in PBS, pH 6.5) for 105 minutes.
- Note: Large error bars in GB portion of test are likely caused by poor wetting of SDD.

Sample	$C_{max,GB}$ (µg/mL)	$C_{max,105\ IB}$ (µg/mL)	$AUC_{0\text{-}105\ IB}$ (min*µg/mL)	C_{105} (µg/mL)
SDD Formulated in IR Tablet	10	81	7,240	65
SDD Formulated in Capsule	45	82	7,350	67

Note that the drug concentration remaining in the supernatant after ultracentrifugation in tests similar to this are 2-5 µg/mL

polymer starts to gel or solidify before the API precipitates, then drug mobility can be significantly reduced by the time the API supersaturates, ending in a homogenous dispersion.

Analyzing Physical Stability of SDDs

After preparing a homogenous metastable amorphous SDD, it is often worthwhile to use phase-appropriate physical stability testing to gain an understanding of the shelf life or long-term physical stability of the powder. In early-stage programs, a few simple experiments can yield comparative stability predictions for multiple formulations and rapidly identify the specific stability challenge for a given formulation. In later-phase programs, where the formulation is more well-defined and more robust predictions are needed, physical stability mapping studies can generate data supporting long-term stability predictions. Ultimately, real-time stability testing is required to support late-phase clinical studies and commercial filing.

A range of tools are used to analyze the physical state of the spray-dried dispersions and the physical stability of SDDs. For instance, Scanning Electron Microscopy evaluates particle morphology changes, such as fusing and crystallization on the surface of particles. Powder X-Ray Diffraction quantifies crystal formation and polymorphism. Modulated Differential Scanning Calorimetry evaluates SDD homogeneity, while Isothermal Calorimetry measures phase separation and crystallization kinetics.

As discussed, the physical stability of metastable amorphous dispersions is all about mobility. **Figure 9** illustrates how guidance is developed for physical stability in early-phase programs. In this experiment, SDD samples were equilibrated to a range of relative humidity conditions. The powders absorb water that plasticizes the dispersion and increases mobility of the system.

For samples where the glass transition temperature is greater than 20°C above the storage condition, the dispersion is predicted to be stable. If a Tg is less than 20°C above the storage condition, crystallization may occur. For example, the sample equilibrated to 75% RH exhibits a Tg only 6°C above the 40°C storage condition. Crystallization was observed within three months of putting the SDD on stability of that condition.

This data can be used to guide formulation in early-phases because both drug loading and polymer choice can impact

Figure 7: Thermodynamics of Homogeneous Drug-Polymer Dispersions

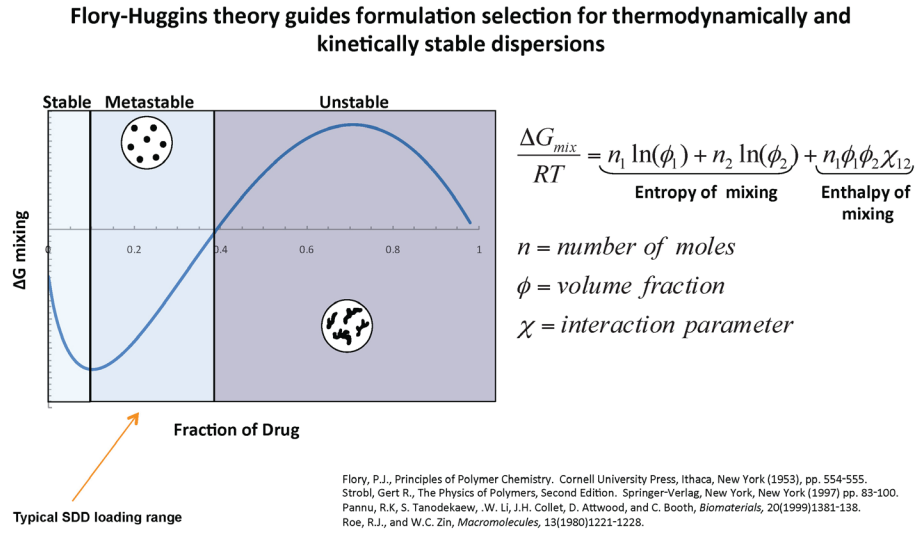
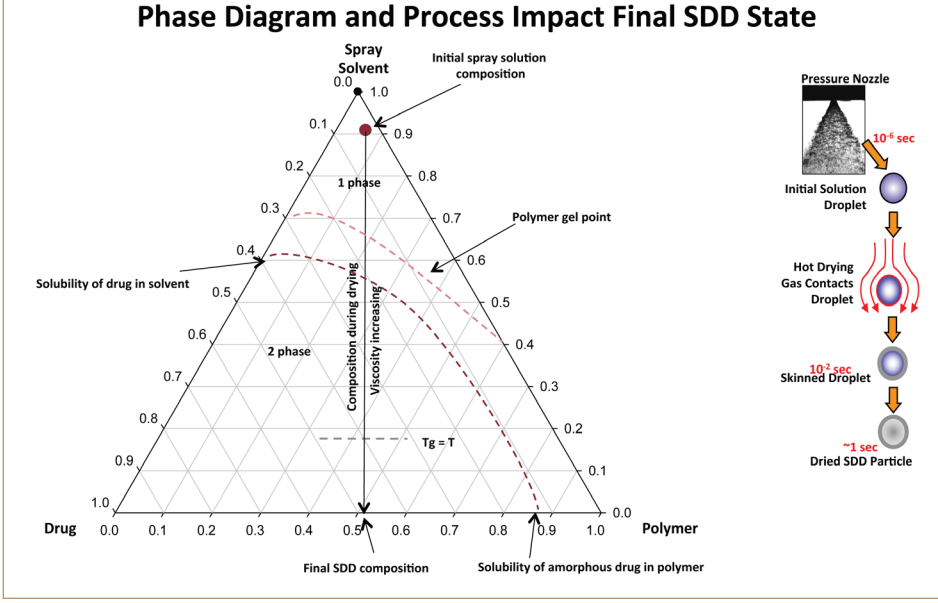


Figure 8: Droplet to Particle Drying History



the glass transition temperature. Additionally, the data might indicate that the SDD should be packaged to protect it from high humidity.

To stabilize metastable amorphous dispersions, the material should be stored at least 20 to 30 degrees below the glass transition temperature of the material at that storage condition. This is a general rule of thumb and can be somewhat API and formulation dependent.

SDD Process and Equipment

Figure 10 shows the spray drying process train. Spray drying begins with solution preparation, during which the APIs and excipients are dissolved in a volatile organic solvent. The resulting solution is fed into the spray chamber and atomized co-currently with an inert drying gas – typically nitrogen. In the spray chamber, the droplets dry, and at the bottom of the spraying chamber, the particles pass into a cyclone. The cyclonic action separates the particles from the drying gas. From the cyclone, the product is collected and typically dried further to reduce residual solvent to acceptable levels.

The cyclone removes the majority of the SDD from the drying gas stream. From there, the drying gas is passed through a series of filters to remove any residual small particles that may have by-passed the cyclone. For smaller scale dryers, the drying gas coming out of the dryer is discharged; for larger-scale dryers, the drying gas is recycled.

In a closed-loop recycle operation, the drying gas passes into a condenser, in which the majority of the solvent is condensed out of the drying gas. The drying gas passes to a heater and then back into the system.

Process development and scale-up of spray drying operations are best performed using models and engineering knowledge. It is not uncommon for process parameters to be re-tuned as scale is increased. This can be a time consuming process, unless good engineering models are used.

SDD Methodologies

Bend Research has developed material-sparing methodologies for formulation and process development as well as process scale-up. The purpose of these methodologies is to minimize the amount of API and time required to get to a robust formulation and process. These tools also help lay the

Figure 9: Thermodynamics of Homogeneous Drug-Polymer Dispersions

- **Physical changes possible for SDDs stored at or near the T_g.**
- **Qualitative prediction of long-term stability.**
- **Data used to identify appropriate storage conditions for long-term stability tests and to assess need for protective packaging. Prefer T_g of SDD > 20°C relative to storage condition**

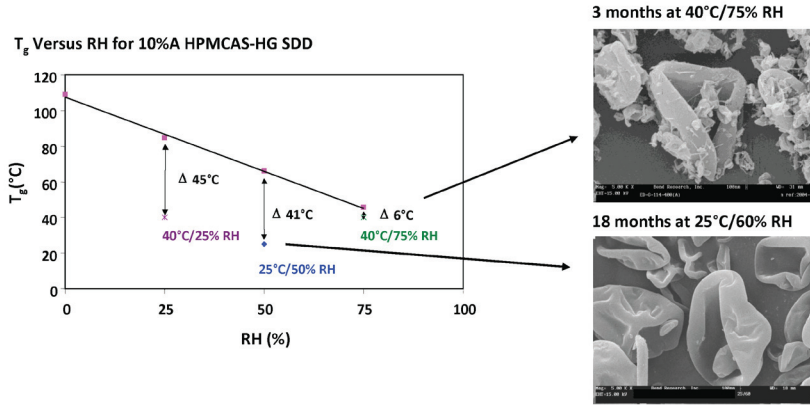
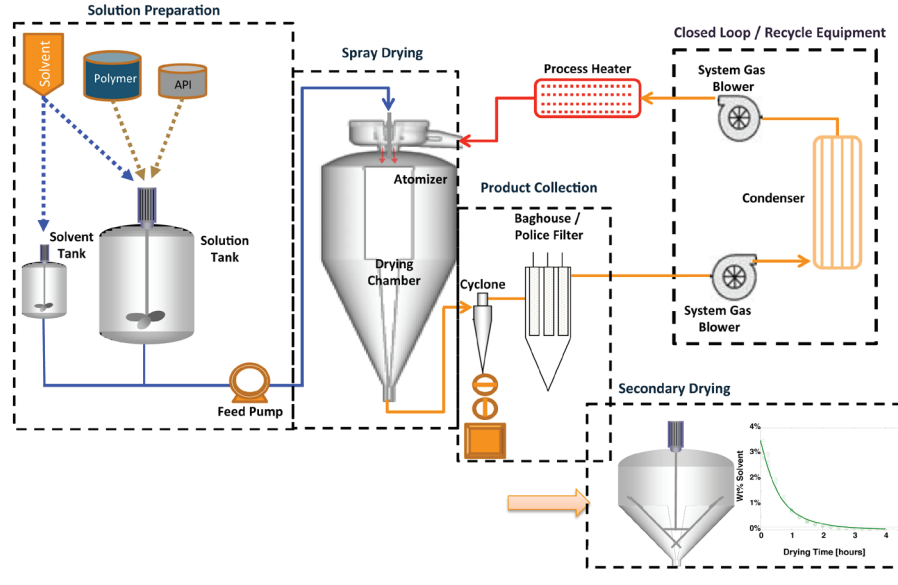


Figure 10: Physical Stability Mapping



foundation for a Quality-by-Design (QbD) filing approach.

The main aspects of spray drying are droplet formation (atomization) and droplet drying (thermodynamics), as seen in **Figure 11**. Thermodynamic modeling is a major tool in the formulation and process development tool kit. Note that standard mass and energy balances indicate a considerable amount about a process before experiments even begin: namely how much energy input from the drying gas is required for a given solution composition and throughput of solution.

Due to the nature of the film-forming polymers used, a polymer skin forms during droplet drying. Cooler and higher relative solvent saturation conditions result in slow droplet drying, and the polymer skin remains pliable as the particle forms such that the particle collapses upon itself resulting in an SDD with a shriveled raisin-like morphology with high density, lower compressibility, and higher residual solvent levels. Hotter conditions of lower relative solvent saturation result in fast droplet drying. If the drying rate is sufficiently fast, the skin is more rigid resulting in significantly diminished diffusion rates for solvent through the solidified skin. In this case, the partial pressure of solvent within the drying particle can exceed that outside of the particle resulting in ballooning of the particle and a spherical SDD particle with low density, high compressibility, and comparatively lower residual solvent levels. Thus, drying rate dictates morphology, density, compressibility, and residual solvent content of particles.

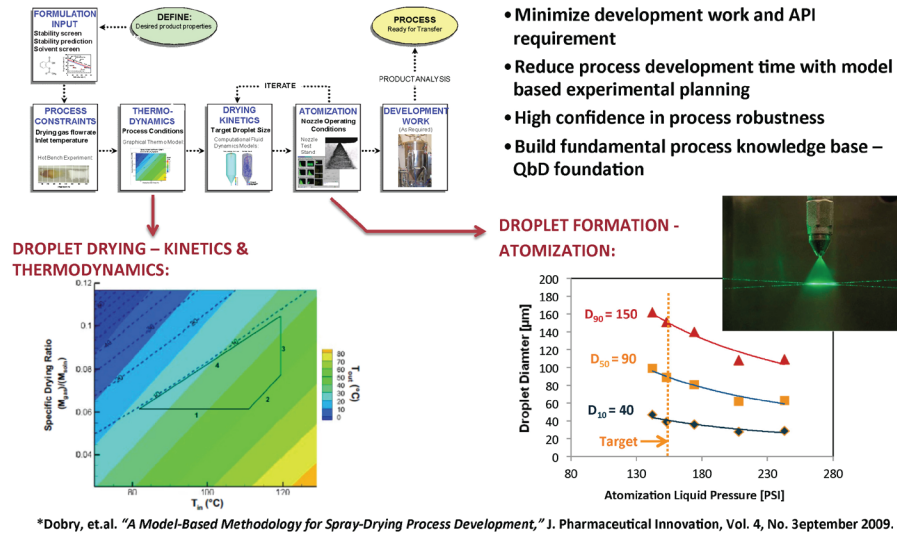
With regard to atomization, a Phase Doppler Particle Analyzer (PDPA) system can be used to measure the characteristics of atomization. The PDPA is used to determine droplet size and droplet velocity for a given solution viscosity, nozzle geometry, flow and atomization pressure. Typically, a placebo solution of similar viscosity to the active solution can be used for PDPA measurements. For a given solution composition the droplet size distribution requirement for achieving a target particle size distribution can be determined. Upon scale-up, matching droplet size is critical, and knowledge of the droplet to particle size correlation and the ability to measure droplet size distribution can be used to successfully select the scaled-up nozzle in short order.

A Summary of Spray Drying Process Parameters

Figure 12 highlights the spray drying process parameters:

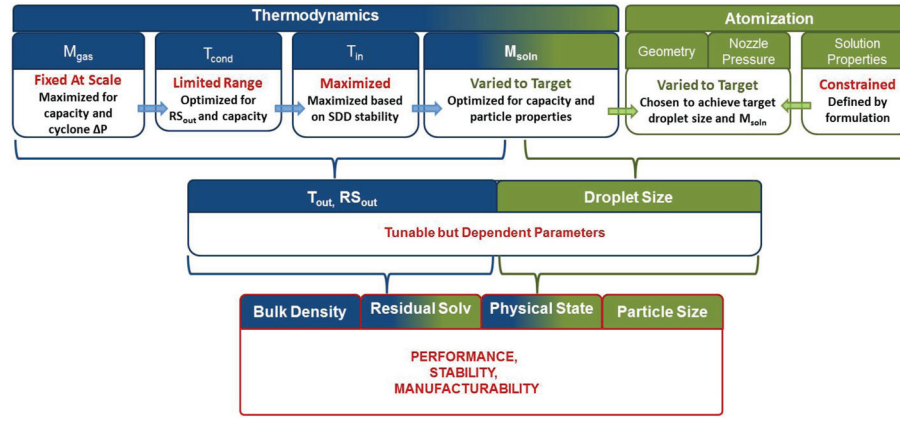
In summary, thermodynamic and atomization parameters determine SDD properties. Solution flow rate and composition as well as condenser temperature, drying gas flow, and drying gas temperature determine outlet temperature and outlet relative

Figure 11: Spray Drying Process Development Methodology*
Early Process Development – Late Stage and Commercial Foundation



*Dobry, et.al. *"A Model-Based Methodology for Spray-Drying Process Development,"* J. Pharmaceutical Innovation, Vol. 4, No. 3eptember 2009.

Figure 12: SDD Physical Stability



saturation, and hence drying rate. Nozzle geometry, atomization pressure, and solution properties dictate droplet size. Droplet size and drying rate impact powder properties which subsequently determine downstream manufacturability. The glass transition temperature and propensity of an SDD to absorb water impact stability. SDD speciation behavior drives absorption.

Using the tools outlined here, the functional relationships between the target product profile and the SDD critical quality attributes can be determined. Understanding the relationships and dependencies highlighted above is the foundation for a strong CMC filing and successful commercialization of pharmaceutical products.

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