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SPRAY DRYING DISPERSION TECHNOLOGY AS A NOVEL TECHNIQUES FOR SOLUBILITY ENHANCEMENT OF POORLY SOLUBLE DRUG –REVIEW

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ABSTRACT:

This chapter provides an in-depth review of spray-drying technology and its application to the formulation of poorly water-soluble drugs. In the early part of the chapter, the fundamentals of the process are discussed, including process theory, process components, equipment options, equipment by scale, various feeds, and typical solvent systems. In the latter part of the chapter, the application of spray drying to the formulation of poorly water-soluble drugs is discussed. Particular emphasis is given to spray drying for amorphous solid dispersion systems. The path toward developing an amorphous spray-dried dispersion and conversion to a final dosage form is covered in detail. Additionally, several academic and industrial examples are presented, illustrating the benefits of the process as a formulation technology and its commercial viability. Finally, the application of spray drying to inhalation as well as emerging applications, i.e., sprays congealing and micro-encapsulation, is reviewed. This chapter provides comprehensive coverage of the spray-drying process and its uses as a formulation technology toward the enhancement of drug delivery with poorly water-soluble compounds.

KEYWORDS:

spray drying, Biopharmaceutical Classification System (BCS), Spray-dried dispersions (SDDs), Scanning Electron Microscopy, atomization parameters, Isothermal Calorimetry, Tm,Tg.

INTRODUCTION:

Spray Drying:

It is a method of changing a dry powder from a liquid or slurry by rapidly drying with a hot gas. This is the preferred method of drying of many thermally-sensitive materials such as foods and pharmaceuticals or materials which may require extremely consistent, fine particle size. Air is the heated drying medium; however, if the liquid is a flammable solvent such as ethanol or the product is oxygen-sensitive then nitrogen is used.[I]

Spray-Dried Technology:

An SDD is a single-phase, amorphous molecular dispersion of a drug in a polymer matrix. It is a solid solution with the compound molecularly "dissolved" in a solid matrix. As the name suggests, SDDs are obtained by dissolving drug and polymer in an organic solvent and then spray-drying the solution.[II]

All spray dryers use some type of atomizer or spray nozzle to disperse the liquid or slurry into a controlled drop size spray. The most common of these are rotary disk and single-fluid high pressure swirl nozzles. Atomizer wheels are known to provide broader particle size distribution, but both methods allow for consistent distribution of particle size.[III] Alternatively, for some applications two-fluid or ultrasonic nozzles are used. Depending on the process requirements, drop sizes from 10 to 500 μm can be achieved with the appropriate choices. The most common applications are in the 100 to 200 μm diameter range. The dry powder is often free-flowing.[IV]

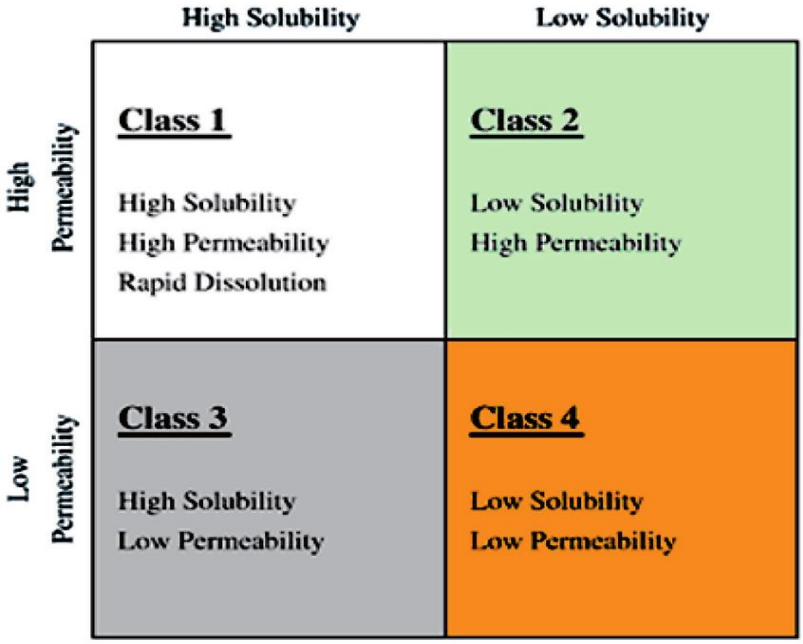
The most common type of spray dryers are called single effect. There is a single source of drying air at the top of the chamber (see n°4 on the diagram). In most cases the air is blown in the same direction as the sprayed liquid (co-current). A fine powder is produced, but it can have poor flow and produce much dust. To overcome the dust and poor flow of the powder, a new generation of spray dryers called multiple effect spray dryers has been produced. Instead of drying the liquid in one stage, drying is done through two steps: the first at the top (as per single effect) and the second with an integrated static bed at the bottom of the chamber. The bed provides a humid environment which causes smaller particles to clump, producing more uniform particle sizes, usually within the range of 100 to 300 μm. These powders are free-flowing due to the larger particle size.

The fine powders generated by the first stage drying can be recycled in continuous flow either at the top of the chamber (around the sprayed liquid) or at the bottom, inside the integrated fluidized bed. The drying of the powder can be finalized on an external vibrating fluidized bed.

The hot drying gas can be passed in as a co-current, same direction as sprayed liquid atomizer, or counter-current, where the hot air flows against the flow from the atomizer. With co-current flow, particles spend less time in the system and the particle separator (typically a cyclone device). With counter-current flow, particles spend more time in the system and are usually paired with a fluidized bed system. Co-current flow generally allows the system to operate more efficiently.

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 Biopharmaceutical 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.[V]



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. 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 cornerstone s of a successful development program are performance, stability and manufacturability.

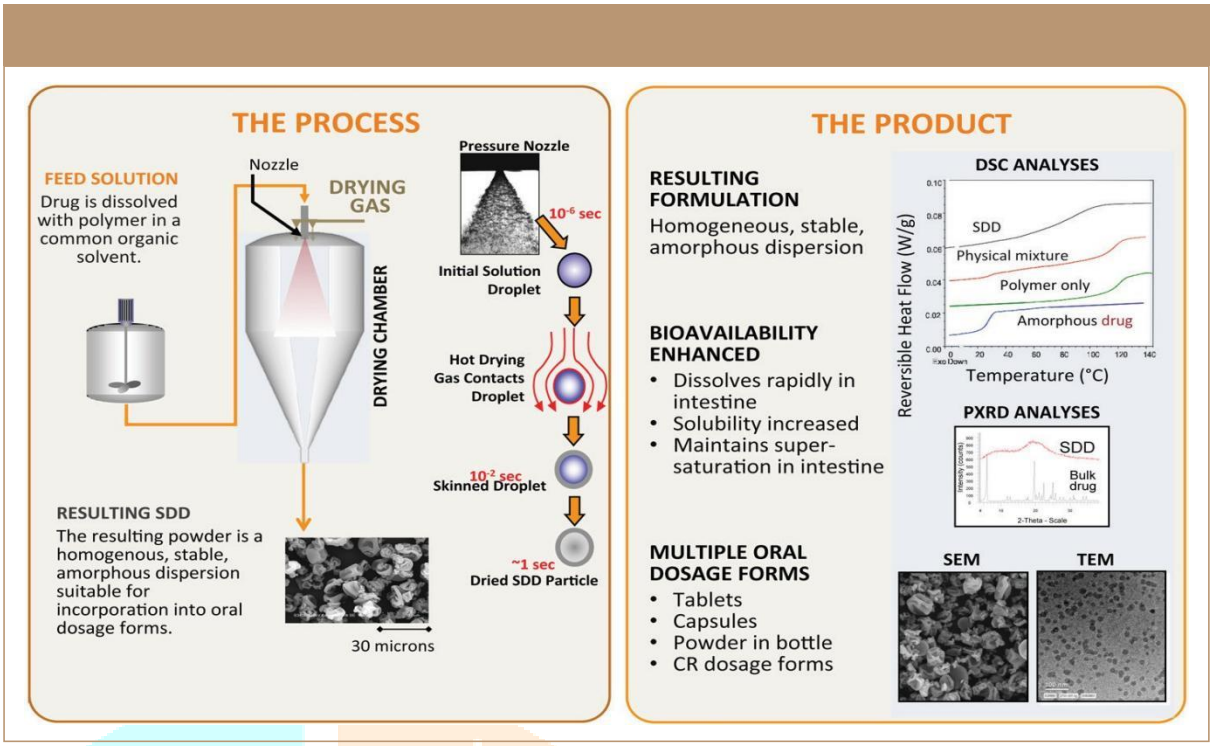


Figure 1: Spray-Dried Dispersion – What Is It?

ADVANTAGES:

1. Continuous and easy to control process.
2. Rapid and non-contact draying.
3. The droplets are small
4. Applicable to toxic and explosive materials.
5. Good properties for the spray-dried powder so it can be easily compressed into the form of tablets.
6. Labor cost is low since the materials is dried in single operation without handling.
7. One advantage of spray drying is how readily excipients can be incorporated into the process.[VI]

DISADVANTAGES:

1. Solid materials cannot be dried.
2. The equipment is very costly and bulky.
3. There is a lot of heat wasted.
4. Heat degradation possibilities in high temperature spray drying.

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 bio-modeling 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. 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, highsurface area repositories for amorphous drug that maintain supersaturation and resupply free drug to the intestinal media as it is absorbed.

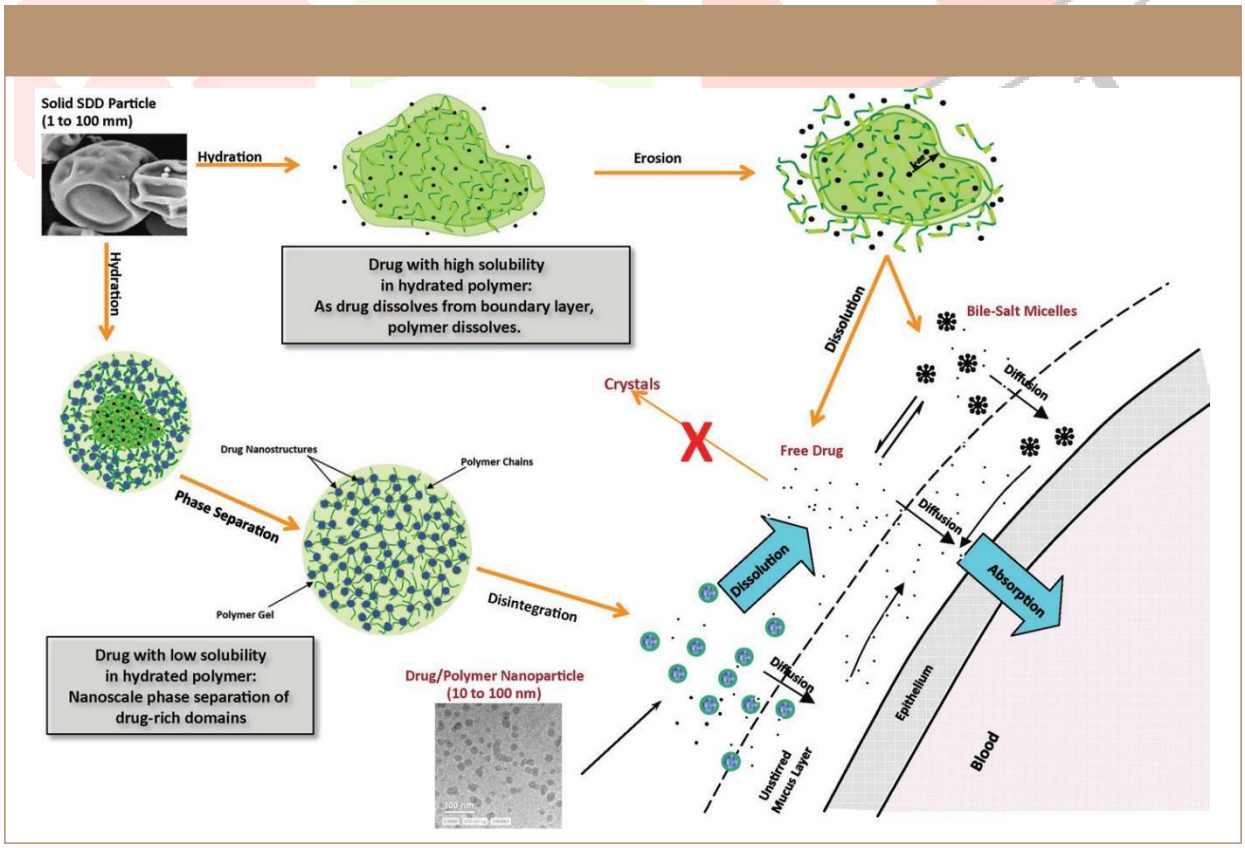


Figure 2: SDDs Enhance Bioavailability by Increasing Solubility and Dissolution Rate

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 3*. 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 nano-particles that might be sourced by the formulations. SDDs may also be dosed in capsules.

Much of the same testing and formulation requirements for IR tablets are also applicable for dosage forms.. One advantage of using capsules is rapid dose titration for clinical trials.

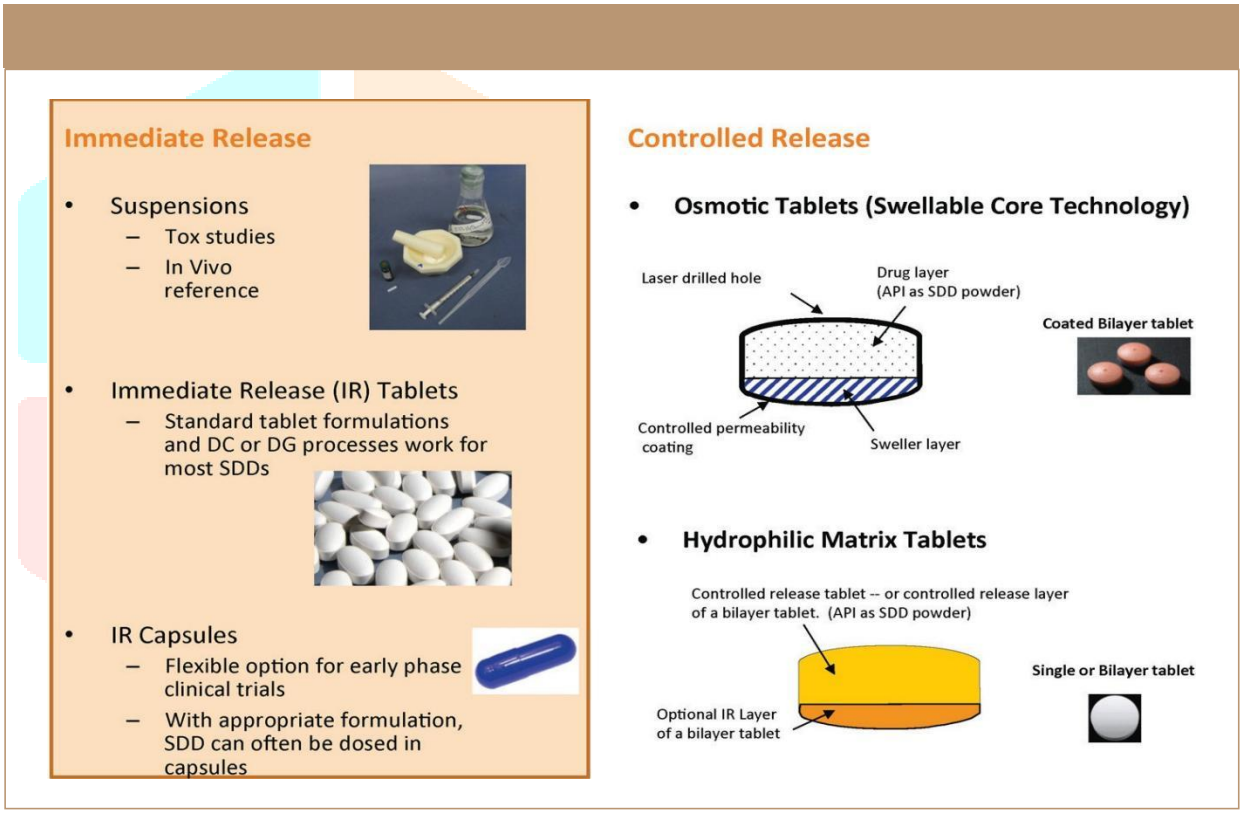


Figure 3: Common SDD Dosing Options

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 Calorimeter 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 4* 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.

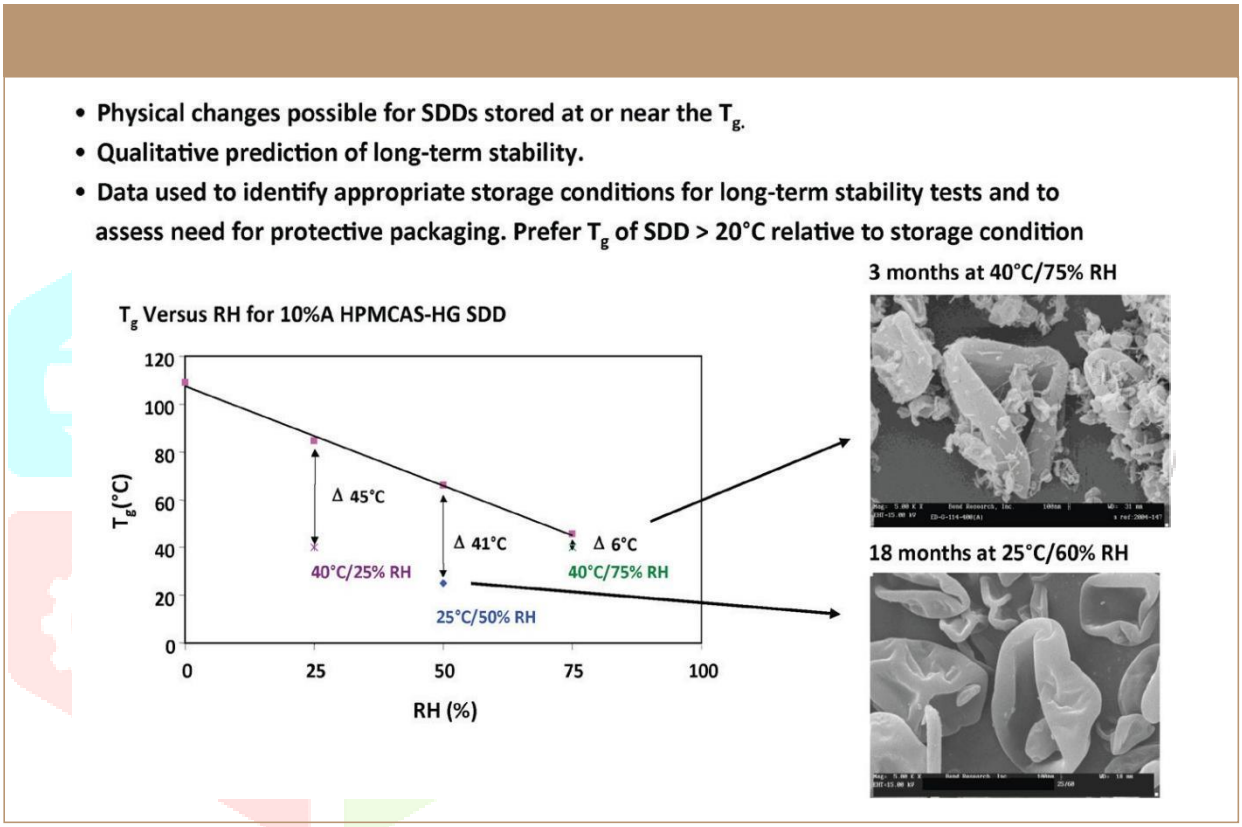


Figure 4: Thermodynamics of Homogeneous Drug-Polymer Dispersions

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.[VII]

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 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:

Spray dryers consist of a few basic elements: air filter, intake fan, heat source, feed source, feed pump, atomizer, drying chamber, cyclone separator, bag filter and/or electrostatic precipitator, and exhaust fan. Air is drawn through a filter into a spray-dryer using a fan.

The filter not only prevents contamination of the product, it also removes particles that could possibly ignite. The air is heated through direct or indirect heating. The feed source tank may be heated to lower the product viscosity prior to spray-drying. Peristaltic, piston, and progressive cavity pumps can be used to feed the spray-dryer[VIII].

Figure 5 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 large 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.

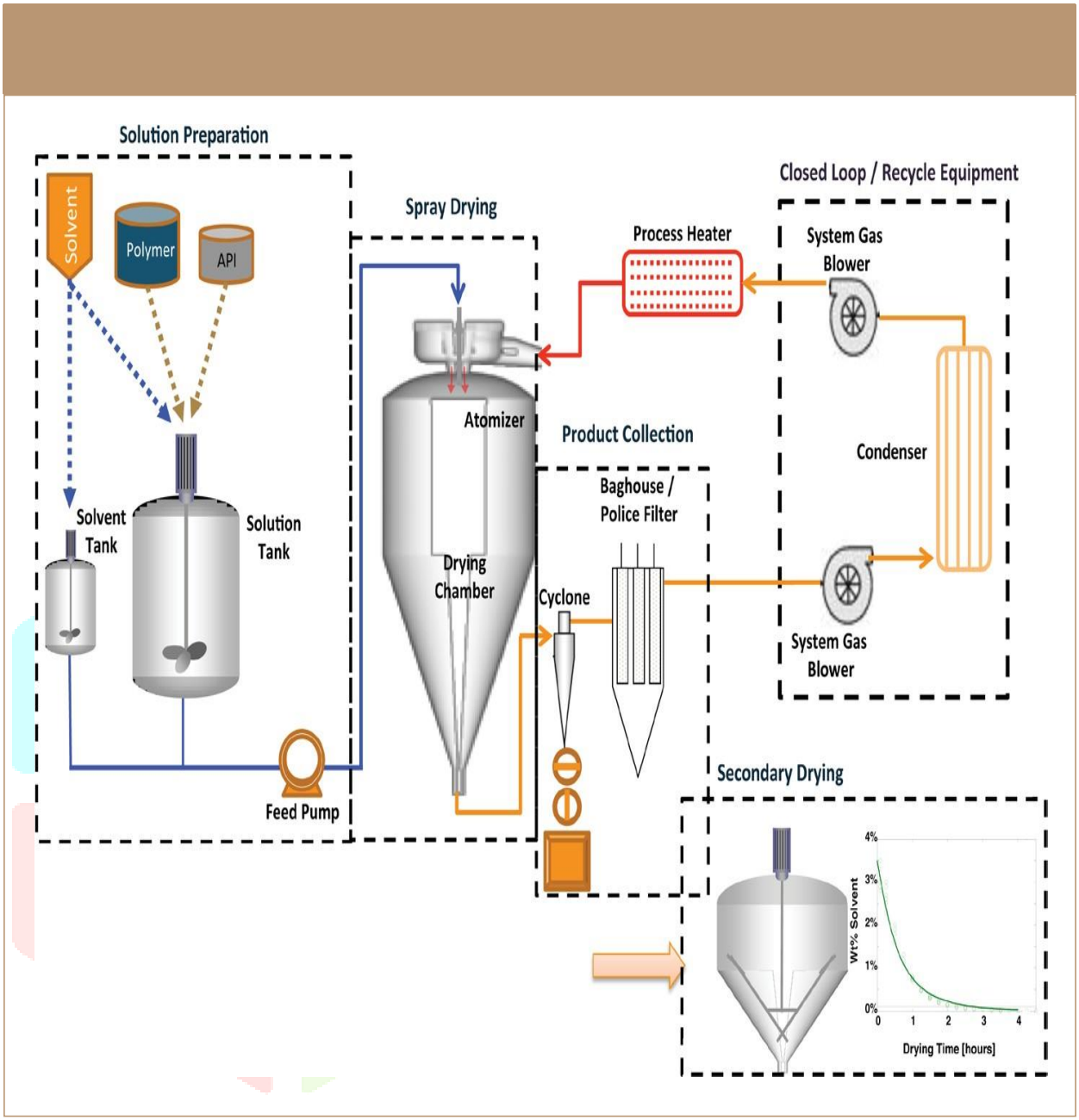


Figure 10: Physical Stability Mapping

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 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 6.*

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 PDPA system can be used to measure the characteristics of atomization. Full Form of PDPA system is Phase Doppler Particle Analyzer .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.

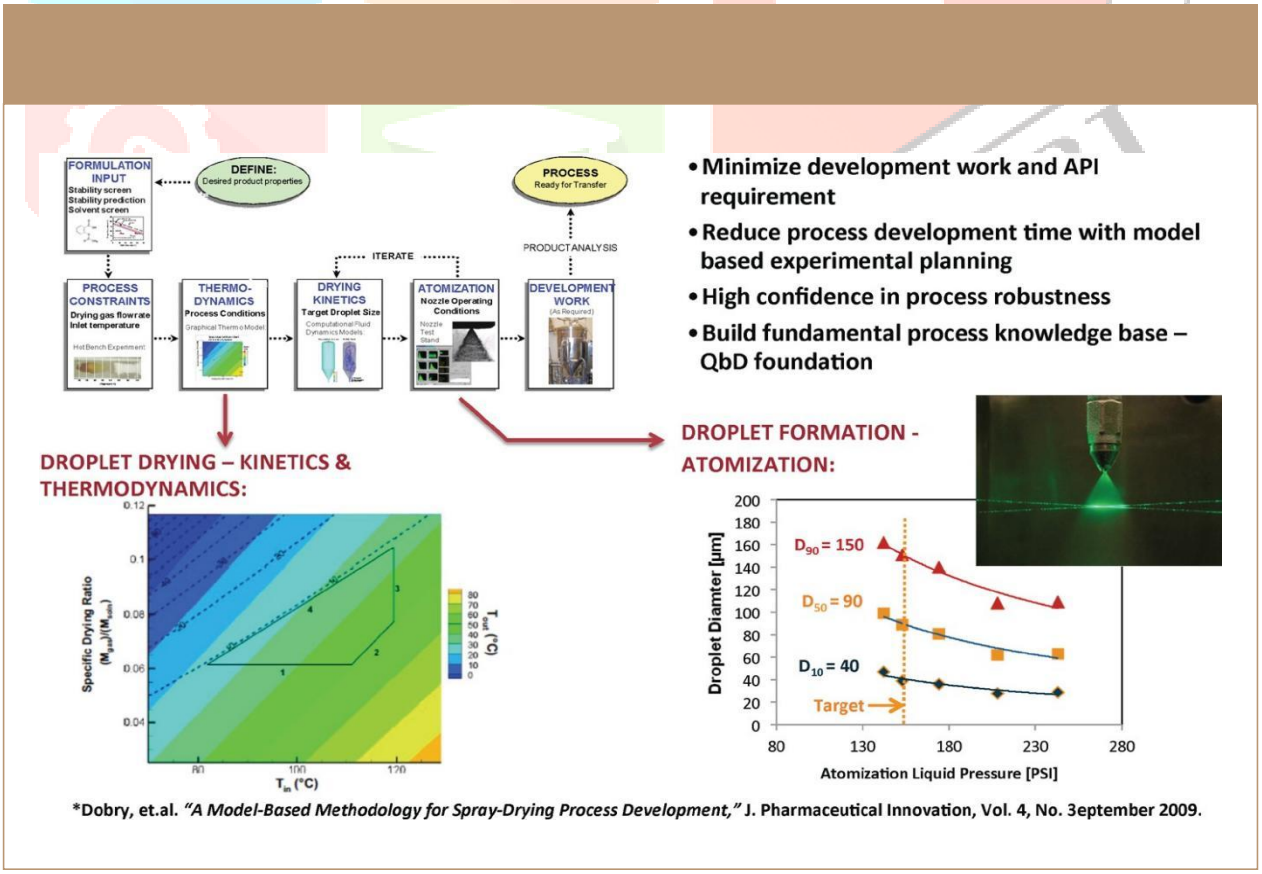


Figure 6: Spray Drying Process Development Methodology*

Early Process Development – Late Stage and Commercial Foundation

A SUMMARY OF SPRAY DRYING PROCESS PARAMETERS:

Figure 7 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 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

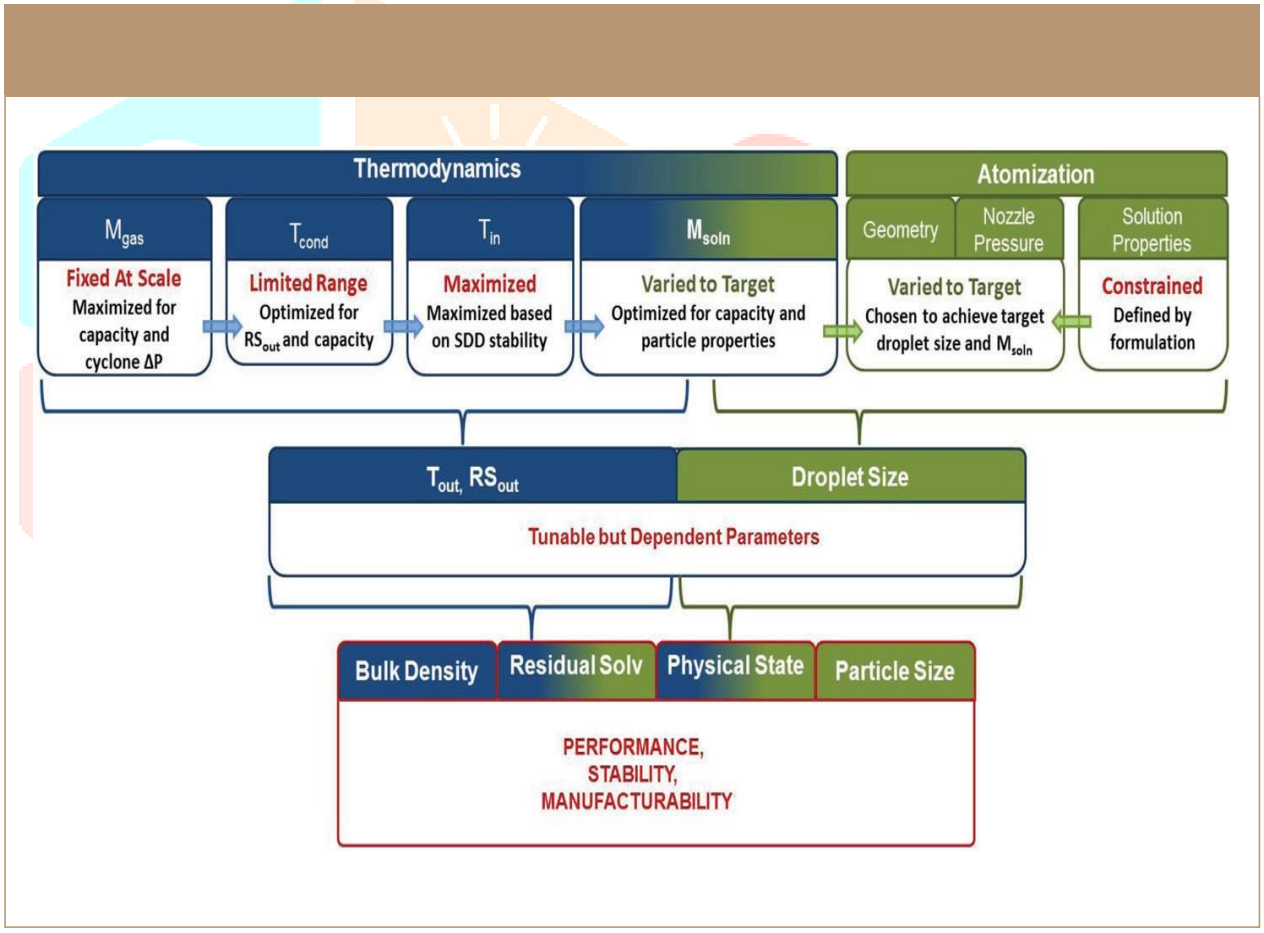


Figure 7: SDD Physical Stability

Dependencies highlighted above are the foundation for a strong CMC filing and successful commercialization of pharmaceutical products.

COMMERCIAL APPLICATIONS:

Some common applications of Spray-drying,

1. In food processing include conversion of fruit and vegetable juices into instant powders and mixes.
2. Preparation of instant coffees and teas, drying of eggs and dairy products, ice cream mixes, and encapsulated flavors and bioactive nutra-ceuticals
3. Spray-dried dispersions (SDDs) are usually amenable for incorporation into a variety of final oral dosage forms, including capsules, tablets and sachets.

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