Spray Drying: A Proven Approach to Enhance the Solubility of APIs

Spray drying is an established particle engineering technology that offers several advantages over other methods used for improving API bioavailability.

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Low aqueous solubility of active pharmaceutical ingredients (APIs) often translates to poor **Bioavailability** that can be a cause of failure during drug development. For this reason, improved aqueous solubility is a primary objective of formulation development. **Spray Drying** is an established particle engineering technology that has been widely used to enhance the solubility of oral, inhaled, and **Topical** drugs. It involves producing dry powders from a fluid material by atomization into a hot drying gas medium, usually air or nitrogen.

A main advantage of spray drying is its capacity for continuous operation that enables the implementation of process analytical technology to safeguard highly reproducible drug production. Spray drying is also faster, more cost-effective and easier to manage than many other particle engineering technologies, and is readily scalable, especially in the hands of an experienced **API** **CDMO** .

Notably, with the number of poorly soluble small molecule drugs continuing to grow, the demand for spray drying capacity is on the rise and production slots are booked well in advance. While next generation spray drying technologies promise to help

alleviate the bottleneck, Wavelength Pharmaceuticals continues to invest in both current and novel spray drying methodologies, to deliver on these strategic market needs. With spray drying expertise gained from more than 30 years of developing and manufacturing its own product portfolio Wavelength has invested in state-of-the-art equipment to support a wide range of manufacturing requirements, from small-scale clinical drug development projects through commercial-scale **GMP** production.

Low aqueous solubility is a major problem

Oral dosing represents the most convenient form of **Drug Delivery** and is commonly associated with high patient **Compliance** . However, low aqueous solubility can be a major problem when developing oral dosage forms since it restricts drug absorption within the gastrointestinal tract to limit bioavailability. Low aqueous solubility can also present problems when developing inhaled drugs, or products that will be applied as topical, **Transdermal** , or **Ophthalmic** treatments. Addressing low aqueous solubility is therefore a primary objective of formulation development to help assure regulatory approval and bring urgently-needed **Therapeutics** to patients.

To rationalize formulation development, the Biopharmaceutics Classification System (BCS) categorizes drug substances according to aqueous solubility and permeability—the two main factors influencing drug absorption.
Based on the BCS criteria, Class 1 drugs are characterized by high solubility and high permeability, Class 2 drugs by low solubility and high permeability, Class 3 drugs by high solubility and low permeability, and Class 4 drugs by low solubility and low permeability (Figure 1). Both Class 2 and Class 4 drugs are candidates for solubility enhancement.

Formulation development addresses aqueous solubility

Formulation development involves determining which excipients will be combined with the API in the final product to provide the delivery **Dosage Form** , whether that be solid, liquid, or semi-solid (e.g. a hydrogel). Critically, formulation development is where API aqueous solubility issues are best addressed, typically through designing different API salts, developing co-crystals, or through particle engineering.

Although designing different API salts is a familiar approach, it is largely based on trial and error as the link between salt form and solubility is currently poorly understood. Moreover, because some APIs lack the functional groups required for salt formation, comparing different salts is not always a viable strategy. Co-crystallization overcomes this problem by combining the API and one or more co-formers in the same crystal lattice. It provides opportunities for developing solid-state forms other than conventional salts and polymorphs, and is also open to supramolecular engineering—the exploitation of supramolecular interactions such as Van der Waals forces, hydrogen bonding and electrostatic interactions to improve the physicochemical properties of the API.

Particle engineering technologies include micronization, **Lyophilization** and spray drying. Micronization functions to reduce the average particle diameter of a solid

material through collisions with moving parts of the milling system (e.g., ball-milling, pin-milling, or hammer milling) or with itself (e.g., jet milling). A main drawback of this method is that the mechanical stresses it generates can cause local heating that may **Lead** to melting, degradation, or structural defects; micronization also offers only limited control over key particle characteristics and has high associated material losses. Lyophilization and spray drying are more controllable and instead involve rapid drying of a liquid containing the dissolved API to generate an amorphous solid dispersion (ASD). Spray drying provides several important advantages over lyophilization, including elimination of the need for a post-drying milling step, as discussed below.

Spray drying is an established solubility enhancement technology

Spray drying has been successfully applied across multiple industries (predominantly the food and pharmaceutical industries) to convert a liquid feed into a powder. In drug manufacturing, it is an established particle engineering technology that involves dissolving the API in a solvent with one or more polymers (to prevent crystallization) and any necessary excipients, before injecting the mixture into a specialized spray dryer apparatus. As the liquid enters the spray dryer, it is atomized by a nozzle to form small, spherical droplets; these are then rapidly dried by a powerful blast of heated air (or nitrogen when working with organic solvents) within the spray drying chamber.

Following any additional drying cycles, and particle separation in a cyclone, the resulting ASD is collected and can be used to manufacture the final **Drug Product** . The main objective of the spray drying process (Figure 2) is to transform the API into an ASD exhibiting improved solubility and physical **Stability** compared to the parent material.

Advantages of spray drying

A major advantage of spray drying over other particle engineering technologies is its capacity to operate as a rapid, continuous process. This removes any limitations on **Batch** size, as well as allowing for the implementation of process analytical technology to ensure reliable operation. Moreover, unlike technologies such as micronization and lyophilization, spray drying avoids the need for a milling step (during lyophilization, milling is occasionally required to convert the dried material into a fine powder) that can compromise the performance of thermolabile APIs or biologics that are sensitive to abrasion or shearing.

Perhaps most importantly, spray drying provides tight control over critical product parameters such as particle size, density, and morphology; these can be fine-tuned by adjusting key process parameters or changing the sprayed **Solution** composition to ensure consistent production of a high-quality product. Additionally, when compared directly with lyophilization, spray drying is more cost-effective and compatible with a broader range of solvents; these include both water-based solutions and class 3 solvents such as methanol, ethanol, acetone, and ethyl acetate, which can be recovered and recycled.

Challenges of spray drying

Despite being a leading technology to enhance drug solubility, spray drying requires an experienced operator to accurately control particle quality and yield. Factors that must be considered include the composition, concentration, and stability of the parent solution (both the drug and any polymers need to dissolve in the solvent system) and whether heating is required to decrease the viscosity of the feed; in this scenario, both the API and any excipients must be stable at high temperature.

It is also important to select an appropriate nozzle. While pressure nozzle atomization may be more suitable where a larger average particle size is required, rotary nozzle atomization is often preferred for achieving a narrower particle size distribution (PSD), and multi-feed nozzles should be used where two or more liquids will be injected in parallel. Other considerations include whether the air/nitrogen should be blown from the bottom of the drying chamber or the top (the latter is frequently employed as a means of preventing over-heating), and the temperature at both the inlet and the outlet points, which is critical for producing stable particles and ensuring process robustness. The size of the spray dryer will be dictated by the required production scale; models range from benchtop size for initial development stages through larger commercial scale spray dryers capable of producing kilograms of material per hour.

Partnering with an experienced API CDMO

The effective use of spray drying for solving solubility and bioavailability challenges in drug manufacturing hinges on strong expertise in process design and development, as well as a robust working knowledge of all quality and regulatory requirements for GMP commercial production. Experience is also critical to establish early on whether a particular **Drug Substance** is an appropriate candidate for spray drying or more suitable for other bioavailability enhancing technologies, and to efficiently identify formulation conditions that provide the desired solubility, dissolution rate, content uniformity, and bioavailability. One way of accessing this knowhow is to partner with an API CDMO experienced in the use of spray drying for a broad range of drugs—including high potency APIs (HPAPIs)—and offering the right equipment, team and facilities for the job.