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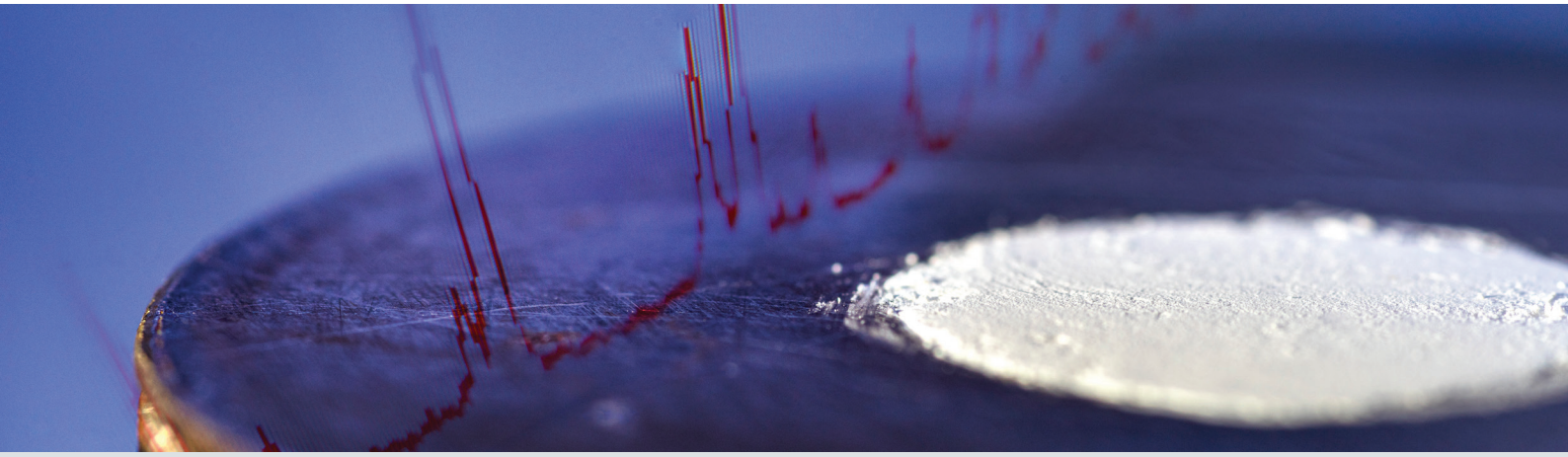
White paper



Access the Advantages of Spray Drying with an Experienced API CDMO

A rapid, continuous, and cost-effective technology for improving API bioavailability, spray drying is experiencing huge demand as the number of poorly soluble small molecule drugs grows.

Low aqueous solubility of active pharmaceutical ingredients (APIs) often translates to poor bioavailability that can be a cause of failure during drug development. As such, improved aqueous solubility is a primary objective of formulation development, especially for oral, inhaled, and topical drug treatments. Spray drying is an established particle engineering technology that involves producing dry powders from a fluid material through atomization into a hot drying gas medium, usually air or nitrogen. It offers several advantages over other particle engineering technologies, not least the capacity for continuous operation that removes any limitations on batch size. Other benefits of spray drying include rapid, scalable, cost-effective operation, and implicit compatibility with process analytical technology to safeguard highly reproducible drug production. Spray drying is also more controllable, especially in the hands of an experienced API CDMO.

> *Spray drying is a rapid, continuous, cost-effective, reproducible, and scalable process for producing dry powders from a fluid material, and is widely used to improve the solubility and bioavailability of APIs.*

As the number of poorly soluble small molecule drugs increases, the demand for spray drying capacity is on the rise. Production slots are booked well in advance, creating a bottleneck that threatens to prolong time-to-market. To alleviate this situation and deliver on strategic market needs, Wavelength Pharmaceuticals continues to invest in both current and next-generation spray drying technologies to address solubility and bioavailability challenges for a broad range of therapeutics. With spray drying expertise gained from more than 30 years of developing and manufacturing its own product portfolio, Wavelength offers state-of-the-art equipment to support diverse manufacturing requirements that span small-scale clinical drug development projects all the way through to commercial-scale GMP production.

Low aqueous solubility can be a major problem

Low aqueous solubility can be a major hurdle for many dosage forms in various routes of administration. This is especially the case in oral dosing (the most convenient form of drug delivery, commonly associated with high patient compliance), where low aqueous solubility can significantly restrict oral drug absorption within the gastrointestinal tract to limit bioavailability. Consequently, addressing low aqueous solubility is a primary objective of formulation development to help assure regulatory approval and bring much needed therapeutics to patients.

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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. Both Class 2 and Class 4 drugs are candidates for solubility enhancement.

The Biopharmaceutics Classification System (BCS) as defined by the FDA after Amidon et al

Figure 1. The Biopharmaceutics Classification System (BCS) as defined by the FDA after Amidon et al.

Addressing aqueous solubility through formulation development

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, providing opportunities for developing solid-state forms other than conventional salts and polymorphs. Notably, **co-crystallization** also enables improvements to the physicochemical properties of the API through supramolecular engineering – the exploitation of supramolecular interactions such as Van der Waals forces, hydrogen bonding, and electrostatic interactions.

> *Critically, formulation development is where API aqueous solubility issues are best addressed.*

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. During lyophilization, milling is occasionally required to convert the dried material into a fine powder.

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 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 is to transform the API into an ASD exhibiting improved solubility and physical stability compared to the parent material.

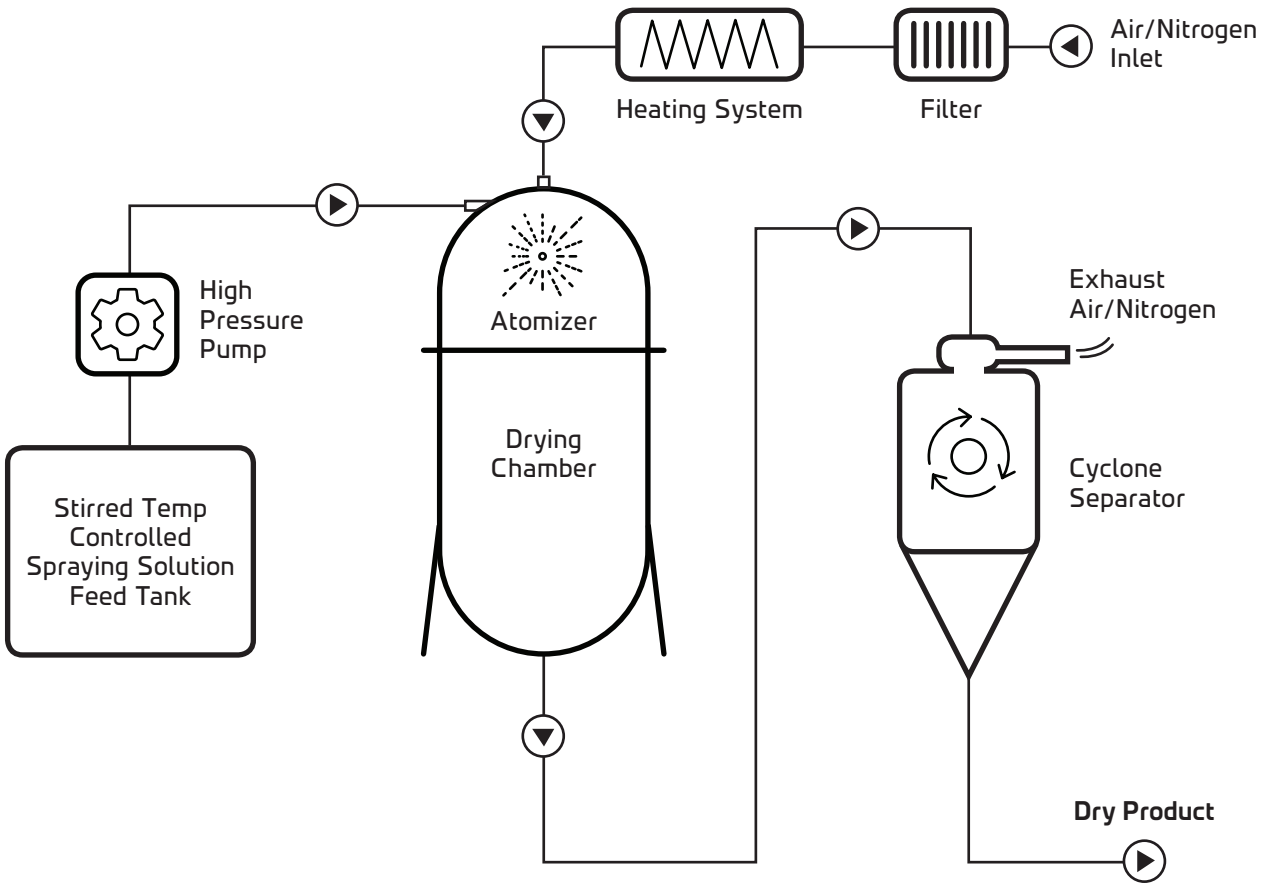


Figure 2. The spray drying process.

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. Unlike technologies such as micronization and lyophilization, spray drying avoids the need for a milling step that can compromise the performance of thermolabile APIs or biologics that are sensitive to abrasion or shearing.

A further important benefit of spray drying is that it provides tight control over critical product parameters, such as particle size, density, and morphology, that can be fine-tuned by adjusting key process parameters or changing the sprayed solution composition to ensure **consistent production** of a high-quality product. Spray drying is also readily **scalable** and, when compared directly with lyophilization, is both 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.

Advantages of spray drying over other particle engineering technologies

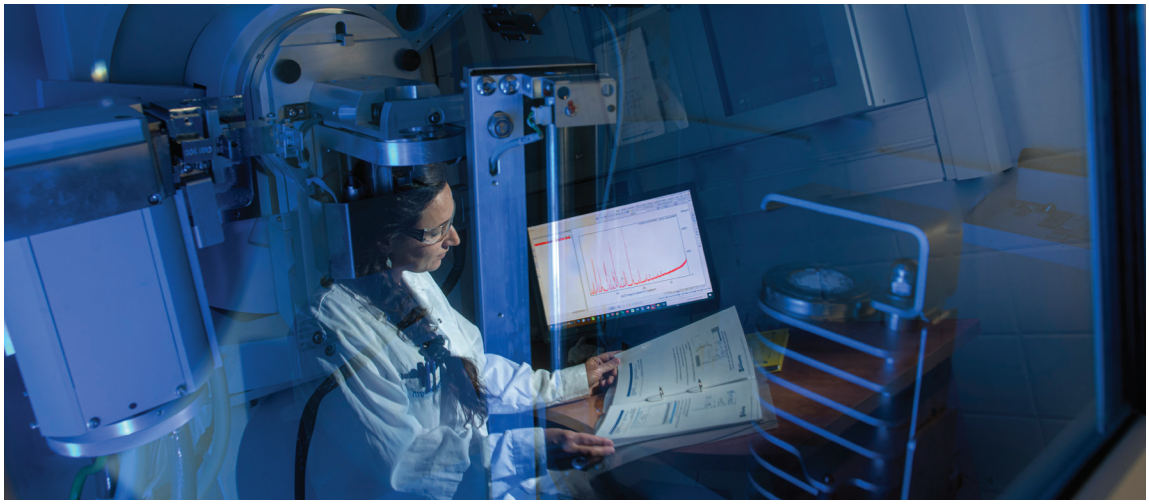
- Operates as a rapid, continuous process – avoids limitations on batch size and allows for the implementation of process analytical technology
- Eliminates the need for a milling step – compatible with thermolabile APIs or biologics that are sensitive to abrasion or shearing
- Provides tight control over critical product parameters – enables fine-tuning of particle size, density, and morphology for a consistent, high-quality product
- Scalable – streamlines transition from small-scale clinical drug development through commercial-scale GMP production
- Cost-effective – high productivity saves both time and money
- Compatible with a broad range of solvents - including water-based solutions and class 3 solvents (e.g., 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 the latter 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.

> *Spray drying requires an experienced operator to accurately control particle quality and yield.*

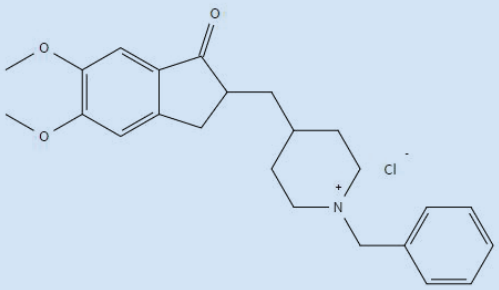
Other considerations include whether the air / nitrogen should be **blown from the bottom of the drying chamber or the top** (the latter is frequently employed as a means of preventing over-heating), and **the temperature at both the inlet and the outlet** points, which is critical for producing stable 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.



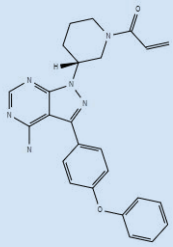
Spray drying experience

Wavelength has applied its expertise in spray drying technology to improve the solubility and bioavailability of a broad range of APIs. For example, by pre-mixing Donepezil Hydrochloride (a cholinesterase inhibitor used to treat dementia associated with Alzheimer's disease) with lactose for spray drying, Wavelength has enhanced the chemical and physical stability of this widely used drug.

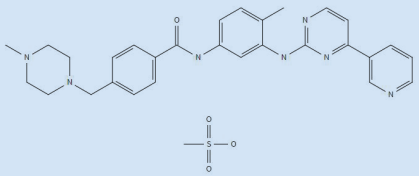
Other APIs benefiting from Wavelength's spray drying capabilities include Ibrutinib and Imatinib Mesylate (tyrosine kinase inhibitors used to treat cancer), Montelukast Sodium (a leukotriene receptor antagonist for treating asthma), and Rocuronium Bromide (a muscle relaxant used in anaesthesia).



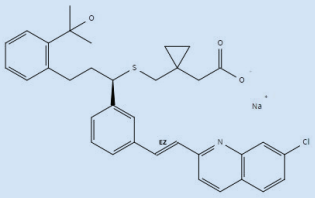
Donepezil Hydrochloride



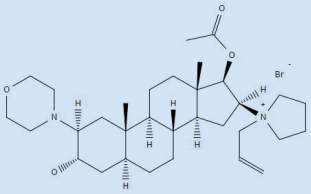
Ibrutinib



Imatinib Mesylate



Montelukast Sodium



Rocuronium Bromide

Wavelength Pharmaceuticals – strong expertise in spray drying

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 for establishing 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.

> *Experience is critical for establishing early on whether a particular drug substance is an appropriate candidate for spray drying.*

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 team, equipment, and facilities for the job. With spray drying expertise gained from more than 30 years of developing and manufacturing its own product portfolio, and a proven track record in quality and regulatory compliance, Wavelength Pharmaceuticals is your partner of choice for development and scale up of unique spray drying solutions. Through ongoing investment in state-of-the-art equipment, backed by a culture of transparency with its clients, Wavelength has supported diverse manufacturing requirements that span small-scale clinical drug development through commercial-scale GMP production for market launch.

Scale up capabilities: pre-clinical grams to commercial scale

- Wavelength's spray dying capabilities span gram-scale clinical drug development through multi-ton commercial-scale GMP production, ensuring timely delivery of a consistent product to meet any manufacturing requirement.

To ensure partners receive the most appropriate solution for addressing solubility and bioavailability issues, Wavelength's highly knowledgeable team maintains an up-to-date working knowledge of established spray drying technologies and next-generation techniques. And, by accommodating the growing demand for spray drying as the number of poorly soluble drug molecules in development continues to grow, Wavelength Pharmaceuticals is well-positioned to help address potential bottlenecks and bring essential drugs to market sooner.

If you're looking to improve the aqueous solubility and bioavailability of your API, we have everything you need to succeed.

Contact us at **marketing@wavelengthpharma.com** to discuss how we can help bring your drug to market.

Wavelength is a customer-focused backward-integrated world-class developer and manufacturer of Active Pharmaceutical Ingredients (APIs). It is the independent company of choice for pharmaceutical industry leaders that require advanced API solutions and reliable supply to gain sustainable competitive advantage. The company is on the same wavelength as its customers – a partner in tune with the results required to best support their needs. Founded in Israel in 1987, with more than 280 customers in 50 countries, Wavelength produces more than 630 metric tons of commercial products every year, across a wide range of technologies including injectables, inhalables, highly potent, cytotoxic and controlled substances. Its cGMP-compliant facility is a first-class operation recognized for excellence in safety and environmental stewardship. Wavelength has achieved an exceptional track record for more than 30 years with all leading global regulatory authorities, including USFDA, EU-EMA, PMDA, TGA, KFDA, ANVISA and COFEPRIS. The company includes experts in complex chemistry, process development and scale-up, enzymatic reactions, crystalline forms and particle design, spray drying and other bioavailability-enhancing solutions. Wavelength offers end-to-end customized solutions to meet individual customer requirements, including full-spectrum API CDMO services from pre-clinical grams to multi-ton commercial scale – always with uncompromising consistent quality, regulatory compliance and exceptional customer service.

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