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SPRAY-DRIED DISPERSIONS

An Innovative Solution for Poorly Soluble Molecules in Early-Phase Drug Development

IN THIS ISSUE

we examine spray-dried dispersions (SDDs) as an effective method to improve solubility and bioavailability of your active pharmaceutical ingredient (API) in early-phase drug development. We review the spray drying process, which converts a liquid into a dry powder, and how the resulting SDDs benefit from improved characteristics for further development. We also discuss the combination of spray drying with nanomilling for further bioavailability improvements and flexible downstream processing.

Additionally, we explore the applicability of testing proof-of-concept, as well as creating material for first-in-human (FIH) clinical trials. Leveraging our in-house preclinical services, we also have the unique capability to test spray-dried material versus raw API *in vivo*, generating meaningful data to compare with *in vitro* test results.

HOW SDDs IMPROVE EFFICIENCY OF EARLY-PHASE DRUG DEVELOPMENT

In drug development, SDD technology is often used to **enhance the solubility and bioavailability of poorly water-soluble APIs** by incorporating them into a polymer matrix. This polymer matrix helps to stabilize the API in an amorphous, high-energy state, providing greater solubility than its crystalline form. In contrast to the crystalline API structure, the amorphous (or "formless") version of the API has a much lower lattice energy cost, which allows the body to break down and absorb more of the API during its bodily time course. The polymer in the SDD plays an integral role, acting as a carrier and stabilizer that prevents the drug from recrystallizing and maintains its improved solubility.

Spray drying also **supports particle engineering** by allowing precise control over particle size, shape, and morphology, which is crucial for optimizing drug delivery, particularly for inhalation and nasal delivery systems.

Spray drying can enable poorly soluble compounds to become viable drug products, even in cases where no clear path forward previously existed. As over 70% of New Chemical Entities (NCEs) are considered poorly soluble, spray drying offers a path forward for these otherwise abandoned molecules and allows them a chance to become marketed drugs.

In the early phases of product development, proof-of-concept (POC) can be established by producing small quantities of material (milligram quantities) and comparing its solubility to that of the unformulated API. This type of POC testing can demonstrate that enhanced solubility leads to more efficient product use and substantial API cost savings over the course of a development program. Additionally, preparing small batches of SDDs for preclinical animal studies provides valuable pharmacokinetic (PK) data to support the selection of an appropriate enabling technology for later development stages and the final commercial drug product.

APPLICATIONS AND BENEFITS OF SPRAY DRYING IN EARLY-PHASE DRUG MANUFACTURING

Spray drying can convert APIs into amorphous forms with enhanced dissolution properties, making this technology ideal for APIs with poor aqueous solubility. With spray drying, drug developers can improve their API's formulation in a number of ways, depending on the specifics of each individual program.

1 Enhancing Solubility and Bioavailability

Spray drying improves the solubility and bioavailability of poorly water-soluble drugs by converting APIs into an amorphous state and dispersing them in a polymer matrix.

2 Producing Inhalable Powders

Aqueous spray drying produces inhalable powders for pulmonary drug delivery. The fine, uniform particles are ideal for delivery to the lungs, where they can be rapidly absorbed into the bloodstream.

3 Formulating Controlled Release Drugs

The polymer matrix can release the drug at a controlled rate, providing a sustained therapeutic effect over an extended period.

4 Encapsulating APIs

Spray drying encapsulates APIs in a protective matrix, shielding them from environmental factors such as moisture, heat, and light. This encapsulation enhances the stability and shelf life of the drug.

5 Providing Taste Masking

With the API encapsulated in a polymer matrix, the typical bitter API taste is not discernable.

6 Developing Vaccines and Biologics

Spray drying stabilizes sensitive biological molecules and converts them into a dry powder form, making vaccines and biologics easier to store and transport.

7 Easy Scalability for Later Phases

The spray drying process is suitable for both small-scale and large-scale production. This flexibility ensures that spray drying can be used in various stages of drug development, from preclinical studies to commercial manufacturing.

8 Reducing Costs

Compared to other methods (like freeze-drying), spray drying is a cost-effective and scalable method for producing high-quality pharmaceutical powders. It allows for efficient use of materials and energy, reducing overall production costs, making it ideal for early-phase research and final dosage form development.

9 Higher Drug Loading

Spray drying allow for a small tablet or capsule to contain fewer functional excipients, and therefore, more API. During early-phase development, we can test optimal excipients and maximize drug load, which can help scale the drug product to clinical trial material or beyond.

Spray drying technology offers a versatile and efficient approach for **formulating low-dose, high-potency APIs**, particularly when uniform API distribution within a carrier matrix is critical. The rapid solvent evaporation characteristic of spray drying minimizes thermal and moisture exposure, making it especially suitable for APIs that are sensitive to heat or humidity. Additionally, the process allows for precise particle engineering, enabling control over particle size, morphology, and surface properties to meet the requirements of various delivery routes, including inhalation, oral, and parenteral, as well as reconstitutable dosage forms.

For programs with complex formulation needs, spray drying can also be effectively combined with other technologies, such as nanomilling, to achieve synergistic performance benefits.

The decision to implement an SDD—as a standalone approach or in conjunction with complementary techniques—should be guided by a skilled CDMO partner to ensure optimal formulation strategy. A CDMO can provide critical insights into feasibility, scalability, regulatory considerations, and the technology's risk–benefit profile.

ADVANCES IN SPRAY DRYING TECHNOLOGY FOR PHARMACEUTICAL DEVELOPMENT

Recent advances in spray drying technology have further enhanced its capabilities and applications in pharmaceutical development. Advances such as using dehumidified air or vacuums have helped to overcome challenges like thermal degradation and the stickiness of particles.

Other Recent Evolutions in the Field

Advanced Atomization Techniques and Novel Nozzle Designs: New atomization techniques, such as ultrasonic and electrostatic atomization, enable better control over droplet size and distribution, leading to more uniform particle sizes, enhanced product quality, and improved process efficiency.

Real-Time Process Monitoring: Advanced process monitoring technologies which minimize human intervention provide real-time data on the spray drying process, allowing for precise control and optimization of the parameters. This ensures the consistent production of high-quality spray-dried powders.

Integration With Continuous Manufacturing: Integrating spray drying with continuous manufacturing processes offers significant advantages in terms of efficiency and scalability. Continuous manufacturing supports the production of large quantities of spray-dried powders in a streamlined and cost-effective manner.

Use of Novel Excipients: The development of novel excipients with enhanced solubilizing properties has expanded the applications of spray drying. These new excipients offer improved compatibility with a wider range of drugs, further enhancing the solubility and bioavailability of challenging compounds.

Formulation of Biologics: Spray drying technology is now being applied to the formulation of biologics, including peptides and proteins. This offers new opportunities for improving the stability and delivery of these complex molecules.

THE USE OF SPRAY DRY TECHNOLOGY IN EARLY-PHASE DEVELOPMENT OF PROTEINS AND PEPTIDES

In addition to its applicability in improving bioavailability and solubility for small molecule APIs, spray drying can be used to improve the formulation of certain biologics. In the development of biologics, particularly peptides and proteins, the use of spray dry technology has some variations due to distinct differences in molecular size, structure, and stability of these molecules.

Molecular Stability and Structural Integrity

Peptides are smaller and generally more robust than full-length proteins. They can tolerate moderate stress during spray drying (e.g., temperature, shear, and dehydration) if properly formulated with stabilizing excipients. SDD is a viable method for converting peptides into stable, solid dosage forms, especially for oral, pulmonary, or subcutaneous delivery.

Proteins are larger, more structurally complex, and highly sensitive to denaturation and aggregation during spray drying. The high surface area exposure and thermal/mechanical stress can disrupt tertiary/quaternary structures. For these reasons, spray drying proteins is more challenging and often requires careful control of process parameters and inclusion of protective excipients (e.g., sugars, surfactants).

Formulation Considerations

SDDs for **peptides** often use polymers, such as PVP or HPMC-AS, as carriers to enhance dispersion and protect against degradation, while encapsulation in amorphous matrices can improve both physical stability and bioavailability, especially for non-parenteral routes.

For **proteins**, the choice of excipients is more limited due to their sensitivity. Stabilizers like trehalose, mannitol, or amino acids are commonly used. However, forming a true molecular dispersion (as in traditional small-molecule SDDs) is more challenging, as proteins may be embedded in a matrix without fully dissolving, resulting in more of a spray-dried powder than a true SDD.

Bioavailability and Delivery Route

SDDs can significantly improve the oral or pulmonary bioavailability of **peptides**, which are otherwise rapidly degraded in the GI tract or poorly absorbed. They can also be engineered for sustained release.

Due to the size and degradation sensitivity of **proteins**, oral delivery via SDD is less feasible. Most applications focus on pulmonary, intranasal, or long-acting injectable routes. Even so, maintaining protein activity post-spray drying is a significant limitation.

Development Stage and Regulatory Acceptance

Peptide applications are more advanced in terms of SDD adoption, with several candidates in clinical development or approved for alternative delivery systems (e.g., inhaled insulin peptides, oral GLP-1 analogs).

SDD use is still largely exploratory for **proteins**. Due to its gentler processing, lyophilization remains the dominant technique for protein stabilization in most commercial biologics.

FEATURE	PEPTIDES	PROTEINS
Molecular Size	Small	Large
Structural Sensitivity	Moderate	High
SDD Feasibility	High (with stabilizers)	Moderate to low
Common Routes	Oral, pulmonary, SC	Pulmonary, nasal, injectable
Bioavailability Benefit	Improved via SDD	Challenging to maintain bioactivity
Regulatory Use	Increasing clinical and commercial use	Limited, mostly in research

HOW THE SPRAY DRYING PROCESS WORKS: IN FOUR STEPS

1 Dissolving

The drug and polymer are dissolved in a suitable solvent, often a volatile organic solvent like ethanol, acetone, dichloromethane, DMSO, or tetrahydrofuran. The choice of solvent is an important consideration; CDMO experts will select the most appropriate solvent based on program specifics.

2 Atomizing

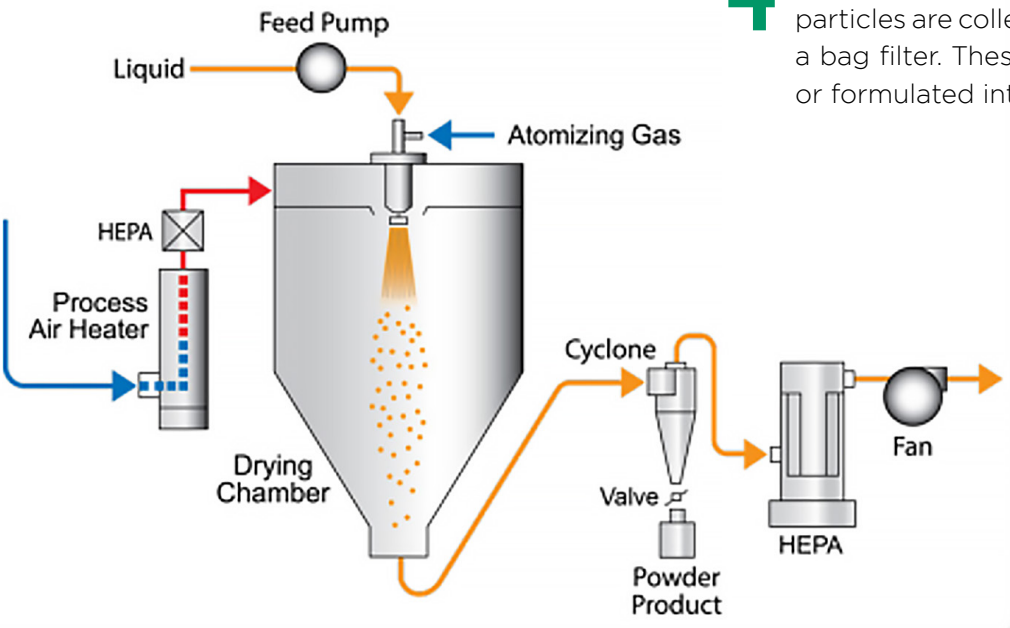
The solution is then atomized into a fine mist of droplets using either a rotary atomizer or a nozzle atomizer. This breaks the liquid into tiny droplets, increasing the surface area for efficient drying.

3 Drying

The fine droplets go into a drying chamber, where they are dried with hot air ranging from 100°C to 200°C, depending on the API's thermal sensitivity. The hot air rapidly evaporates the solvent, leaving behind solid particles of the drug product.

4 Collecting

Now in an amorphous solid dispersion, the dried particles are collected using a cyclone separator or a bag filter. These particles are further processed or formulated into the final product for testing.



KEY CONSIDERATIONS FOR THE DEVELOPMENT OF SPRAY-DRY PHARMACEUTICALS

There are currently no specific, prescriptive regulations solely for spray drying processes. That said, spray drying is a manufacturing process that should follow broader regulations, particularly Good Manufacturing Practices (GMP) and quality control. Documentation and record keeping, microbiological controls, and other standards outlined in the regulations apply to spray-dried materials.

Important parameters that relate directly to the spray drying process itself include solvent selection, process parameters, polymer selection, and product characterization.

Solvent Selection

It is important to choose a solvent that can dissolve the pharmaceutical compound and be easily removed during the drying process. Common solvents used in spray drying include water, ethanol, and acetone. The type of solvents used largely depend on the type of API and the overall chemical stability of the API. For instance, volatile solvents are generally used when the API is thermodynamically unstable, such as CBD and biologics (like peptides), and the volatile solvent can be removed at a lower temperature while maintaining the API's integrity. The objective is to use a solvent that effectively dissolves the components, evaporates rapidly during drying, and leaves minimal residual solvent in the final product. CDMO experts will select the most appropriate solvent based on program specifics.

Process Parameters

Optimization of the spray drying process parameters, such as inlet temperature, feed rate, and atomization method, ensures the formation of high-quality spray-dried powders. These parameters can significantly impact the particle size, morphology, and stability of the final product. Heat-sensitive APIs, such as itraconazole, benefit from higher solution feed rates by reducing their exposure duration to heat. Itraconazole is dissolved in volatile organic solvents, like ethanol or acetone, which rapidly evaporate when atomized, reducing high-temperature exposure and risk of recrystallization. This improves encapsulation efficiency in an amorphous state within the polymer matrix.

Polymer Selection

It is critical to use a polymer that is compatible with the drug and enhances its solubility. Commonly used polymers include hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), and ethyl cellulose.

Product Characterization

Thorough characterization of the spray-dried powder to ensure it meets the desired specifications is a crucial step. Your CDMO will evaluate the particle size distribution, morphology, solid-state properties, and dissolution rate of the powders.

HOW ALTASCIENCES CAN HELP

Partnering with a CDMO that has the latest in spray dry technology, expertise in testing and analysis for the final project, and the ability to integrate with earlier and later phases of drug development, delivers measurable value for sponsors.

We have the **MOST ADVANCED EARLY-STAGE SPRAY DRYING MACHINERY** and capabilities available on the market today. Our PROCEPT Spray Dryer is a complete process tool that generates reliable, repeatable, and scalable results in a minimum of time.

Its Unique Features

- High process yields (>90%) from 1 ml (10 mg) to 10 L batch size
- Particle size control from 1-350µm
- PC control with real-time trending and Excel data reporting
- Aqueous and organic solvent processing
- Part 11 Compliance for FIH GMP Material Preparation

With our nanomilling expertise, we can reduce the particle size of your substance to the nanoscale (typically 10-1000 nanometers) and convert a liquid feed containing those nanoparticles into a dry powder by using an aqueous spray processing. With these techniques and capabilities, we can create stable, solid dosage forms of nanomaterials, potentially preserving the nanocrystal size and enabling controlled drug release, while also improving the stability of your nanomilled products.

Our experts can compare *in vivo* results (in rodent or even canine/swine models) to *in vitro* results (assay or dissolution testing) on account of our in-house preclinical services. This integration between the formulation and preclinical stages ensures that enabled technology is needed for the product and going to SDD will be beneficial in a real metabolic environment.

We are fully equipped and have the preclinical and CDMO facilities to spray small amounts of product (mg to g scale) to conserve your API, and then send the SDD to one of our four preclinical facilities to test in animals, while *in vitro* testing is performed directly at our CDMO site.

Our cross-functional preclinical and clinical teams enable concurrent development activities, ensuring seamless transfer and efficient scale-up, while our regulatory experts—well-versed in global requirements—guide you through your IND/CTA submissions. This fully integrated CRO/CDMO model helps streamline timelines and reduce costs from preclinical to commercial manufacturing.

Our **turnkey pharmaceutical development and manufacturing services** include:

- Full analytical and physical characterization of your molecules
- Pre-formulation testing, formulation, and process optimization
- R&D and cGMP manufacturing—from early development through to clinical trial supply (Phases I to IV)
- Handling of potent and non-potent APIs
- In-house spray nanomilling and spray drying equipment
- Manufacturing of all dosage forms, including tablets, powder and liquid-filled capsules, terminally sterilized injectables, nanomilled suspensions, gels and creams
- Over-encapsulation, labeling, and clinical packaging
- Scale-up and engineering batch manufacturing
- Late-phase and commercial-scale manufacturing of finished dosage forms

ALTASCIENCES' RESOURCES

Scientific Publications

Spray Drying Nanosuspensions eBook

The Altascientist Issue 22—Nanomilling for Better Solubility and Improved Bioavailability

The Altascientist Issue 17—Maximizing Drug Formulation for First-in-Human Trials

Webinars and Podcasts

Webinar—Successful Manufacturing of Clinical Trial Supply

Webinar—The Development of Nanosuspension Formulations for Poorly Soluble Drugs

Podcast—Tips to Ensure Successful Formulation for Nonclinical Testing

Fact Sheet

A Novel Approach for Improved Bioavailability in Solid Dosage Forms

Webpages

Wet Nanomilling and Vial Filling Services

Pharmaceutical Contract Manufacturing Services

ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 30 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.