# Spray-Drying Formulation and Process Development Advances Expand Opportunities for Formulations Via Intranasal and Pulmonary Delivery

## INTRODUCTION

Dry powder inhalers (DPIs) are a leading drug-delivery platform for the treatment of respiratory diseases and have been used successfully to deliver intranasal and pulmonary formulations for a wide range of active pharmaceutical ingredients (APIs) and medical conditions. Increasingly, DPIs are also being considered for systemic drug delivery due to the rapid onset of action of inhaled drug products and exposure to the pulmonary vasculature.

Engineered spray-dried (SD) particles have the potential to expand the choices available to formulators as they consider DPIs as a delivery platform. Pulmonary formulations using SD drug product have market precedence in DPI delivery, and SD particles have been shown to enable rapid development timelines; provide excellent powder homogeneity; and facilitate flexibility in the choice of APIs, excipients, and drug-delivery profiles.

This white paper provides an overview of inhaled drug delivery and formulation options for DPI delivery using SD technology pioneered by Bend Research, a division of Capsugel Dosage Form Solutions, and specially designed capsules developed by Capsugel. A case study is presented that describes an integrated approach to formulation, process design, and drug-delivery system selection. This case study is focused on the formulation and delivery of albuterol sulfate using a capsule-based DPI delivery system that employs Capsugel VCaps® hydroxypropyl methylcellulose (HPMC) capsules. A fundamentals-based formulation strategy was used to produce engineered SD particles that met the target quality attributes for successful pulmonary delivery. The case study demonstrates how the right formulation, processing conditions, and delivery approach can be successfully combined to optimize drug delivery, while minimizing development time, cost, and materials.

To enhance understanding of our approach in this case study, we present background information on (1) inhaled drug delivery; (2) SD technology, including formulation and process considerations for inhaled applications; and (3) DPI delivery systems.

## BACKGROUND

### Background: Inhaled Drug Delivery

Inhaled drug delivery via intranasal and pulmonary routes is of increasing interest to drug formulators seeking to improve the performance of New Chemical Entities (NCEs) and extend the lifecycle of existing drugs. While inhaled delivery can prove challenging, it is an attractive drug delivery route for local and systemic drug delivery.[1]

Currently, inhaled delivery is most commonly used to treat respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD), which are becoming more prevalent as populations age globally and air pollution increases in developing countries.[2] According to IMS Health, asthma/COPD is one of the top 10 indications, based on spending by therapy class, in the developed and emerging markets, and relative spending on this indication

[1] Anderson, P.J., "Delivery Options and Devices for Aerosolized Therapeutics," *Chest*, 120:3(2001)89S-93S.
[2] Mannino, D.M., and S.A. Buist, "Global Burden of COPD: Risk Factors, Prevalence, and Future Trends," *The Lancet*, 370:9589(2007)765-773.

is projected to rise through 2017.[3] Inhaled delivery is also being explored to treat systemic diseases since it offers the potential for (1) improving the bioavailability of drugs that are otherwise poorly absorbed within the gastrointestinal tract, (2) providing a needle-free route for administering treatments for infectious diseases such as influenza,[4] (3) administering pain medication for rapid relief, and (4) delivering biologics such as gene therapies and vaccines.[5]

Inhaled formulations can be delivered using several types of devices, but DPIs are increasingly popular because they offer technical and environmental benefits over metered-dose inhalers (MDIs), which use aerosols as propellants. DPIs are compact portable devices that are convenient and easy to use and can deliver between 0.1 and 40 mg of medication without the use of propellants. In addition, they are not dependent on hydrofluoroalkane (HFA) solubility or suspension stability. DPIs have established market precedence, having been used successfully to formulate inhaled insulin and antibiotics (e.g., TOBI®),[6] and an extensive record of success in treating many respiratory conditions.[7] In 2011, DPIs accounted for nearly 40% of the inhalation devices used in Europe.[8]

Successful formulation of inhaled formulations using DPIs requires in-depth knowledge of how API and excipient characteristics and process variables affect key quality attributes, which include mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), emitted fraction (EF), and fine particle fraction (FPF). To ensure the API is effectively delivered, drug and carrier must disperse easily upon inhalation. The particles in the aerosol must be uniform in size, shape, density, and surface area to ensure they do not aggregate. Past research has shown that disparity in these physicochemical properties can negatively affect the drug's performance.[9,10,11,12]

**Background: SD Technology**

Engineered SD particles offer a particularly promising approach to the production of particles with the desired characteristics for inhaled delivery. Bend Research has demonstrated that with the proper selection of formulation components and process conditions, engineered SD formulations can readily be optimized for inhalation delivery. Engineered SD particles have been shown to offer substantial advantages over conventional formulations (e.g., blends containing micronized API and a lactose carrier) for inhaled formulations, including

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3 IMS Health Thought Leadership, "General Use of Medicines Report, September 2013.

4 Anon., "Daiichi Sankyo Receives Approval for the Use of Inavir® To Prevent Influenza," http://www.daiichisankyo.com/media_investors/media_relations/press_releases/detail/006052.html.

5 Laube, B.L., "The Expanding Role of Aerosols in Systemic Drug Delivery, Gene Therapy and Vaccination," *Transl. Respir.,* 2(2014)3.

6 Hollander, P.A., "Evolution of a Pulmonary Insulin Delivery System for Patients With Diabetes," *Med. Gen. Med.,* 9:1(2007)45.

7 Atkins, P.J., "Dry Powder Inhalers: An Overview," *Respir. Care*, 50:10(2005)1304-1312.

8 Lavorini, F., C.J. Corrigan, P.J. Barnes, P.R. Dekhuijzen, M.L. Levy, S. Pedersen, N. Roche, W. Vincken, and G.K. Crompton, "Retail Sales of Inhalation Devices in European Countries: So Much for a Global Policy," *Respir. Med.*, 105:7(2011)1099-1103.

9 Dunbar, C.A., A.J. Hickey, and P Holzner,"Dispersion and Characterization of Pharmaceutical Dry Powder Aerosols," *KONA*, 16(1998)7-45.

10 Gonda, I., "Targeting by Deposition," in *Pharmaceutical Inhalation Aerosol Technology*, A.J. Hickey (Ed.), 2(2004)65–88.

11 Telko, M.J., and A.J. Hickey, "Dry Powder Inhaler Formulation," *Respir. Care,* 50(2005)1209-1227.

12 Donovan, M.J., and H.D. Smyth, "Influence of Size and Surface Roughness of Large Lactose Carrier Particles in Dry Powder Inhaler Formulations," *Int. J. Pharm.,* 402:1-2(2010)1-9.

- ***improved efficiency***—more drug is delivered to the lung and less waste occurs due to the tighter particle-size distribution achievable with SD technology;
- ***improved formulation flexibility***—SD formulations are suitable for crystalline or amorphous drug forms, do not require jet-milling, are compatible with lactose, and are suitable for aerosolization;
- ***suitable for a wide range of APIs***—SD formulations are suitable for compounds with low aqueous solubility and can be used for protein delivery, for instance, because they avoid lactose-incompatibility issues; and
- ***suitable for different formulation types***—SD formulations are suitable for formulations containing API alone; API bound to lactose; API with a range of carrier and aerosol-enhancing excipients (e.g., sugars, polymers, amino acids, surfactants, and salts); and combination therapies containing multiple APIs.

***SD Formulation***

Bend Research develops SD formulations using a well-defined process methodology, which includes analysis of the API's key physicochemical parameters, including melting temperature ($T_m$), glass-transition temperature ($T_g$), organic and aqueous solubilities, and partition coefficient.

The first step is to develop a stable spray solution or suspension that incorporates API, excipients, and a suitable solvent. Thorough understanding of the organic and aqueous solubility of the API and excipients (or lack of solubility) is key to preparation of a stable spray solution or suspension, preventing API precipitation or destabilization before spray-drying. This understanding also helps define the final state of the API and excipients in the engineered SD particles. The physical state of these formulation components directly affects physical variables that are important in drug formulation and ultimate manufacturability of finished dosage forms, such as solvent burden, manufacturing yield, distribution and position of the API and excipients within the final dried particle, particle morphology, particle surface energy, and anticipated aerosol characteristics, as well as short- and long-term formulation stability. This understanding is particularly important for combination therapies with multiple APIs and/or formulations with multiple excipients.

To assist in formulation, Bend Research uses "biomodels" that help predict and understand the impact of formulation variables on pharmacokinetic and pharmacodynamic values. Use of these biomodels, which are derived from data generated during the advancement of hundreds of compounds, minimizes the empirical testing required, saving development time, money, and materials.

***The SD Process***

During spray-drying, the spray solution or suspension is atomized through a nozzle into a drying chamber, as shown in Figure 1. There, a current of drying gas is used to evaporate solvent and produce dried solid particles, which are collected using a cyclone. The resulting amorphous particles contain the same molar ratio of API and excipients as existed in solution or suspension prior to atomization.

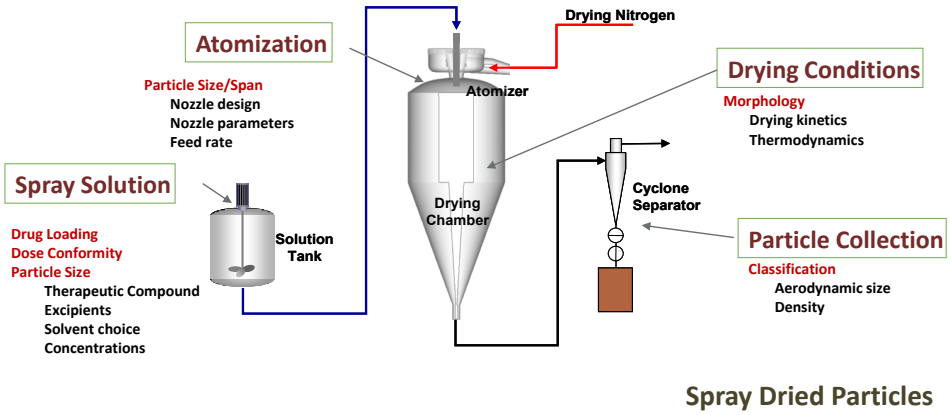


**Figure 1: SD Process Used To Produce Uniform Particles for Use in Inhaled Formulations**

The SD manufacturing process is tightly controlled, tunable, and scalable. The selection of the solvent, excipient type and amount, nozzle type and size, spray-solution feed rate, drying conditions and kinetics that govern particle size, drug state (amorphous or crystalline), and batch size can be altered based on the desired product profile and drug development stage.

When developing SD formulations, Bend Research uses specially designed pharmaceutical SD process trains at a variety of scales, as shown in Figure 2. Capacities range from mini spray dryers, which are used to


**Figure 2: SD Process Trains Available at Bend Research**

produce quantities as low as 25 mg for development purposes, up to PSD-2 and larger process trains, which can produce metric-ton quantities. These larger spray dryers are used to produce supplies for Quality by Design (QbD) and toxicology studies, as well as for current Good Manufacturing Practice (cGMP) late-stage development, commercial launch, and commercial production. Process trains are in place for safe handling of compounds with a wide range of safety classifications, as well as processes that employ organic solvents.

Recently, Bend Research added a flexible high-containment facility that can be used for high-potency APIs (Occupational Exposure Band [OEB] 4 and 5 compounds) and a variety of compound types including biologics and small molecules. This investment is aligned with industry trends toward more highly potent active ingredients in the drug development pipeline. The facility is designed for maximum safety through state-of-the-art clean room design coupled with engineering controls at the equipment level.

***In-Depth Characterization***

After spray-drying, in-depth testing is performed to ensure that the SD particles have the proper characteristics for inhaled delivery. Testing includes use of

- a next-generation impactor (NGI) to determine aerodynamic particle size;
- laser diffraction to ensure that particle sizes are within the target size range and that the FPF distribution is high enough to ensure adequate aerosol performance;
- modulated differential scanning calorimetry (mDSC) and powder X-ray diffraction (PXRD) to assess the amorphous and crystalline drug content and to determine any changes during long-term stability studies; and
- Karl Fischer titration (KF) and dynamic vapor sorption (DVS) to measure water uptake and water content, respectively.

By combining well-defined raw materials, particle engineering, and precise process controls, it is possible to produce inhalation-grade SD particles with uniform sizes of approximately 2.5 µm and GSDs of less than 2 µm. FPFs for SD particles can exceed 90% of the total powder mass and the ED can exceed 80% using DPIs. The homogeneity of the SD powder (i.e., dose uniformity) is ensured by the physical integration of carrier excipients with the API—an attribute inherent to the SD formulation process.

**Background: Delivery Systems**

The final step in developing an inhaled formulation is identification of the optimal delivery system for the application of interest. The most common methods of delivering doses of medication in DPIs are prefilled reservoir devices, aluminum blister-based units, or capsules made from gelatin or HPMC (i.e., hypromellose).[13]

The case study presented here is focused on the use of Capsugel VCaps HPMC capsules. The use of two-piece capsules such as these with DPIs has become common, because of several advantages offered by capsule-based DPIs versus other options. Capsules provide a uniform dose, can accommodate large doses (up to 40 mg), allow formulation flexibility, and protect medication from moisture. As a result, capsule-based DPIs have been shown to

[13] Kleinstreuer, C., Y. Feng, and E. Childress, "Drug-Targeting Methodologies with Applications: A Review," *World J. Clin.*, 2:12(2014)742-756.

maintain good powder flow and ensure that drug particles are effectively and efficiently delivered during inhalation, improving overall performance.[13]

In addition, many patients prefer capsule-based DPIs because they are portable, easy-to-use, and cost-effective. Capsules can be conveniently carried and facilitate patient compliance—i.e., patients can readily check whether they have taken a dose by looking at empty capsule shells or by counting how many individual capsules are left in a dose pack.

Selection of the best type of capsule is based on understanding the type of device, the dosage required, and the nature of the formulation. Key parameters include (1) formulation hygroscopicity; (2) the device mechanism (e.g., whether it pierces, cuts, or separates the capsule into halves); (3) the quantity of the dose required; and (4) the need to check the capsule for residual medication after use.

**CASE STUDY: FORMULATION AND DELIVERY OF ENGINEERED SD PARTICLES FOR DPI DELIVERY**

This case study describes a streamlined approach to the formulation and delivery of engineered SD particles containing a model compound, albuterol sulfate, using a DPI delivery system based on Capsugel VCaps HPMC capsules.

Work included formulation selection, manufacture of engineered SD particles for inhaled delivery, characterization of bulk powders to determine their solid-state and aerosol properties, capsule selection and loading, and aerosol testing to confirm the effectiveness of this approach.

***Formulation Selection***

A critical goal was to create a stable formulation that would produce SD particles with the desired quality attributes for pulmonary delivery. Excipients were evaluated based on solubility, function, chemical stability, and precedence of use.

For this case study, we focused on unoptimized demonstration formulations that contained albuterol sulfate, lactose, and leucine in various concentrations, as well as sodium chloride. Lactose, which has precedence in inhalation applications, was used as a bulking excipient and matrix component. It was chosen because lactose concentrations can be modified relative to the desired API concentration to match the desired dose range[14] and because its aqueous solubility was approximately the same as that of albuterol sulfate. Leucine was chosen as a surface-modifying excipient to enhance aerosolization.[15] In this case study, the solubility of leucine was much lower than that of other formulation components, enhancing its role in functionalizing the surface of the SD particles. Leucine improves particle dispersal during delivery and decreases powder retention in devices. Sodium chloride was added to improve powder handling and powder encapsulation.

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[14] Prime, D., P.J. Atkins, A. Slater, and B. Sumby, "Review of Dry Powder Inhalers," *Adv. Drug Deliv. Rev.*, 26:1(1997)51-58.

[15] Feng, A., M. Boracy, M. Gwin, P.R. Finlay, P. Kuehl, and R. Vehring, "Mechanistic Models Facilitate Efficient Development of Leucine Containing Microparticles for Pulmonary Drug Delivery," *Int. J. Pharm.*, 409:1-2(2011)156-163.

Formulation decisions were based on a well-defined process methodology, which included analyzing the key physicochemical parameters (e.g., $T_m$, $T_g$, aqueous and organic solubilities, and partition coefficient) of formulation components and using biomodels developed from extensive data from hundreds of previous compounds.

***Manufacture of Engineered SD Particles***

Four batches of engineered SD particles were spray-dried, using albuterol sulfate concentrations of 10% and 40%. The lots were spray-dried at two scales: using a custom bench-scale BLD-35 spray dryer, which can manufacture SD quantities from 100 mg to 10 g, and using a PSD-1 spray dryer, which can manufacture from SD quantities from 10 g to 1 kg. The formulations and processing conditions were chosen based on a streamlined methodology that links the manufacturing process and the formulation, based on fundamental understanding of the physics of spray-drying. Using this methodology, which has been built on years of experience and deep scientific inquiry, formulation development is more efficient and development risks are reduced.

***Characterization of Bulk SD Powder***

Following manufacture, tests were performed to determine the solid-state characteristics of the engineered SD particles. Table 1 summarizes some of the results of a standard battery of solid-state characterization tests. As the table shows, the physical characteristics of the four formulations were consistent across scale and formulation. mDSC testing did reveal a small difference: the $T_g$s of formulations containing 40% albuterol sulfate were lower than those of the formulations containing 10% albuterol sulfate. This was as expected, since the $T_g$ of albuterol sulfate is relatively low (about 60°C).

Water content is a particularly important variable for inhalation applications, because it impacts molecular mobility; thermal characteristics (e.g., $T_g$); and particle aggregation. The water contents of the formulations were consistent and well within the 1- to 5-wt% range that is desirable for SD manufacturing.

**Table 1. Solid-State Characterization Results for Four Albuterol Sulfate Formulations**

| Component | Lot 1 | Lot 2 | Lot 3 | Lot 4 |
|---|---|---|---|---|
| Albuterol sulfate content (%) | 10 | 10 | 40 | 40 |
| Spray dryer | BLD-35 | PSD-1 | BLD-35 | PSD-1 |
| $T_g$ (by mDSC) (°C) | 110.7°C ± 0.33°C | | 91.2°C ± 0.3°C | |
| Water content (by KF) (wt%) | 2.0 ± 0.2 | 2.1 ± 0.1 | 2.2 ± 0.1 | 2.7 ± 0.1 |
| Physical state (by PXRD) | Crystalline leucine | | | |

Particle size was consistent across all four batches which, given the differences in manufacturing conditions based on the two scales used, demonstrates the robustness of the processing approach. Scanning electron micrography (SEM) analysis revealed that each of the formulations consisted of wrinkled spheres with rough surfaces. Such roughness (rugosity) is desirable for powders destined for the lung, because it decreases solid-state and water capillary forces between the particles and increases entrainment in the air flow. Combined, these characteristics reduce clumping of the formulation and result in efficient delivery of powders during inhalation.

***Capsule Selection and Loading***

For this case study, the engineered SD particles were loaded into Capsugel VCaps HPMC capsules designed specifically for DPI delivery. These capsules were selected for three main reasons: (1) their successful precedence of use with DPIs; (2) their ability to protect API from water uptake, preventing SD agglomeration; and (3) their

suitability for use after storage under dry conditions. These capsules have been shown to not shatter when pierced, even when stored at a relative humidity (RH) of 5%, thus avoiding the polymer shards that may be produced by gelatin capsules under the same conditions.

In addition, the Capsugel VCaps HPMC capsules meet several important conditions for oral capsule use with DPIs. Their design ensures a residual lubricant content of less than 500 ppm, avoiding minor retention of the powdered drug in the capsule and, thus, inconsistent dosing. Second, they meet strict microbial standards to avoid the chances of infection via inhalation. Additionally, Vcaps capsules do not contain bile-tolerant gram negative bacteria and contain less than 10 colony-forming units (CFU) per gram of total yeast and molds.

A Capsugel Xcelodose® micro-dosing system was used to prepare capsules with various fill weights. Consistent fill weights were observed at 5 mg, 10 mg, and 20 mg of total powder. Relative standard deviations (RSDs) were between 1.7 mg and 2.3 mg, decreasing as fill weights increased. These fill weights were selected because they match the fill weights for inhalation drug products and demonstrate that nearly three orders of magnitude of dose ranges are achievable with this technology.

***Aerosol Testing***

Aerosol tests were conducted with a next-generation impactor (NGI) to better understand the impact of albuterol loading and scale on the flight potential of the powders. The results are summarized in Table 2 and Figure 3. As the data show, each of the formulations had excellent characteristics: MMADs between 2 and 3 µm, high EFs from the capsule alone and from the capsule and DPI. Significantly, variation of the API content, sugar content, and manufacturing scale did not significantly affect the MMAD, EF, or NGI pan distribution for the loaded capsules.

**Table 2. Results of Aerosol Evaluation of Engineered SD Formulations**

| Component | Lot 1 | Lot 2 | Lot 3 | Lot 4 |
|---|---|---|---|---|
| Albuterol sulfate content (%) | 10 | 10 | 40 | 40 |
| Spray dryer | BLD-35 | PSD-1 | BLD-35 | PSD-1 |
| MMAD (µm) | 2.6 ± 0.1 | 2.8 ± 0.1 | 2.8 ± 0.1 | 2.9 ± 0.1 |
| GSD | 1.8 ± 0.1 | 2.0 ± 0.1 | 1.7 ± 0.1 | 1.8 ± 0.1 |
| Capsule EF (%) | 96.9 ± 0.5 | 93.3 ± 1.0 | 96.5 ± 1.5 | 1.8 ± 0.1 |
| Capsule + DPI EF (%) | 89.8 ± 1.2 | 83.6 ± 1.5 | 86.9 ± 2.3 | 96.5 ± 1.2 |
| FPF[a] (%) | 81.5 ± 2.7 | 75.4 ± 1.6 | 76.6 ± 1.2 | 77.1 ± 3.6 |
| [a] Fine particles are defined as particles less than 5 µm. | | | | |

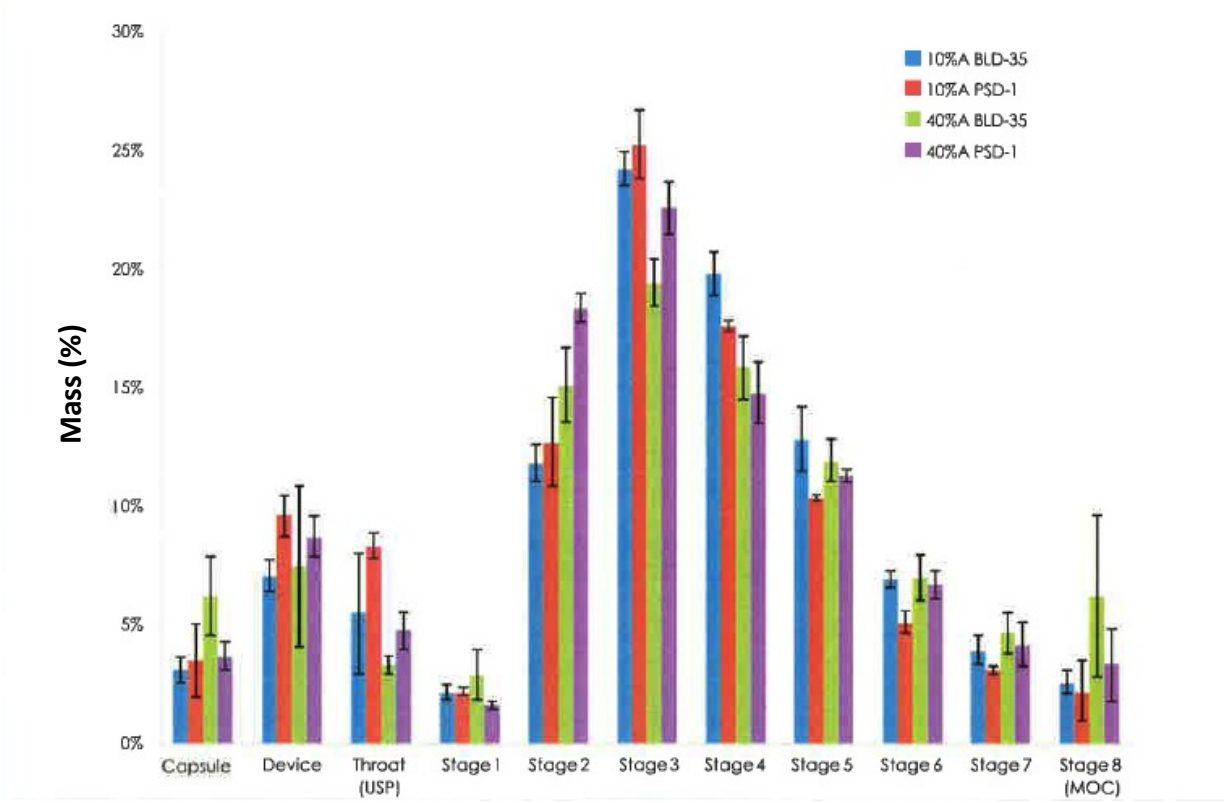


**Figure 3. NGI Results for Engineered SD Formulations Containing Albuterol Sulfate**

## CONCLUSIONS

This case study demonstrates the strong promise of engineered SD particles for inhaled drug delivery, showing that engineered SD particles can be effectively used to meet target product profiles for DPI applications. The case study highlights the robustness of the technology, showing product consistency across formulations and manufacturing scale. In addition, the benefits of specially designed DPI capsules were demonstrated.

A fundamentals-based process for developing an SD inhalation formulation—which is based on a thorough understanding of the spray-drying process and a history of deep scientific interrogation—reduces development risk and saves time, money, and materials. Such an approach is ideally suited to intranasal and pulmonary delivery, since successful development requires in-depth understanding of formulation components and delivery-platform variables to optimize drug delivery to the patient and achieve the most efficacious outcomes.

The case study presented here was limited in scope to a technology demonstration for a model compound. Formulation components were chosen based on their ability to (1) create an amorphous dispersion with albuterol; (2) decrease the surface energy of the particles and, as a result, increase the aerosol properties; and (3) mitigate the buildup of electrostatic charges on the particles to improve powder handling and filling. No effort was made to optimize the formulation for yield or long-term stability, since the goal of this case study was to demonstrate the suitability of the SD process from the standpoint of functional excipients.

Ultimately, the use of sugars, amino acids, and salts must be considered in a formulation approach that also takes the following factors into consideration: API stability in the liquid and solid state; the minimum and maximum delivered dose from a toxicology testing and clinical perspective; the physical properties of the API (e.g., $T_m$ and partition coefficient), especially in regard to potential excipients; and the need, if any, for novel excipients.

This technology is ready for deployment and the development of formulations intended for pulmonary or nasal delivery. Capsugel's Dosage Form Solutions business unit combines the extensive formulation and SD manufacturing expertise of Bend Research with Capsugel's comprehensive capabilities in capsule-based delivery technologies to provide clients with a broad range of development choices, building on several key advantages:

- expertise in developing optimized formulations for delivery to the lungs or nasal cavity;
- flexibility in manufacturing scales for a wide range of compounds;
- the use of proven technologies with market precedence;
- a streamlined methodology that saves time, money, and materials; and
- capability of rapid progression to proof of concept (POC) while minimizing the amount of compound required for development.