CAPSUGEL®
Dosage Form Solutions

Inhalation Drug Delivery

Inhalation formulations for nasal and pulmonary drug delivery continue to grow driven by the prevalence of respiratory diseases especially COPD (chronic obstructive pulmonary disease). Capsugel Dosage Form Solutions offers an inhalation drug delivery formulations based on proven spray-dried dispersion technology pioneered by Bend Research. This broadly applicable technology has a number of benefits over traditional lactose blend formulation approaches.

- Enables compounds not compatible with other inhalation technologies
- Can be modified for challenging drug forms
- Is compatible with combination therapies
- Requires minimal amounts of active pharmaceutical ingredient (API) for proof of concept (POC) and feasibility
- Is easily scalable for rapid progression from feasibility to first-in-human (FIH) clinical studies

Industry Problem Statements and Solutions

Drug development for conventional dry-powder inhalation formulations is a crowded field with limited access to enabling technologies. Conventional formulation strategies typically encounter several challenges:

- The physical properties of the API may be unsuitable for aerosolization
- The API characteristics make it inappropriate for milling
- Process and scale-up are difficult
- Content uniformity is difficult to achieve (particularly in combination therapies)
- Progression of new chemical entities (NCEs) to dry-powder formulations is slow and can consume large quantities of the API-enabling technologies

A number of technologies enabled by particle engineering and spray-drying expertise are available to solve inhalation drug-delivery challenges, some of which are highlighted in Figure 1.

Dispersion	API and matrix dissolved in (co)-solvent
Crystalline API in Amorphous Matrix	API wet-milled or jet-precipitated in aqueous media with dissolved matrix
Nano-amorphous API Amorphous Matrix	Emulsion formed with: • API dissolved in immiscible organic • Matrix dissolved in H_20
Mixed Approaches	Solution/suspension(s) from above combined prior to spray-drying

Figure 1. Formulation Concepts Available Through Spray-Drying

Inhalation Powder Manufacturing

A flexible high-containment facility is in place to handle a wide range of compound types and safely classifications, ranging from biologics to small molecules, and inhalation to oral delivery. This stand-alone facility is separated from the company's other development and cGMP manufacturing facilities and features the latest best-practice design features and finishes. The facility is designed for safety using state-of-the-art clean room design coupled with engineering controls at the equipment level, and is ideal for spray-drying manufacturing and capsule filling to enable progression of formulations through Phase 1 and 2.

Design details for the inhalation powder-manufacturing suite include:

- Maintained to ISO Class 8 Clean Room Classification standards
- High-efficiency particulate air (HEPA)-filtered supply air, with up to 50 air changes per hour
- Low-wall-exhaust HEPA units with isolation dampers and monitored dew points
- Safe-change HEPA filters at the face of exhaust grills
- Separate suite ingress and multiple egress capabilities for gowning, decontamination, and de-gowning
- Flexible air-pressurization rebalancing options for biologics and high-containment operating modes
- Highly cleanable and robust PVC walls, biological clean room doors, and fixtures

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Wide Range of Services and Project Definition

Capsugel Dosage Form Solutions offers a full range of services, from POC, formulation identification, powder manufacture for toxicity and stability studies, as well as cGMP manufacture and capsule filling in a low bioburden environment, optimized for inhalation drug development.

This suite of proprietary engineered particle technologies is available for application to client projects and co-development of products. Formulation and process development are guided using a rational flowchart approach.

Case Study

Dry-Powder Formulation of Albuterol and Dextran

Five dry-powder formulations – consisting of amorphous solid dispersions of albuterol sulphate and dextran, with albuterol loadings ranging from 5% to 75% – were spray-dried and evaluated for *in vitro* aerosol performance using impaction. As shown in Table 1, consistent performance and high respirable fraction were observed for the five formulations across the wide range of drug loadings.

Albuterol Sulphate Loading (%)	MMAD[a] (µm)	FPF[b] (% emitted)	GSD[c]
5	2.85	65	1.9
10	2.36	72	2.1
25	2.61	79	1.8
50	2.71	75	1.8
75	2.71	79	1.7

Table 1. *In vitro* Aerosol Performance for Selected Albuterol Sulphate and Dextran Formulations

a. MMAD = mass median aerodynamic diameter
b. FPF = fine particle fraction (i.e., particles < 4.6 µm)
c. GSD = geometric standard deviation

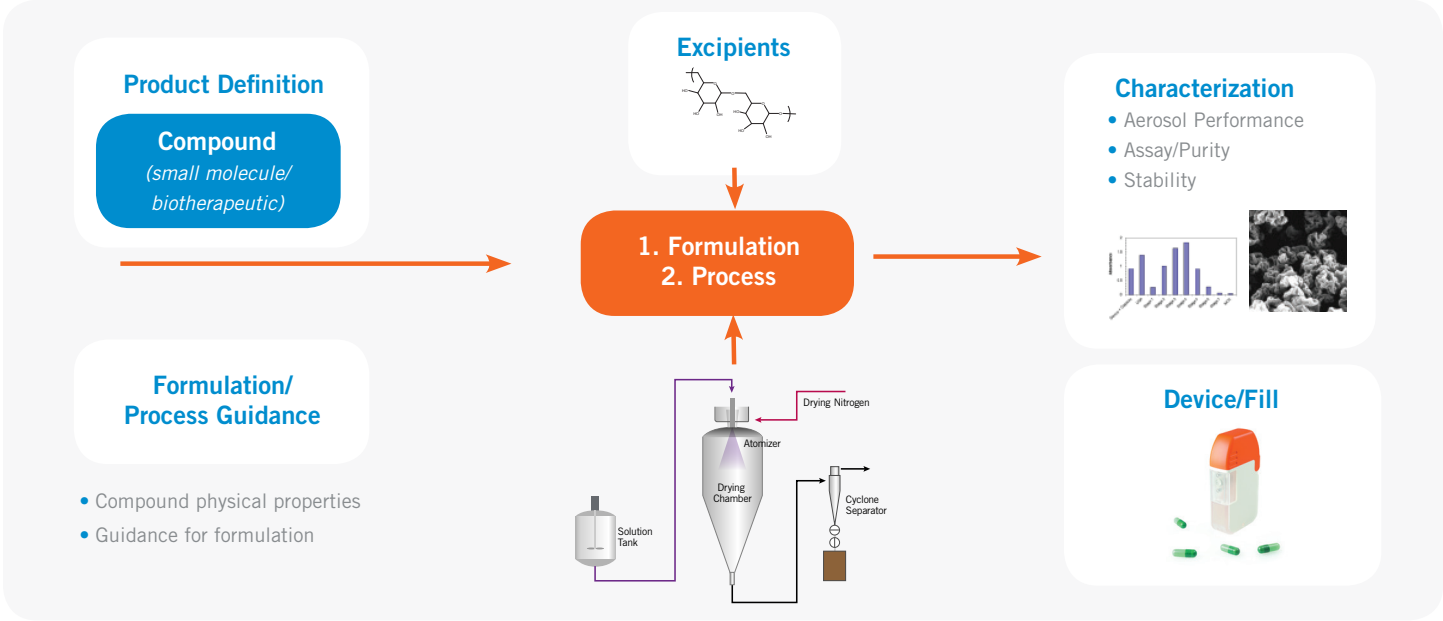

Figure 2. High-Level Project-Definition Flowchart

For more information on our inhalation drug delivery technology contact us at DFSinquiry@capsugel.com, visit capsugel.com, or reach a Capsugel representative directly at:

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