Inhalation Drug Delivery

Engineered-Particle Technology Enables Delivery to the Deep Lung

Overview
Bend Research has developed an inhalation drug-delivery platform based on engineered particles. This broadly applicable technology:

- reproducibly delivers a high-fraction dose,
- enables delivery of challenging drug forms,
- improves combination therapies, and
- offers excellent physical stability (e.g., resistant to humidity and temperature),
- enables rapid progression to proof of concept (POC) while sparing bulk compound.

Problem Statement
Conventional commercial dry-powder formulations comprise micronized active pharmaceutical ingredient (API) and a lactose carrier. This type of formulation typically presents several challenges:

- dose efficiency is poor and variability is high,
- the physical properties of the API must suit the formulation,
- the API must be appropriate for milling,
- process and scale-up are difficult,
- content uniformity in combination therapies is difficult to achieve, and
- progression of new chemical entities to dry-powder formulation and testing is slow and can consume a lot of API.

Technology Status
Bend Research’s inhalation-delivery technology package leverages 15 years of dispersion formulation experience and particle-engineering expertise. The technologies, listed from higher precedence to higher generic applicability, include:

- spray-dried API for use with carrier technology,
- engineered particles with approved excipients,
- engineered particles using dextran,
- engineered particles using Bend Research proprietary dextran derivatives, including dextran propionate succinate (DPS).

Case Study: Dry-Powder Formulation of Albuterol and Dextran
Five aerosol 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.

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

<table>
<thead>
<tr>
<th>Albuterol Sulphate Loading (%)</th>
<th>MMAD(^a) (μm)</th>
<th>FPF(^b) (% emitted)</th>
<th>GSD(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>2.85</td>
<td>65</td>
<td>1.9</td>
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<tr>
<td>10</td>
<td>2.36</td>
<td>72</td>
<td>2.1</td>
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<tr>
<td>25</td>
<td>2.61</td>
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<tr>
<td>50</td>
<td>2.71</td>
<td>75</td>
<td>1.8</td>
</tr>
<tr>
<td>75</td>
<td>2.71</td>
<td>79</td>
<td>1.7</td>
</tr>
</tbody>
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\(^a\) MMAD = mass median aerodynamic diameter.  
\(^b\) FPF = fine particle fraction (i.e., < 4.6 μm).  
\(^c\) GSD = geometric standard deviation.

To evaluate the in vivo efficacy of these dry-powder formulations, a crossover study was conducted with a...
dry-powder formulation (containing 95% dextran and 5% albuterol sulphate) and a commercially available albuterol formulation. Ragweed-sensitized beagles were used for this study, in which bronchoconstriction (i.e., airway resistance) was used as the pharmacodynamic end point.

As shown in Figure 1, the attenuation of allergen-induced bronchoconstriction was equivalent between the dry-powder formulation and the “off-the-shelf” albuterol formulation. Figure 2 shows the scanning electron microscope (SEM) images of 10% Albuterol Sulphate:Dextran 10 inhalable particles and 75% Albuterol Sulphate:Dextran 10 inhalable particles.

Inhalation Powder Manufacturing Suite

Bend Research has recently added a flexible high-containment facility that is relevant for a wide range of compound types and safety classifications ranging from biologics to small molecule, and inhalation to oral. This stand-alone facility is separated from the company’s other development and current Good Manufacturing Practice (cGMP) manufacturing facilities and uses 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. It is ideal for spray-dry manufacture and capsule fill to enable progression through Phase 1 and Phase 2.

Inhalation Powder manufacturing suite design details:
- maintained to ISO Class 8 Clean Room Classification standards
- HEPA-filtered supply air, 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/multiple egress capabilities for gowned, decontamination, and degowned
- flexible air-pressurization rebalancing options for biologics and high-containment operating modes
- highly cleanable and robust PVC walls, biological clean room doors, and fixtures

About Bend Research

For more than 35 years, Bend Research has worked with clients to solve their most difficult scientific and technical problems, advancing new medicines that improve human health. This success is based on a solid understanding of scientific and engineering fundamentals, enabling Bend Research to develop, progress, and commercialize pharmaceutical technologies.

Bend Research provides formulation and dosage-form support, assists in process development and optimization, manufactures clinical-trial quantities of drug candidates in its cGMP facilities, advancing promising drug candidates from conception through commercialization. It is a leader in novel formulations, including solubilization technologies such as spray-dried dispersions and hot-melt extrusion formulations, as well as controlled-release, inhalation, and biotherapeutics.

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