# ACCELERATING APPROVAL AND REDUCING COSTS OF SPRAY DRIED DRUGS THROUGH DEVELOPMENT BY DESIGN (DBD)

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Contract development and manufacturing organizations (CDMOs) with unique technical capabilities and expertise are able to speed up the development and commercialization of novel medicines. Effective application of its extensive knowledge, data base and Development by Design (DbD) approach has enabled Hovione to accelerate spray drying development, simultaneously reducing cost and time to get challenging drugs to patients in need.

## GROWING DEMAND FOR SPRAY DRYING

The application of sophisticated drug discovery methods has led to much better, but also more complex, chemical entities that suffer from poor water solubility/bioavailability. In fact, 40% of drugs currently on the market and 90% of candidates in the pipeline fall into this category.[1] These complex small-molecule drug substances require enabling drug delivery technologies to achieve the desired level of efficacy.

A number of approaches can be taken to overcome the poor solubility of oral drugs, including particle size reduction, salt or cocrystal formation, lipid-based self-emulsification and the formation of amorphous solid dispersions (ASDs). ASDs, which are prepared by combining drug substances with polymeric materials, are effective because the drug substance exists in an amorphous state and is therefore more readily dissolved and absorbed. It is reported that over 80% of ASDs offer improved bioavailability.[2] Spray drying, hot

melt extrusion and coprecipitation are the three most commonly used techniques for the manufacturing of ASDs.

Spray drying is a continuous process that involves flash drying under mild conditions (often below 50°C for less than one minute) of the drug substance/polymer mixture. It also allows for careful control of particle properties (particle size, bulk density, degree of crystallinity, etc.), provides for numerous formulation options and is readily available at all scales. In addition, it is particularly suitable for thermally sensitive materials. Not surprisingly, spray drying is becoming the most used technology to manufacure ASDs.

## ROLE OF CDMOS

The role of contract development and manufacturing organizations (CDMOs) has changed considerably over the past two decades. Initially, CDMOs supported mostly technology transfer and in essence provided compliant manufacturing of intermediates, active pharmaceutical ingredients and final dosage forms. Today, CDMOs have a much broader and deeper contribution to pharma. Some have become the experts and key providers of unique and enabling technologies that address modern drug delivery challenges; even the largest pharmaceutical corporations have limited pipelines to justify the investment in expertise, installation and operation of capital-intensive drug delivery technologies. Spray drying is a key example of those.

CDMOs, on the other hand, through their multiple pharmaceutical partners, have the opportunity to develop extensive pipelines that de-risk such investment. Their broad experience, arising from working with a vast number of molecules and from being exposed to all kinds of process and scale-up challenges, is of utmost importance when developing new drugs. They are best positioned to anticipate challenges and to accelerate drug development through effective knowledge management and by the application of strong science and process understanding that is only affordable to those that do it on a routine basis.

Hovione has been providing commercial spray drying services to the pharmaceutical industry for the last 12 years. Over this period, we have not only amassed a significant amount of knowledge, we have also made a conscious effort to understand and master the fundamentals of technology. That knowledge is being applied on a regular basis to minimize the need for testing at commercial scale, thus reducing the material requirements and development costs and accelerating the CMC development activities. In fact, at Hovione, we believe it is our responsibility, as experts and key providers of emerging technologies, to apply our accumulated knowledge for the benefit of our customers and, ultimately, to the patient looking for new, more efficacious and cost-effective treatment. This is particularly relevant for drugs under accelerated programs, as those with breakthrough therapy designation, where the CMC development timelines often come in critical path for drug approval.

## ENHANCED PROCESS UNDERSTANDING

Traditionally, scale-up of spray drying processes, as with many other drug product and drug product intermediate manufacturing technologies, requires considerable testing at scale, consuming tens or even hundreds of kilograms of product – this is a very expensive and time-consuming venture. Recognizing this, we made a concerted effort to reduce the costs and time needed for the development of spray drying processes.

Being a pioneer in the Quality by Design (QbD) initiative was instrumental to Hovione because it forced us to understand the fundamentals of spray drying and build mathematical models for prediction of critical quality attributes of spray dried materials.[3] The results, obtained using both statistical and mechanistic approaches, were analyzed and compared. In particular, the impact of thermodynamic behaviors, changing process conditions, drying kinetics and specific process parameters on particle attributes such as size, shape and morphology were modeled. The knowledge about these microscopic properties and behaviors were then correlated to the bulk properties of numerous compounds from an ever-growing database built over many years across all scales, formulation patterns and process conditions.

## DEVELOPMENT BY DESIGN

Hovione's focus on learning the underlying principles of spray drying processes resulted in the generation of large quantities of data that now reside in our extensive database. By combining our modeling capabilities with this extensive prior knowledge, it is now possible for Hovione to closely correlate laboratory conditions to those that will be attained at commercial scale. The lab studies are done with minimum product expenditure, and from there we can assure the best scale-up parameters and guarantee results in terms of yields and product attributes. As a result, the time and material needed to establish an effective commercial scale spray drying process are significantly reduced.

This Hovione approach is referred to

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**IMPACT OF HOVIONE'S DEVELOPMENT BY DESIGN APPROACH TO SPRAY DRYING PROCESS DEVELOPMENT**

| | 1ST QbD PROJECT (2005-2010) | 2ND QbD FILLING (2007-2013) | TODAY UNDER DbD |
|---|---|---|---|
| # Runs at full scale | ~ 270 | ~ 60 | ~ 9 |
| Material needed | ~ 900 kg (~ $9MM*) | ~ 200 kg (~ $2MM*) | ~ 40 kg (~ $0.4MM*) |
| Days at full scale | ~ 4 months | ~ 4 weeks | ~ 4 days |

*Assumes $10,000/kg as a reference

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as Development by Design (DbD). It is a systematic methodology that involves the use of predictive tools, scale-independent correlations and prior knowledge. It enables Hovione to achieve a great balance between costs and risks, and to reduce the experimental burden of multiple scale-up stages by focusing resources where and when they are really needed.

There are four stages to the DbD process:
[1] Familiarization, during which scale-independent correlations are established;
[2] Scale-up supported by laboratory data and simulation tools;
[3] Process intensification, during which process throughput and cycle time are optimized while maintaining product properties; and
[4] Commercialization, when the experimental work to define the design space at commercial scale is complete.

Process development in DbD is therefore performed in a stagewise, timely and cost-effective manner using minimal quantities and materials resources, and with guaranteed results.

## DRAMATIC RESULTS

The development by design approach is benefitting customers of Hovione through a dramatic reduction in the drug substance quantities required and by shortening development times. Rather than tens to hundreds of Kg, as little as 30g may be required for testing.

These results clearly demonstrate that we have been able to combine our modeling skills and extensive process knowledge to accelerate the development and commercialization of drugs. Consequently, we are helping our customers more quickly and cost-effectively deliver needed drugs to patients.

## CONTINUOUS IMPROVEMENT FOR ACCELERATED DEVELOPMENT

With 60% of the novel drugs approved by FDA in 2015 falling into one or more expedited approval categories (Fast Track, Breakthrough Therapy, Accelerated Approval and Priority Review),[4] there is tremendous pressure on drug manufacturers to accelerate process development. Under these programs, work that traditionally takes ten years often must be compressed into two or three. Often specialized experience and expertise is required to successfully develop robust and cost-effective processes that assure the same levels of quality.

Hovione's DbD approach has enabled us to reduce the time and cost to develop robust spray drying processes at any scale. Customers today can have a commercial-scale process within six months and thus deliver novel medicines to the market more quickly.

We remain committed to continually improving our spray drying capabilities. Our ultimate goal is to be able to scale-up spray drying processes with a single confirmation run at manufacturing scale. While this goal will not be achieved in the immediate future, we are determined to work with our sponsors and regulators to make it possible. Part of the effort will involve the thorough demonstration of our ability to develop processes at any scale that are robust and meet the design space built from accumulated knowledge. P

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**Dr. Filipe Gaspar** is the Vice President of R&D at Hovione and leads a group of 300 highly qualified individuals, both in the U.S. and Portugal. His areas of interest include knowledge management, particle engineering, quality by design, industrial marketing and business development. At Hovione he was involved in more than 200 projects and was the scientific leader of four projects that reached the commercial stage, including the first at Hovione submitted under QbD.


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