Pharma Intelligence
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Utilizing Spray Drying In API And HPAPI Drug Development

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Pharma companies across the globe are continually looking to further optimize their drug development processes. To do so, they can utilize many methods of manufacturing, but some compounds pose a greater production challenge than others. In particular, niche/technically complex active pharmaceutical ingredients (APIs) and highly potent APIs (HPAPIs) can be extremely difficult to handle, which is why it is important that pharma companies partner with a contract development and manufacturing organization (CDMO) with a high level of specialist expertise and experience, and state-of-the-art equipment.

Spray drying is an example of a specialist manufacturing technique that a high-level CDMO, as a partner to a pharma company, can use to improve efficiency and reduce costs. For APIs, this efficient method can achieve amorphous solid dispersions with suitable excipients, to improve the bioavailability of APIs[1]. Indena, a full-service provider and a reliable partner in the development and manufacturing of APIs, has been incorporating spray drying of solutions containing organic solvents in its processes for decades, and has specialized capabilities in API pre-formulation activity. In addition to the company's existing large-scale equipment, which can handle 240 kg/day of spray drying material on average, a new PSD2 spray dryer has recently been installed. This expansion brings new possibilities to its pharma customers, by offering solutions to the extensive

problems they face in the pre-formulation of APIs and, in the near future, of HPAPIs, thanks to the installation of a spray dryer dedicated to highly potent compounds.

ADVANCING THE POTENTIAL OF SPRAY DRYING

Spray drying offers versatility in the manufacturing process – the ability to achieve a wide range of products through correct use: fine particles for pulmonary delivery, large agglomerated powders for oral dosages, amorphous and crystalline products and the potential for one-step formulations[2].

Federico Franceschi, CDMO and product development manager at Indena, noted that this potential has resulted in increased interest from pharma companies, especially in API production. "More and more pharma companies are asking about spray drying APIs, because they have special characteristics that allow them to work with powder in a certain way." He continued: "What they are looking for is some sort of physical property, or a particle size that is not easily produced with a standard crystallization technique."

Spray drying can therefore cater to clients with varying priorities. As interest in the technology has increased, client demand has become more specific. According to Franceschi, "Often clients come with a very straight specification on the particle size, and they need a particle size distribution that is focused on a very sharp value. That is because they have already checked what works best for their final formulations, and that is the particle size they are looking for."

The new PSD2 spray drying system can handle organic solvents and is designed to carry out the production of APIs and pre-formulated APIs with an occupational exposure limit (OEL) of ≥10 µg/m.

One particular requirement that has become more commonplace is for smaller-scale development, but, unfortunately, large-scale spray dryers are unable to accommodate such production. Indena responded to this need accordingly, Franceschi recalled: "Nowadays a remarkable demand is for smaller-scale production. When we realized we were not covering that part of the market we decided to invest in smaller equipment." The new PSD2 spray drying system can handle organic solvents and is designed to carry out the production of APIs and pre-formulated APIs with an occupational exposure limit (OEL) of ≥10 µg/m[3].

MEETING SCALABILITY CHALLENGES

Another benefit of having access to different spray dryers is scalability. For example, early-stage companies are more likely to produce on a small

scale initially, mainly for clinical trial purposes, with hopes of increasing capacity to commercial level following successful study results and product approval. Although scale-up can pose challenges, an understanding of the production issues combined with exceptional equipment and carefully considered collaboration means a CDMO can guide its clients through growth milestones.

In particular, a collaboration with a US modelization software start-up has allowed Indena to ensure a seamless scalability transition for its clients. "You simply input the physical characteristic of your equipment, along with the bigger model into which you would like to transfer the process, and a very heavy software runs for weeks calculating all the parameters. At the end, what you are provided with is the optimum change of parameters you should apply from smaller scale to larger scale," Franceschi explained.

While this does come with higher costs initially, in practice it is likely to work out economically for the customer in the long term. The client could reach the same end result by conducting testing and trials – which would take a couple of months – but at a significant cost. Additionally, in the time spent gathering this insight, a company could have started production at a scaled-up level and be closer to market and subsequent financial benefits. Nevertheless, it is the client's choice. "Some customers really trust the software approach, while others do not and prefer to see physical results after two months of development," Franceschi stated.

FACING THE CHALLENGE OF HPAPIs

Spray drying has become established as a specialty technique in the manufacturing of a multitude of products, and it is also a reliable production method for HPAPIs. These ingredients are gaining prominence in the life sciences industry for their ability to target disease more precisely than alternative compounds and at lower doses. Thus, projections for the HPAPI market are unsurprisingly very positive, with an estimation of a CAGR of 10.3% between 2014 and 2025[3].

Naturally, the potency of these compounds poses challenges for manufacturers; safety and ensuring compliance with strict regulations are critical considerations. Franceschi acknowledged the responsibility to meet high standards: "In addition to the standard inspections and authorizations by the authorities, which are common to all plants in which you can handle APIs, suites dedicated to HPAPIs require an additional layer of safety measures to guarantee the absolute safety of the workers and of the environment. It's a big responsibility and a large undertaking to keep up our high standards."

Customers are looking for safety guarantees; they are increasingly careful to choose suppliers that pass inspections from the most important authorities and have the highest standards for HSE. Franceschi noted that Indena's customers are now willing to pay more to conduct their operations in what are considered to be "low risk" geographies, with an increasing attention to aspects of safety and business continuity. A change in priorities is reflected by this shift within the industry, as previously some companies were more focused on achieving cost-savings, opting to partner with CDMOs located in Asian countries.

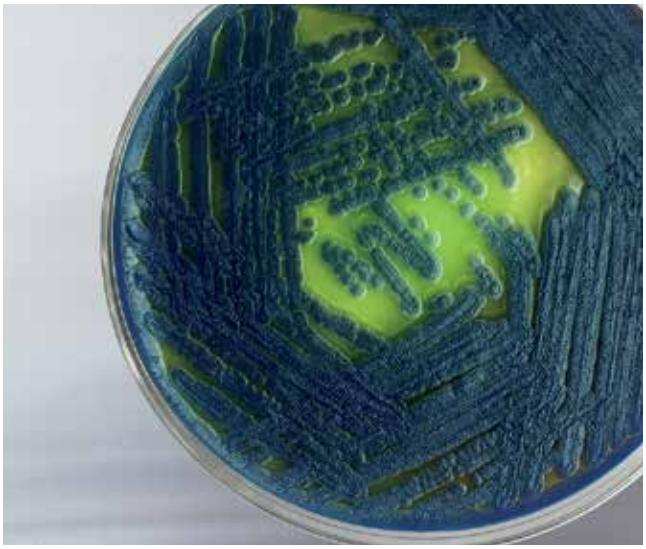
This shift follows a period during which many pharmaceutical companies selling on the North

American market, that had chosen potentially cheaper suppliers, received warning letters from the FDA due to problems in the integrity of their data. "When it comes to this, the FDA will shut down the plant and customers are stuck, needing to find a 'Plan B.' So, what I see is that an increasing number of big pharma companies are happy to pay more when there is a guarantee that certain things will not happen, and their supply chain will be maintained," said Franceschi. Therefore, it is clear that merely having the spray drying equipment is not enough; it has to provide quality results and be used in a robust GMP system by a reputable company.

Adding to this, widespread lack of attention to safety and environmental aspects of manufacturing have led to dramatic accidents and to multiple shutdowns not only of single Asian suppliers, but of entire industrial parks. Last but not least, the recent issue of genotoxic impurities found in several APIs from Asian countries has created a safety issue for end-users and spurred the recall from the market of a number of finished products.

For HPAPIs, spray drying has an inherent technical challenge. When working with especially potent compounds during the spray drying process a fine powder is emitted, which needs to be effectively contained within the equipment and collected once complete. "The safest way to do this is within a glove box, but it is not so easy or evident as to how to put a spray dryer within a glove box," Franceschi noted.

However, as pharma companies search for increasingly high potency compounds to utilize, manufacturers need to be able to facilitate the use of spray drying for these ingredients within their



production suites. Indena takes the time to listen to its customers, to ensure it continues to meet their needs, which spurred significant investment in the CDMO's comprehensively equipped site in Settala, Italy. "We're anticipating market changes, having invested heavily in the new plant for the last three years, but today we realize we need to invest more to follow what our clients require," said Franceschi.

True to its word, Indena is in the process of further expanding its spray drying portfolio with a dryer that can be placed inside a glove box, to meet the requirements of increasingly demanding HPAPIs. "We are planning to expand the plant with an even smaller piece of equipment," Franceschi continued. "This will be in a high-containment production suite so we can carry out spray drying of HPAPIs in small volumes, which need to be handled in a very confined and protected environment. We should be ready to offer this service to our customers next year."

INCREASING PRODUCTION POSSIBILITIES

There are of course other manufacturing technologies that might be used alongside spray

drying for the same compound. However, if pharma companies are looking to utilize more than one method, it is expected they will either need to procure the services of different manufacturers, or at the very least – if able to use the same partner for all steps – they will need to send their compounds to different sites. These can be located on the opposite side of the world in some cases.

In contrast, Indena has invested vast resources into its Settala site to ensure its big pharma customers have every piece of equipment available to them in one single location. Equipment includes a HPAPI kilolab, a pilot pharmaceutical plant and an upgraded fermentation plant for multipurpose use alongside the spray dryers. This provides significant convenience, and there are also notable cost-savings from avoiding the need to transport compounds to different sites for each manufacturing step. Supply chains can be optimized to their fullest potential, while not compromising on quality.

Franceschi has found when speaking to new customers that they very much appreciate the possibilities opened up to them by this comprehensive suite: "It is rather common for customers to require more than one of the technologies, but it's not common to have all of the technologies integrated and on the same site. When they realize they have all these possibilities, they are happy to discuss utilizing them. It's a rare opportunity and very appreciated."

Complementing the extensive equipment, customers want their partner to have in-depth understanding of their products and how to most effectively approach manufacturing throughout their lifecycle. Indena provides such know-how through its years of experience in the field, and finds the most effective partnerships arise when its services are acquired from the start of manufacturing operations. Franceschi said, "What we appreciate most is to have contact with customers from the very start of their clinical phase, so we can follow and develop the process along the way."

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Although true of standard origin APIs and HPAPIs, when it comes to the specialism of working with natural origin APIs, critically, Indena should be consulted at the start. This is because of the highly complex nature of dealing with botanicals. "There are very few companies that can take care of the supply chain of botanical starting material," Franceschi asserted. "Other companies do not have the botanical knowledge of cultivation and selection of the right botanical species, of which the API is most abundant in. Planning, harvesting, extraction, purification and spray drying – all of these phases must be done following strict rules, and when dealing with APIs everything has to be tracked from the beginning."

Thus, there are also obvious benefits with related to regulatory filings if pharma companies continue with the same manufacturing partner throughout. However, Franceschi recognizes that there may be some circumstances where Indena is not consulted first but can still work with a customer: "There are cases where customers have started the process with another company, but for some reason they have not been satisfied with the service and then have approached us."

A SPECIALIST MANUFACTURING SERVICE

Spray drying offers pharma companies great flexibility in their product development, and when matched with the potential of APIs and HPAPIs to provide more precise and effective treatments for patients, it is a process surely set to grow in popularity. However, it is clear that extensive understanding of the handling of these potent compounds is critical for successful and safe execution. When working with a specialist CDMO such as Indena, customers can be assured their products are in capable hands.

Further, in an area of rapid growth, it is important that providers constantly innovate and expand their offerings. Franceschi echoed this sentiment and acknowledged the responsibility Indena has to its customers to offer new opportunities and expertise to help them grow their operations: "What we're doing is not easy, of course, it has to be planned, funded, built, checked and tested. It's a big challenge, but we try to keep focused on what we hear our customers discussing and be on time so we can follow the direction of their choosing."

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