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WHITE PAPER

OPTIMISING DPI PRODUCTION: FILLING TECHNOLOGIES FOR PRECISION AND PERFORMANCE

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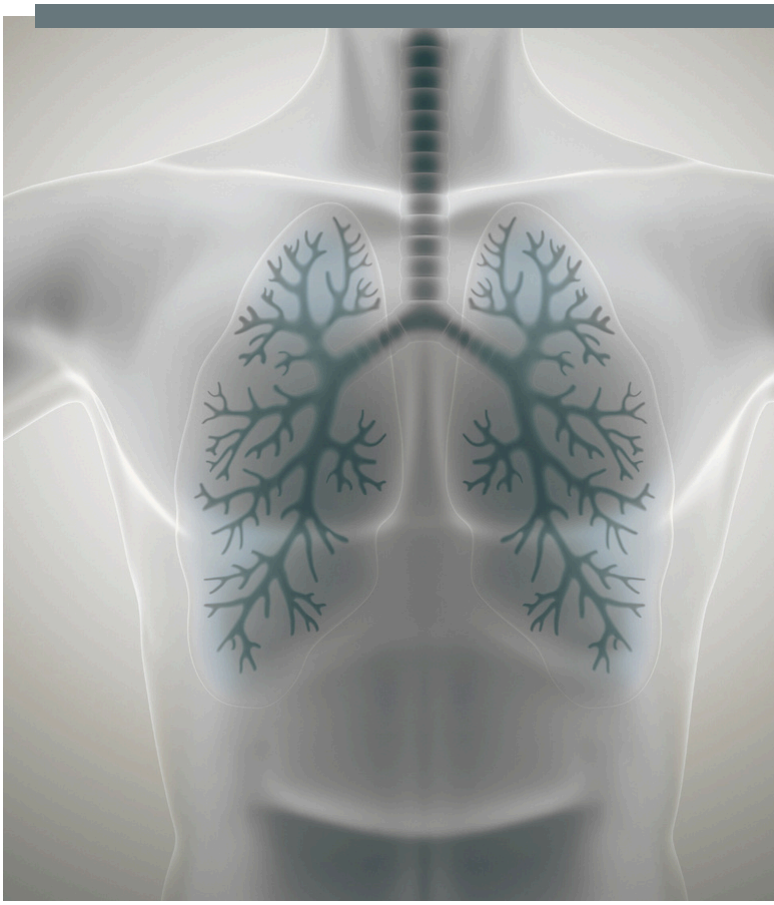
Driven by the increasing prevalence of respiratory illnesses and global competition for dry powder inhaler filling technologies, 3P innovation has developed a range of equipment to meet the needs of benchtop, development and commercial applications.

Introduction

Without doubt, the global market for inhalable drugs is not only well established and burgeoning, it's also expected to grow during the coming years.

Driven by the increasing prevalence of respiratory illnesses such as asthma, a quick search of Internet resources suggests that the "respiratory inhalers" sector is forecast to reach a value of $62.7 billion by 2030 (at a compound annual growth rate [CAGR] of 6%), "asthma inhaler devices" will be worth $3.07 billion by 2032 (at a CAGR of 7.97%), and the "asthma therapeutics business" will turnover $45.96 billion by 2033.



Current figures state that asthma - referred to as a common chronic disease - affects more than 300 million people globally. This level of prevalence is just one factor contributing to the expansion of the inhaler market, as is the research and development (R&D) being done to create more effective and affordable devices. Another aspect that's boosting the growth opportunities in this area is the increasing number of distribution channels. Although online pharmacies are expected to grow at the fastest rate, hospital pharmacies are expected to remain dominant because of the need for trained medical professionals to administer certain treatments.

Inhalation as a drug delivery method has a long history, mainly because of its ability to carry medicines directly to their site of action in the respiratory system. As such, it's an obvious administration route for lung diseases. And being a fast acting, pain-free technique that's ideal for self-administration regimes, inhalation offers unique advantages for both medical professionals and patients.

Furthermore, medicines that are designed for inhalation also benefit from a rapid onset of action, a reduced risk of systemic side-effects, and high and long-term pulmonary efficacy. One dose of inhalable medicine may contain only a fraction of the active ingredient used in a solid dosage form, for example, but produces the same result if taken properly.

Although the main applications will continue to be asthma, chronic obstructive pulmonary disease (COPD), lung cancer, bacterial pneumonia, tuberculosis (TB), infectious and other respiratory diseases, the rising pervasiveness of non-respiratory conditions such as Parkinson's and diabetes is also accelerating market growth.

At the same time, it's widely predicted that the increasing incidence of respiratory morbidity and mortality, coupled with an ever-expanding geriatric population, rising air pollution levels and higher levels of urbanisation - particularly in Asian countries such as India and China - will drive growth in the inhalable drug and respiratory devices market.

Of course, with the need to treat an increasing number of patients and sufferers comes an absolute requirement for machinery to manufacture the devices and, in particular, filling technologies for dry powder inhalers. Developing an inhalation product involves multiple disciplines, including device, particle and formulation technologies, aerosol and manufacturing sciences, as well as regulatory expertise.

Keeping a keen eye on developments in this field is Tom Bailey, founder and Director of 3P innovation - a UK based automation company that specialises in the integration of high-precision powder filling and handling systems. A chartered mechanical engineer by training, Tom has been active within the pharmaceutical and medical device industry for more than 30 years and is committed to developing automation solutions that enable companies to bring novel and innovative products to market.

During the last 15 years, for example, Tom has been responsible for the development of a variety of innovative powder filling systems for inhaled and oral drugs.


GSK Diskus inhaler

He led the technical development of (and patented) a high-speed powder filling system for the **GSK Diskus inhaler** - which is also now being used for the GSK Ellipta inhaler - and is currently involved in the development of novel filling systems. Which are capable of dosing pure active pharmaceutical ingredients (APIs) into capsules and dosing powders for reconstitution into vials and syringes.

Tom's filling patent for Diskus essentially describes a method to load a container with a defined quantity of product that comprises;

- Closing off a perforation in a perforated plate
- Directing powder into the closed-off perforation by the sweeping action of a first director blade
- Transferring the contents of the perforation to a container.

The method, similar to a tablet press principle, is characterised by the relative rotary motion of the perforated plate and the first director blade (suitable apparatus is also described in Patent EP1490263B1).[1]

A Brief History of Diskus

The Diskus inhaler is a widely used device to deliver medications in powder form to treat respiratory conditions such as asthma and COPD. It was developed to provide an easier and more efficient way to administer inhaled medications, particularly for patients who need regular treatment.

Introduced in the 1990s, the invention of the device was inspired by the need to create a dry powder inhaler (DPI) to provide an alternative to the more traditional metered-dose inhalers (MDIs). This method of drug delivery was preferred because it doesn't require a propellant (making them more environmentally friendly) and is easier for patients to use, especially for those with co-ordination issues.

Within the decade came the first major product launch: Flixotide (fluticasone propionate). The Diskus provided a simpler method to administer the drug - a steroid used for the long-term control of asthma - directly into the lungs. A huge benefit was that patients could control the dosage with greater ease compared with MDIs. The device's simple, breath-actuated mechanism meant that it could be used without the need for complex hand-breath synchronisation, which is a common issue for many asthma and COPD patients using MDIs.

Continuing on its upward trajectory, the Diskus saw significant growth in the early 2000s as it was incorporated into various combination therapies, including Advair (fluticasone propionate and salmeterol), a popular medication for asthma and COPD that combined a corticosteroid and a long-acting beta-agonist (LABA). Its ease of use, compact size and ability to reliably deliver medications to the lungs were key drivers.

With time, various design improvements were implemented to make the device more user-friendly and effective. And, as a result, the Diskus remains a key device for the treatment of asthma and COPD. Particularly because of its established track record, it continues to be used with a range of medications; more recently, generic versions have been developed for various treatments, further expanding its accessibility. In addition, the development of ultrafine particles and advanced powder formulations has further improved the performance of DPIs.

To date, the process developed for Diskus and now being used for Ellipta provides a robust, high speed method of dosing powder for inhalers and is particularly suitable for blister strip filling. It is more tolerant to formulation variability than other systems on the market and is the Gold Standard for companies planning to produce Inhalers of this type.

Of note, however, is the expiration of the filling patent, a development that 3P innovation is closely monitoring. As generics companies seek equivalent technologies to enter the market, 3P innovation is well-positioned to respond. "With several members of the original engineering team on the payroll, we believe that we're in a good position to take advantage of that," notes Tom.

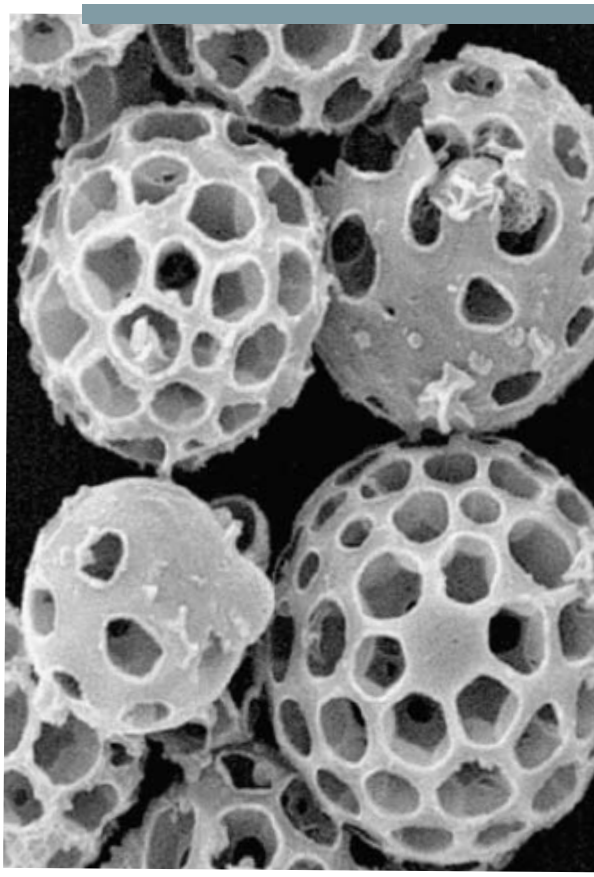
DPIs: Progress and Challenges

Ongoing research by pharmaceutical companies has focused on several aspects of DPI technology to improve their functionality and the patient experience. For example, steps are being taken to optimise drug formulations as well as enhance their stability, aerodynamics and overall performance. Novel excipients and carrier particles have been introduced to ensure accurate and efficient drug delivery. In addition, the advent of sensor technology has facilitated the creation of smart DPI devices that are capable of tracking usage, providing dosage reminders and transmitting data. This offers benefits in terms of patient adherence and personalisation. Likewise, breath-actuated DPIs have made drug delivery more reliable and consistent, especially for patients with compromised lung function.

Hurdles remain, however; ensuring consistent and accurate drug dosage in DPIs remains a challenge because of humidity, particle aggregation and patient inhalation technique. The human condition is still a contributing factor; work remains to be done to provide user-friendly interfaces and clear instructions to prevent misuse, especially as DPIs become more technologically complex. And, inevitably, patient variability regarding inhalation patterns and lung functions makes it very difficult to produce a one-size-fits-all solution.

Hollow particles: Inhalable therapies present opportunities to address large patient populations that traditionally had very few treatment options. Key therapy areas with unmet needs include Parkinson's, multiple sclerosis, Alzheimer's, dementia and a number of other central nervous system (CNS)-based diseases. Most treatments are only able to address the symptoms and provide palliative care because they are unable to cross the blood-brain-barrier (BBB).

Now, however, recent developments in particle engineering have resulted in the ability to produce a dosage form that overcomes all the previously mentioned obstacles. It is now possible to produce powders of significantly reduced particle size. In addition, these can be formed with hollow centres, such that the overall weight and density are also reduced - often by an order of magnitude. Compatible with traditional spray drying technologies and/or spray-freeze drying and even 3D printing, of key importance, though, is their ability to cross the BBB and avoid the GI tract (fewer side-effects).



Yet, because these particles are both small and hollow, they're also very delicate. Of paramount importance for their effective use is the ability to process them without affecting their characteristics. Because low dose size, concentration and weight are all critical, it's necessary to weigh every single dose and minimise any work induced by the processing equipment. Unfortunately, the physical properties of the powders that make them efficacious also make them unsuitable for processing by conventional powder dispensing technologies.

Spray drying: In recent years, spray drying has become a frequently used technique to convert liquid pharmaceutical formulations into powders. It's a quick and cost-effective technique that lends itself well to the production of particles with consistent properties - size, stability, solubility - for DPI therapeutics. For example, the atomization process can be used to control the particle size distribution, thereby affecting the drug's dissolution, bioavailability, etc. Likewise, spray drying can improve the stability of certain pharmaceutical compounds by removing water and/or other volatile solvents. This results in a dry powder with a longer shelf-life that's more resistant to degradation and can sometimes remove the need for aseptic processing in non-sterile applications. Finally, by formulating the drug in an amorphous solid dispersion with certain excipients, its bioavailability can be enhanced.

New therapy groups and CGTs: The pulmonary delivery of cell and gene therapies by inhalation enables both localised treatment and enhanced drug absorption. Yes, the loss of nucleic acid integrity during the aerosolisation process, pulmonary clearance, and undesirable drug deposition pose major challenges for local delivery (REF). Formulating nucleic acids as a stable inhalable pharmaceutical preparation would therefore be advantageous and DPIs may provide the requisite vehicle to do so.

The main advantage of spray drying is the production of micro or submicron particles with controllable size, shape, and other morphologies, including crystallinity and porosity, which are governed by the setting parameters of the machine and solution feed. Furthermore, the absence of a propellant as a drug solvent and shear forces during aerosolisation and the ease of operation make DPIs the best option for gene therapy via pulmonary delivery.

Of Devices and Designs: There are three types of DPI drug storage systems on the market today (capsules, blister packages and reservoirs). Capsules for DPIs are typically composed of gelatin or hydroxypropyl methylcellulose (HPMC) but may comprise different materials depending on the formulation. Ideally, the capsules should be inert and not interact with the formulation. These capsules are fitted into the DPI device and punctured using a pin. As such, the drug is released from the capsule and delivered to the patient as they inhale.

By contrast, blister packages are usually foil-based containers that are either peeled or punctured to release the drug powder formulation. Finally, reservoirs are small container fittings for the DPI that carry the drug powder formulation as a bulk product and either go through a metering system for a multi-dose device or are stored in disposable reservoirs for single-dose devices. The various devices derive from the need to optimise the formulation for delivery and patient use. Some of the important functions of a DPI device are as follows:

- protect the drug formulation from environmental factors (humidity, light, dust)
- minimise residual drug remaining after device actuation
- consistently deliver a metered dose
- have a resistance appropriate to achieve the desired flow rate
- enable patient compliance and be easy to use with minimal dose administration steps.

Furthermore, depending on the frequency of dosage and the API, devices will be either single or multi-dose systems and may also be reusable or disposable. The formulation and clinical application also dictate how the drug will be stored in the device to maximise the emitted dose.

When it comes to filling the capsules, notes Tom, there are two technologies that can be applied: one is this perforated plate or partial compaction technology, which is a generic option, and the other one is 3P innovation's **Fill2Weight** product, which is a gravimetric system.[2] This is particularly appropriate when it comes to difficult to dose or engineered powders and has been highlighted in a recent OnDrugDelivery paper.[3] An alternative solution is detailed in the next section.

DPI Blister Filling Technology from 3P innovation

When adopting a new technology or working with novel powders - whether that's a spray dried product, hollow particles or those with a different shape profile - it's important to balance the equation of delivering the therapy and being able to dispense it. A key criterion when producing the ideal product from an efficacy perspective is to ensure that it can be manufactured in a reproducible, reliable and cost-efficient way. Even the most effective drug in terms of formulation becomes useless if the technology isn't available (or affordable) to manufacture or fill it at scale.

With this in mind, the early stage unit uses two sets of die punches to lightly compress powder in a perforated plate to form soft, frangible, pellets and seal them within a blister strip. Designed for benchtop use and dry powder inhaler (DPI) applications, this equipment is used predominantly for R&D applications and directly mimics the Diskus/Ellipta filling process: it can be scaled-up for clinical/commercial use and total-lifecycle support. Plus, a suite of ancillary equipment can be supplied to suit blister devices such as forming, sealing, cutting and assembly fixtures.

Compression Blister Filler
Discover Range

Forming part of 3P innovation's Explore Range, the mid-range **Compression Blister Development Platform** uses the same filling principle as the Discover - Compression Blister Filler and seals them within a blister strip. Designed to form blister strips from laminate web material, it doses powders into preformed blister pockets and ensures precision sealing for reliable product protection.

With an output of up to 2000 strips/hour using a continuous drum (or 600 strips/hour using an intermittent solution), this system is more suitable for clinical trials and low volume production. The fundamental process has been designed with scalability in mind and the accurate precision-adjusted dose weights both minimise product usage and derisk your clinical development. This ensures that you can produce products that comply with the device critical quality attributes.

Furthermore, a commercial-scale unit designed for very high output applications is also available, it can fill blister strips at speeds of up to 6000 per hour. Both units offer a number of key benefits, including the following:

- Optimised compression of pellets to enhance aerosolisation and maximise emitted dose
- Clean filling and ejection process that prevents web contamination (avoiding downstream issues with sealing/peel force)
- Proven performance with magnesium stearate-based powders.

Tom comments: “All of our core technology is scalable, ensuring that your early stage clinical processes can be ramped up for commercial production. This means you won't need to develop and validate costly new technologies with each scale-up.”

In Conclusion

3P innovation believes that, whatever the end-product or process, manufacturers are looking to buy a reliable, cost-effective piece of equipment and/or an end-to-end solution. They also appreciate that such investments are rarely trivial and represent a significant commitment. Likewise, putting powdered materials into the packaging for inhaler devices is a deadly serious application; the health and welfare of patients is at risk. It’s not just big business; it can quite literally be a matter of life and death.

With intensifying competition coming from a variety of geographies, it’s of paramount importance to Tom and his team that any potential customer can invest with confidence. “3P innovation is built on a legacy of knowledge and experience. Your buying decision shouldn’t just be about costs and timescales, it should carefully consider the suitability of the technology as well as who invented it and built it. I encourage you to ask us about our history, our background and our staff - many of whom worked on the original Diskus patent.” He adds: “We also know that the industry is constantly changing and there’s a lot on the horizon, but we understand the goals you need to achieve and the deadlines that have to be met.”

“To meet your DPI filling requirements,” Tom concludes, “we’re the people to come to. As a trusted machinery and process equipment supplier, we have an extensive portfolio of robust and reliable technologies that can deal with a wide range of different powders. The only question that really remains is, with all that know-how and experience in one place, why would you talk to anyone else?”

References & Further reading

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