Expert View

DELIVERING AND MAINTAINING OPTIMAL DPI PERFORMANCE

Chris Gilmor of Sanner Group considers the issues affecting dry powder inhalers and explains how formulators use a range of techniques to ensure dose dispersion and API detachment. He goes on to explain the importance of controlling the moisture level in these devices and how it can affect the drug delivery performance of the formulation.

Demand for inhaled therapeutics continues to grow steadily with estimates suggesting that the market for respiratory inhalers will reach a value of US$41.4 billion (£30.8 billion) by 2030.[1] Rising rates of respiratory illnesses, such as asthma and chronic obstructive pulmonary disease, are the primary driver of growth. Pressurised metered dose inhalers (pMDIs) and dry powder inhalers (DPIs) are the delivery devices of choice for these conditions. Hence, systemic drug delivery via the pulmonary route continues to attract considerable attention.

The high carbon footprint of pMDIs underlines an advantage of DPIs: drug delivery is patient- rather than propellant-driven, which has the additional benefit of co-ordinating dose delivery with patient inhalation.[2] Therapeutics for the treatment of respiratory illness dominate the DPI market with notable successes, including Breztri® Aerosphere (budesonide/glycopyrrolate/formoterol fumarate) (AstraZeneca), Respimat® (Boehringer Ingelheim) and Orbital™ (Aptar Pharma). However, achieving success with a DPI formulation, for either localised or systemic action, is far from straightforward. Advanced powder engineering techniques are routinely deployed to ensure necessary dose dispersion (Figure 1).

Figure 1: An individual using an inhaler.

DPI DEVELOPMENT AND SPECIFIC CHALLENGES

To reach the lower respiratory tract successfully, active drug particles must be less than 5 µm in size; 1–5 µm tends to be the target range. Unfortunately, within this target range, particles tend to be both cohesive and adhesive, with a marked tendency towards agglomeration. Developing an effective DPI that delivers particles of the required size, in the absence of any active device delivery mechanism, is therefore a substantial formulation and engineering challenge.

While carrier-free formulations are an option, a common strategy is to attach the fine API particles to larger carrier particles tens of microns in size. Lactose is a popular choice of carrier because it is well-tolerated by the lungs.[3] The API particles detach from the carrier during inhalation, which goes on to deposit predominantly in the oropharynx due to particle size.[4] With this approach, the carrier accounts for the bulk of the resulting formulation, making it easier to handle and to accurately dose the very small amounts of API required.

Formulators deploy a range of techniques to ensure dose dispersion and/or API detachment, manipulating both the composition of the formulation and particle properties – such as shape, surface morphology and charge – to achieve success. The particle engineering techniques deployed range from jet milling through spray drying and spray freeze drying to supercritical fluid technology, each associated with distinctly different physicochemical property development.[5]

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Testing early formulations in a prototype device is essential, as product developers have the freedom to adapt both device and formulation characteristics to meet drug delivery goals. DPIs use complex internal geometries to translate the pressure drop induced by the inhaling patient into the energy needed for dose aerosolisation, pressure drop across the device being a key differentiator for device design. Iterative development ultimately leads to a formulation device optimised for drug delivery to the lungs for a given API. Yet this is a complex, fine-tuning exercise.[6]

As a result, DPI products are relatively sensitive. They require protection from the external environment, notably from the ingress of moisture but also potentially from oxygen. The requirement is to ensure optimum shelf life and reliable performance, regardless of location. This requirement is also reflected in US FDA guidance relating to stability, which indicates that testing should include both long-term storage at 25°C/60% relative humidity (RH) and at 30°C/65% RH for one-half of the proposed expiration dating period.[7] Understanding the impact of moisture on DPI effectiveness and taking steps to mitigate any potential deterioration are critical for successful product development and use.

EXPLORING THE IMPACT OF MOISTURE ON DPI PERFORMANCE

The moisture level is widely recognised as playing an important role in powder behaviour and can have a significant impact on how a DPI formulation behaves, thereby compromising drug delivery. The low density, high porosity and small size of many DPI particles result in a relatively large specific surface area, making them susceptible to moisture adsorption and a corresponding change in physicochemical properties. Generally, higher moisture levels reduce the amount of drug that reaches the lungs by promoting agglomeration and compromising dose dispersion. However, there are a range of factors that influence the response to moisture of any given formulation, notably the preparation method and the potential for electrostatic effects.[5,6]

In terms of preparation technique, jet milling is a ubiquitous process across the pharmaceutical industry. It uses a highly compressed gas to force energetic high-speed collisions both between particles and with the vessel walls. These comminution processes tend to produce particles prone to having high surface energy and electrostatic charge, with a relatively high concentration of amorphous content. On storage at high humidity, this content can crystalise, thereby promoting agglomeration.[5,8] Similarly, spray drying may produce relatively hygroscopic, somewhat amorphous particles, particularly with lactose-based formulations.[4] Thus, the optimal particle properties achieved through precise process control may be compromised by suboptimal moisture control.

Such inherent process-related tendencies can be reduced by, for example, relaxing particles under controlled temperature and humidity immediately after jet milling, by coating the resulting particles and, in the case of spray drying, by co-spraying with a suitable excipient.[4,5] An alternative option is to select a preparation method, such as supercritical fluid technology, that tends to produce particles with greater crystallinity and fewer amorphous sites.

Preventing moisture ingress to the product is a primary focus. However, excessively dry conditions can also be problematic due to exacerbated electrostatic effects. DPI formulations can pick up electrostatic charge by triboelectrification during formulation preparation, product manufacture and the aerosolisation processes associated with product use, as particles undergo collisions between themselves and interact with the surfaces of processing equipment or the device. Highly charged particles may flow poorly, adhere to device surfaces and/or fail to maintain content uniformity, making electrostatic charge control essential for effective drug delivery.[9]

Water is a highly effective conductor of electrical charge, which is why electrostatic charge is much less likely to accumulate under conditions of higher humidity. A RH of 40% is routinely quoted as the cut-off figure above which sufficient moisture is present to effectively earth a product and minimise electrostatic effects. However, this is a generalised figure. Individual formulations, manufactured in different ways, differ with respect to the electrostatic charge they pick up (typically via triboelectrification), their ability to

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discharge it and the extent to which moisture levels can be elevated to tackle the issue, given other sensitivities to moisture.

In summary, the optimal environment for any given DPI with respect to moisture content depends on an array of physicochemical properties and may vary considerably from product to product. It is not always possible to prevent exposure to high or variable humidity, particularly during product use. Yet moisture control that is well matched to the product requirements can safeguard and optimise DPI performance during routine storage and use.

ENSURING EFFECTIVE MOISTURE CONTROL

The best strategy for protecting any given DPI is dependent on the device involved. There are essentially three types of DPI: single dose, multi-unit dose and multidose reservoir. With a single-dose device, the patient inserts a capsule containing the formulation immediately prior to use. Multi-unit dose devices, in contrast, come preloaded with multiple doses held individually within compartments of a blister pack or cartridge, while in a multidose reservoir, formulation is metered from a single reservoir at the time of use.[3] Each type of product offers different opportunities for moisture control.

Figure 2: Desiccant sachet used to manage moisture.

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For example, capsules for single-dose devices are commonly made of gelatine or hydroxypropyl methylcellulose (HPMC), which protect the formulation from moisture ingress. HPMC capsules, which have a moisture content of between 4.5% and 6.5 % at 35–55% RH, are particularly effective, offering excellent protection against moisture ingress and robust puncturing performance across a range of relative humidities. As such, they may be the preference for hygroscopic products.[10,11] Gelatine capsules, in contrast, pick up water more easily, reaching a moisture content of between 10% and 16% at 35–55% RH.

Primary packaging offers a clear opportunity for moisture control within inhaler packaging to control moisture levels and, in some cases, to additionally address the secondary issue of oxygen ingress.[12] Placing drop-in desiccants, such as desiccant sachets, into the aluminium packaging pouch in which the DPI is supplied is also common practice to safeguard inhaler performance prior to initial use by the patient.

The preceding strategies are analogous to those used for oral solid dosage products using drop-in desiccants (Figure 2). DPIs, however, present the additional opportunity to fit desiccant into the device itself. The range of suitable, commercially available desiccants for DPIs includes silica gel, molecular sieves, activated clay, calcium oxide, calcium sulphate and zeolites. More rarely, a humectant may be used, such as a modified desiccant that can both absorb or release moisture, thereby enabling the maintenance of specified RH, which is a highly desirable characteristic for DPIs. In either case, the desiccant or humectant must, of course, be arranged within the device to prevent any possible contact with the drug.

By deploying the right desiccant technology, in one or more of these ways, DPI manufacturers can safeguard product stability and prolong shelf life while, at the same time, help to ensure consistent performance over the lifetime of the product.

SUPPORTING DPI DEVELOPMENT

Controlling the moisture level in a DPI is crucial, as it can significantly affect the drug delivery performance of the formulation. This article makes a clear case for determining a target level for moisture control on a product-by-product basis for DPIs and underlines the value of considering moisture control strategies at an early stage when the detailed design of the device is still in play. Effective moisture management requires technical know-how of desiccants and related packaging solutions that can be applied from the very beginning of the device development process.

ABOUT THE COMPANY

Sanner is a global German CDMO that develops and produces primary packaging and drug delivery systems for pharmaceutical and healthcare customers. Sanner has specialist knowledge in desiccants and effervescent packaging for the healthcare industry.

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