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Overcoming the Challenges of Developing Inhaled Medicine

Drugs formulated for inhalation or nasal delivery have numerous potential advantages over other dosage forms. For example, medicines delivered to the lungs usually have a more rapid onset of action than those that pass through the digestive tract. Similarly, drugs delivered via the nasal mucosa have more direct access to the central nervous system. This means they have considerable potential for the treatment of neurological disorders.

Inhalation and nasal delivery can also help drugs achieve higher bioavailability than those administered via other routes. This allows developers that are reformulating oral solid dosage forms for inhalation to significantly reduce dosage strength.

In this article with *International Pharmaceutical Industry*, Aditya R. Das, Ph.D., MBA, Director of Business Development at Recipharm, explores the growing popularity of inhaled and nasally deliverable dosage forms. He also outlines the primary considerations that pharmaceutical companies should make during product development, manufacture and the regulatory review process.

Increasing Popularity

Inhaled and nasally administered formulations are well established. Research indicates that inhalation, in particular, has been used as a delivery route for thousands of years[1]. In modern medicine, inhalable formulations have primarily been used for the treatment of diseases of the respiratory tract, like asthma, bronchitis and emphysema, where localised accumulation of the drug in the lungs is required.

In recent years, this focus on respiratory diseases has begun to change in line with growing industry recognition of the benefits delivering drugs via the lungs and/or nasal mucosa can achieve[2]. One of the main advantages is that drugs formulated for inhalation or nasal delivery can reach the systemic vasculature without having to pass through the digestive tract. This means they are not broken down by the liver – known as the 'first pass effect' – and can more easily achieve therapeutic serum concentrations than medicines formulated for oral delivery.

As a result, pharmaceutical companies working on inhalable and/or nasally deliverable formulations can reduce the dosage strengths required in each administration, which significantly lowers the potential for adverse effects.

Diabetes has been an area of particular interest for companies seeking to develop inhalable formulations, with the primary driver being patient demand for alternatives to insulin injections usually used to treat the disease. While it is true that inhalable insulins launched to date have had limited success, this underperformance is related to commercial factors rather than the efficacy of the products[3].

Beyond metabolic disorders, inhalable treatments are also being developed for hereditary conditions. Cystic fibrosis is perhaps the best example, with several companies working on inhalable formulations of gene therapies[4]. In the field of nasal delivery, it is neurological disorders that are the focus. A number of developers are working on nasally deliverable treatments for diseases like Alzheimer's and Parkinson's[5]. The rationale is that nasal delivery offers easier access to the brain than other routes of administration.

Formula for Development Success

Developing any pharmaceutical is a major undertaking, but formulating drugs for oral inhalation or nasal delivery is particularly challenging. Considerable expertise is required to create a stable formulation that can be delivered appropriately using the selected device. For example, producing a successful formulation requires specialised inhalation and characterisation expertise as well as a detailed understanding of the variables that can affect both performance and product quality.

Similarly, proper delivery depends on producing a formulation in which the active pharmaceutical ingredient (API) and excipient are dispersed easily on inhalation. This requires detailed analysis of the active substance particle and variables like the mass median aerodynamic diameter. Likewise, achieving regulatory approval for such formulations can be a daunting prospect for teams more used to working on oral dosage forms.

Manufacturing

Production of inhalable and nasally deliverable formulations is also a highly complex process. To be effective, the API particles need to be a precise shape and optimised to interact with excipients in formulation and to behave correctly when administered using the specified delivery device.

Combining these engineered APIs with excipients to produce a formulation requires the application of a range of advanced manufacturing technologies and techniques.

Fortunately, in recent years various new manufacturing techniques that are ideal for the production of inhalable and nasally deliverable drug formulations have emerged. Spray drying, for example, has become highly popular among producers of inhalable formulations. The approach is a one-step process that can be used to manufacture drugs comprised of particles of precise morphology. These are then combined with excipients to create formulations that are suitable for pulmonary delivery.

One of the main advantages of preparing drug particles using spray

drying is that the process decreases cohesive forces between particles, which improves the efficacy with which an inhaled formulation can be delivered to the lungs. This in turn allows higher doses to be delivered in fewer inhalations.

Spray drying can be applied to a wide range of drug substances, from small molecule ingredients through to proteins and monoclonal antibodies, all of which can therefore be formulated for inhalation or nasal delivery.

Commercial Opportunities

Another positive for pharmaceutical companies interested in developing inhaled formulations is that regulators have begun to support the application of novel delivery approaches that make drugs safer and more effective.

In the US, for example, the Food and Drug Administration (FDA) has introduced the 505(b)(2) new drug application (NDA) pathway, which is designed for companies developing novel formulations of drug ingredients that are well understood.

The 505(b) (2) pathway allows developers to both reformulate products for different routes of administration and to modify dosage strength, which fits very well with the features of inhaled formulations discussed previously.

The overall aim of the new pathway is to allow developers to avoid having to trial drugs that have already been assessed. Full safety and efficacy reports are still required; however, under 505(b)(2) the reports can contain data from studies not conducted by the applicant. Ultimately, the idea is to encourage innovation for drugs that have already gained approval, which makes it ideal for developers of inhalable and nasally-deliverable formulations.

Final Thought

In short, there are a huge amount of benefits to be gained by opting for inhaled medicines, as well as the potential to increase the efficacy of certain treatments. However, before deciding on this dosage form, pharmaceutical companies need to ensure they have access to the right expertise to help them overcome development challenges and ensure project success.

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