

## Advances in Intranasal Therapeutics – Delivery of Dry Powder Pharmaceuticals and Biologics

a report by

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Intranasal (IN) administration of substances for medicinal, spiritual or recreational purposes has occurred since ancient times. Rapid absorption, lack of hepatic first-pass metabolism, bypass of the blood–brain barrier and ease of administration all contribute to the attractiveness of this non-invasive delivery route. Despite the advantages of IN delivery methodologies, few approved drugs or vaccines are administered via this route. There is recent interest in the development of IN delivery systems and approximately half of the approved IN drug products available today have received US Food and Drug Administration (FDA) approval within the last decade. Development of IN therapeutics has been historically focused on locally acting treatments (anti-allergy and decongestants) and drugs targeting the central nervous system.<sup>1</sup> The ideal product profile for IN delivery has traditionally included the following characteristics: high potency, extensive aqueous solubility and a molecular mass of less than 1,000 Daltons.<sup>2</sup> Since the nasal environment has a slightly acidic pH, the pKa of the active ingredient must be taken into consideration to assure rapid and complete absorption. Importantly, an IN product must not inhibit the mucociliary flow rate to any significant extent.

With advances in formulation science, including micro-encapsulation techniques, use of mucoadhesive and surfactant agents and nanotechnology, more new chemical entities can be considered as candidate active ingredients for future IN drug products. Similarly, modern approaches to vaccination may also yield a wide array of new prophylactic and therapeutic products suitable for IN delivery. A key benefit to be expected from an IN vaccine includes the potential for generating both mucosal and humoral immune responses.

Freeze-drying (lyophilisation) of IN pharmaceutical formulations can yield improvements in bioactivity and impart superior physicochemical stability to the finished product. Scientists at BD Technologies, in collaboration with University of North Carolina researchers, demonstrated the benefits of lyophilisation for an IN influenza vaccine containing whole inactivated influenza virus as the immune-activating ingredient.<sup>3,4</sup> Several groups have developed and successfully tested IN dry powder vaccines targeting the *Bacillus anthracis* toxin, the causative component of anthrax infection.<sup>5,6</sup> Sullivan and colleagues reported that, when given as a dry powder, their vaccine was equally effective in generating antibody titres as intramuscular (IM) vaccination. Interestingly, IN vaccination with the dry powder formulation provided 100% protection from a lethal anthrax spore challenge compared with 63 and 86% survival when the same vaccine was given IN as a solution or via IM injection, respectively.<sup>5</sup> The list of potential infectious disease targets suitable for dry powder intranasal vaccine development is significant and includes both human and animal health applications.<sup>7–10</sup>

The challenges inherent in developing a dry powder IN drug product are primarily related to physicochemical properties of the active ingredient and

formulation excipients.<sup>11</sup> The process of lyophilisation involves the sublimation of water from a frozen product under near-vacuum conditions. The remaining dry product (often referred to as 'cake' or 'plug') is typically designed to occupy the same volume as the starting solution. Since most active ingredients are present in low quantities in a given formulation, the balance of solids in the cake arise from excipients including buffering agents, colloids and preservatives. Consideration should be given during the design of the formulation to the amount and type of solids present, as these factors will impact the time required for adequate drying. The mass of the solids is inversely proportional to the drying time, while the particle size of the individual crystals is directly proportional to drying time. Methods for sterility control of lyophilised dry powders typically involve sterile filtration of the solution phase prior to lyophilisation followed by aseptic handling until the final closure is applied to the container. Alternatively, terminal sterilisation of the reconstitution media can be achieved by exposure of the diluents to kGy levels of gamma radiation from cobalt-60. In the vast majority of cases, a given drug substance will manifest greater physical and chemical stability as a dry powder compared with the same material in solution. The advantages of dry powders as a drug product for intranasal administration must be balanced with the cost and complexity of preparing the formulation.

Certain products would be ideally produced and distributed as dry powders. Drug products that are hygroscopic or products susceptible to hydrolytic degradation are the primary candidates for lyophilisation. There are numerous examples of products that must be reconstituted just prior to use due to problems with limited stability in aqueous media. Genotropin® is an example of a subcutaneous injectable recombinant DNA-based product that is dispensed in a two-chambered cartridge. The Genotropin 1.5mg product front chamber contains the active ingredient (recombinant somatotropin) and excipients and the rear chamber contains water for injection. Additional strengths of this product have mannitol and a preservative added to the water in the rear chamber. Examples of other FDA-approved products utilising a dual-chambered design include the following injectable products: Lupron Depot®, Cephazolin® and Clinimix E®.

Many products require special conditions for transport and storage in order to maintain their potency within acceptable limits. The FluMist® influenza vaccine requires storage under frozen conditions and the drug product is thawed just prior to administration and used immediately. A revised formulation of the same product can now be stored under refrigerator conditions (5°C); however, a cold chain remains a requirement. Development of a dry powder vaccine for influenza (such as that described above<sup>3</sup>) would represent a marked improvement in therapeutic options for this important indication. Furthermore, with the spectre of a future influenza pandemic on the horizon, development of novel vaccines that do not require a cold chain and could be self-administered via the intranasal route are critical to mounting a preventative response on a global scale. Dry powder products would be ideal

for distribution within developing nations where sustaining a cold chain is difficult, if not impossible, to establish or adequately maintain. The superior stability of the dry powder product would also allow for stockpiling of the vaccine as governments around the world prepare for the next pandemic.

The technical challenges of delivering a dry powder pharmaceutical to the nasal mucosa have likely inhibited development in this area, as evidenced by the paucity of approved IN products. The forces necessary to deliver even microgram quantities of dry powders require the use of spring-loaded devices or propellants. Even with such devices, the delivery of particulates is marginally reproducible and significant drug losses occur by deposition outside of the target area or via inhalation into the airways. The industry has been migrating away from the propellant-based technology once viewed as the industry standard for reproducible delivery of particulates.

Devices that can combine the advantages posed by dry powder technology with the ease and reproducibility of solution delivery will become the next-generation IN delivery devices. An IN device that could separately store the dry powder and a suitable diluent would allow for long-term storage without the necessity of a cold chain. When the patient or healthcare provider is ready to administer the dose, mixing of the individual compartments – i.e. reconstitution – is initiated and the solution is subsequently delivered using existing technology. An obvious challenge with

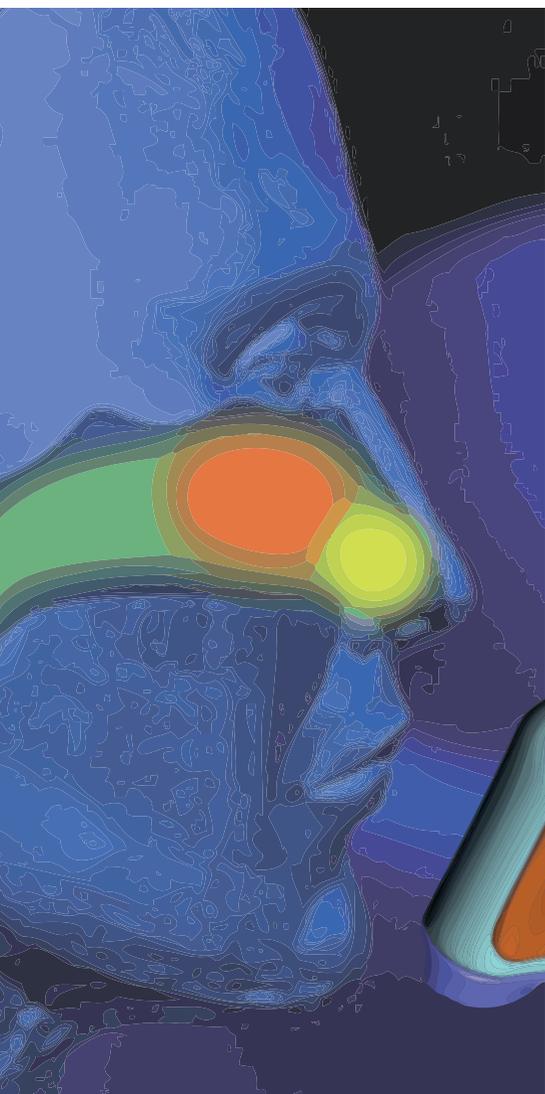
such a device is assuring that the integrity of the individual compartments is maintained during handling, transportation and storage. The composition of the diluting medium should be as simple as possible, with the ideal scenario including only water for injection in the liquid compartment.

In summary, delivery of dry powder drug products to the nasal mucosa will provide a compelling advance in pharmacotherapeutics. Advanced IN devices are currently being developed to improve the delivery profile of dry powders. Companies leading the innovations contributing to the development of this technology include Mystic Pharmaceuticals, Inc. and BD Technologies. These devices will improve stability and allow drug products in dry powder form to be stored for extended periods of time. Reconstitution just prior to administration could obviate the requirement for a cold chain until use, enhancing the value proposition for product development, distribution and use in developing nations. Advanced techniques for controlling spray plume geometry and incorporation of mucosal absorption enhancers will improve the delivery and bioavailability of these products. Needle-free IN delivery systems can be self-administered and will facilitate use and improve compliance in a wide range of patients, including paediatric and geriatric populations. Development of dry powder vaccines coupled with IN self-administration will reduce dependencies on a professional healthcare infrastructure and speed deployment among civilian populations in both developed and developing nations in the advent of a pandemic crisis. ■

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