The route of administration is critical for any medicine. For decades, the most common dosage forms were either oral or for injection. Patients generally preferred oral therapies over injected medications because oral delivery is non-invasive and convenient. Based on this preference and advances in drug delivery technologies, several other non-invasive dosage forms, including orally inhaled dry powders, have been developed and offer excellent alternatives to the more traditional “pills and needles”.

Drug delivery by inhalation presents unique advantages that are not available with other modes of administration. For example, the large surface area of the lung (about the size of a tennis court) provides efficient drug absorption. Additionally, inhalation is simple and convenient, particularly with the newest innovations in inhaler design and function. Even the challenges previously inherent in developing inhalation products are nearing resolution. The concept of translational medicine has been introduced into the development of inhalation products with the advent of advanced inhalation development technologies that directly link the bench and the bedside.

Self-administered inhaled drugs were initially used only to treat pulmonary diseases, like asthma, where direct delivery to the site of action provided a clear advantage. However, inhalation dosage forms have evolved significantly over the past decade expanding their use in a wide spectrum of disease therapies ranging from pulmonary indications routinely treated with inhaled medicines (asthma, cystic fibrosis, chronic obstructive pulmonary disease) to novel applications of the inhalation route to treat systemic diseases (irritable bowel disease, schizophrenia, migraine, diabetes, and obesity).

Notable recent progress in the inhaled drug arena for non-pulmonary indications includes: the development of Staccato® Loxapine for the potential treatment of schizophrenia (Alexza Pharmaceuticals, Mountain View, CA, US); Afrezza® for the potential treatment of diabetes (MannKind Corporation), Levadex™ for the potential treatment of migraine (MAP Pharmaceuticals, Mountain View, CA, US), and Inavir®, an anti-influenza treatment launched by Daichii Sankyo (Tokyo, Japan).

MannKind Corporation develops pulmonary drug delivery systems that combine a dry powder formulation with convenient, patient-friendly devices. Transitioning combination products from concept to clinical practice is simplified by innovative technologies that have been developed by MannKind.

**FORMULATION TECHNOLOGY**

Development of formulations for dry-powder inhalation combination products requires some key considerations including stability and particle architecture. Drug stability should be evaluated in both crystalline and amorphous particles. The particle engineering technology itself must have the capacity to produce powders effectively and efficiently with any desired particle-size range to accommodate a variety of therapies. Finally, the manufacturing technology should be scalable and cost effective.

MannKind’s formulation technology is applicable to both small-molecule therapeutics as well
as proteins and peptides. The Technosphere® technology is based on a novel and inert small molecule excipient that forms particles appropriately sized for inhalation into the deep lung without the traditional requirement for subsequent processing (such as milling, blending, sizing, etc).1-6 These dry-powder formulations can be prepared from a wide range of drugs and demonstrate several distinct advantages over conventional dry powder inhalation formulations.

As an example, standard dry-powder formulations are generally sugar-based (e.g. lactose, mannitol). In most cases, the sugar is blended with micronised drug powders. This process produces heterodisperse particle mixtures with a wide size distribution that necessitates downstream processing to reduce and harmonise particle size. Unfortunately, even after milling, sizing, blending, and micronising, the final powders remain heterodisperse with poorly controlled and nonspecific particle morphology and size.

By contrast, Technosphere powders are monodisperse and low density with particle morphology and size fixed during particle formation by either controlled crystallisation or spray drying. The resultant powder comprises a narrow particle size distribution with a mean geometric diameter of about 2 \( \mu \text{m} \) and a very rapid dissolution profile. The ability to control particle size during particle formation facilitates the preparation of particles in a specific size range. This particle engineering capability can be used to prepare small particles for inhalation into the deep lung or larger particles for deposition in the upper airways.

DEVICE TECHNOLOGY

Powder delivery to the patient occurs with easy-to-use and patient-friendly dry-powder inhalers designed for convenient self-administrations. MannKind has developed two device formats, a re-usable device called Dreamboat® and a single-use, disposable device called Cricket™, to meet therapeutic, patient, and/or manufacturing needs. Uniquely, the inhalers utilise a high resistance design enabling low in-use flow rates that reduce powder deposition in the throat and promote deep lung powder deposition for ease of patient use.7

At the foundation of MannKind’s advanced inhalation development capabilities lies the fact that both Dreamboat and Cricket device formats share a common flow path (shown in Figure 1). This feature makes powder delivery similar and predictable. As a patient inhales, two flow inlet streams converge simultaneously. The first inlet stream lifts the powder from a containment region to fluidise it and deliver it into a second by-pass inlet stream. The intersection of these two inlet streams breaks up the fluidised powder into particle sizes suitable for inhalation. The de-agglomerated powder then travels down a mouthpiece outlet and into the mouth. The powder dispersion occurs rapidly and early in the patient’s inhalation manoeuvre.

Tuning of the flow path to meet a particular patient population or formulation need is readily achieved by adjusting elements of the straightforward schematic (Figure 1). For example, lowering the flow resistance can make more flow available to improve performance for formulations that require more de-agglomeration or for patients with lower inhalation capacity. Importantly, the patient’s breath alone powers the device. This breath-powered mode of delivery is very patient-friendly because the traditional co-ordination between device activation and patient inhalation has been eliminated.

The Dreamboat (re-usable) and Cricket (single-use, disposable) device formats are shown in Figure 2. Each device is pre-metered with up to 15 mg of Technosphere inhalation powder making dose selection for patients uncomplicated. Dose is controlled during product manufacture by pre-metering the required quantity of powder into the cartridge (Dreamboat) or device (Cricket). Both of these dosing formats are designed for single use.

To use the Dreamboat device, patients select a cartridge, place it in the inhaler, inhale the contents, and discard the cartridge. Dreamboat’s intuitive design features five easily molded plastic components making it manufacturing friendly. Yet more simply, the Cricket requires the patient to advance a button, inhale the contents, and discard. It features two easily molded plastic parts that merge the Dreamboat inhaler and cartridge together.

ADVANCED INHALATION PRODUCT DEVELOPMENT TECHNOLOGIES

The development of dry-powder/device combinations for inhalation products has historically been viewed as complicated, challenging,
and limited to pulmonary diseases. MannKind’s inhalation development processes are designed to simplify inhalation product development to make the inhalation route of administration one that is routinely considered early in the development of any drug. With this intent in mind, and in addition to MannKind’s formulation and device combination, MannKind is also pioneering advanced inhalation drug development technologies that can reduce both the cost and time required to bring new products to commercialisation. These innovations can transition pulmonary drug delivery candidates rapidly into patient-friendly medicines in a translational medicine format.

The development of an inhalation drug candidate begins with the identification of a proposed therapeutic regimen. Chronic or frequent administrations may be more suited to the Dreamboat device because it is re-usable. Depending on the powder formulation and clinical indication, this device can be used for periods ranging from 15 days to three months, without cleaning or maintenance, and then discarded.

Conversely, the Cricket device is intended for short duration, time of need, or infrequent therapy administrations because this device is disposable after a single use. Prototype powder formulations are made and filled into one of the device formats for initial performance screening. Several metrics are used including mass percent powder emptying from the device, discharge duration, and geometric particle size of the dispersion. These metrics are key indicators of device efficiency, and they are particularly connected with all aspects of patient use. MannKind therefore adopts a patient-forward approach during all its evaluations.

During the assessment for mass percent emptying, patient-mimicked physiologic inhalation efforts are created using MannKind’s MIDAS (MannKind Inhalation Data Automated Simulator) and BluHale® systems (Figure 3). MIDAS is a linear servo driven syringe pump with a customised algorithm for replicating patient inhalation efforts. It is used in combination with an anatomical model to replicate a patient’s upper airway (mouth and throat). BluHale is a compact, wireless pressure profiling technology used to capture and transmit data from a patient’s inhalation effort. It features a small, discreet, electro-acoustic sensor that outputs a signal calibrated to pressure.8

During testing, a BluHale sensor is adapted onto the selected inhaler format to transmit a patient inhalation effort without drug administration. An anatomical model is placed in series with MIDAS and a second inhaler containing pre-metered dry-powder formulation is connected. As a volunteer inhales through the empty inhaler, BluHale transmits the in-vivo effort to MIDAS which in turn discharges the powder (from the inhaler with drug) through the in-vitro anatomical model. At the base of the anatomical model, a clear tube with filter paper is provided to allow observation and capture of the powder passing through the upper airway.

Insights into throat deposition and discharge time are made qualitatively and quantitatively. Device emptying is assessed gravimetrically after it is removed from the anatomical model. Uniquely, formulation/device combinations can be assessed with any desired inhalation effort to probe device emptying efficiency. Excipients may be added or their ratios adjusted to improve emptying of the powder from the device. Additionally, device and particle geometry may be altered slightly to promote greater powder fluidisation from the device.

In parallel to the device-emptying assessment, MannKind uses a laser diffraction instrument, Helos (Sympatec, Clausthal-Zellerfeld, Germany), to assess geometric particle sizes within the emitted powder plume. A novel adaptation to the instrument’s standard inhaler test module (Figures 4 & 5) was developed to improve test integrity, consistency, and resolution.9

Similar to a discharge from a pressurised metered-dose inhaler (pMDI), the inhaler is placed in a chamber where positive pressure is used to propel the powder from the device. The discharged plume traverses an ambient zone where it is scanned by the instrument’s laser (Figure 6). This approach overcomes pitfalls associated with laser diffraction methodology such as double counting of particles and reported measurement durations which are not in alignment with discharge times.

This novel adaptation results in a high-throughput screening methodology with sufficient resolution to optimise inhaler and formulation combinations. Minor shifts in geometric particle size are easily measured to ensure that optimal powder de-agglomeration is achieved. Interestingly, the equipment is linked with MIDAS to quantify the effects of inhalation effort on particle size and discharge duration. Similar to the emptying, both formulation and device geometry adjustments can be made to achieve the desired particle-size distribution.

A preferred formulation/device combination is identified based on this in-vitro data. Then, an initial clinical study is conducted to define the...
performance of this prototype inhalation product in a representative patient or healthy normal volunteer population using BluHale. The data obtained from the study are used to characterise in vivo dose effects. Taking advantage of the fact that sound generally emanates in all directions, the BluHale sensor is placed outside the inhaler flow path. This configuration allows capture of inhalation data during dose administration without affecting the patient/device interface. An interactive screen receives the BluHale transmission and enables users to visualise their inhalation effort in real time. These data facilitate device “tuning” to meet the needs of the specific patient population (Figure 7). When a clear and readily measured clinical bio-marker is available, pharmacokinetic data are used to establish a relationship, or lack thereof, between dose response and user technique. BluHale can also serve to eliminate unwanted sources of variability associated with varied inhalation technique. Taken together, using BluHale to profile patient inhalation technique helps define the space for the pulmonary system within the intended patient population. This approach to comprehensive understanding for all aspects of the inhaled delivery helps advance the drug candidate quickly along the development timeline.

CONCLUSION

Integration of formulation/device technologies with advanced product development capabilities, translates laboratory bench ideas, designs, and concepts directly to bedside patient medications. Formulation selection combined with device optimisation can be accomplished in a laboratory setting using realistic patient inhalation profiles. Bringing this already advanced formulation/device combination to the clinic has the clear potential to maximise development efficiencies for inhalation products across a wide arena of clinical indications. Inhaled medicines are no longer limited to the treatment of pulmonary disease.

REFERENCES