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INNOVATION IN DRUG DELIVERY BY INHALATION

In this article, Andrea Leone-Bay, PhD, Vice-President, Pharmaceutical Development, Robert Baughman, PharmD, PhD, Vice-President, Clinical Pharmacology & Bioanalytics, Chad Smutney, Senior Director, Device Technology, and Joseph Kocinsky, Senior Vice-President, Pharmaceutical Technology Development, all of MannKind Corporation, describe the powder fomulation technologies and delivery devices the company is developing for drug, including insulin, delivery to the systemic circulation via the lungs.

Historically, the lung has been viewed as a filtering organ not amenable for drug delivery. However, the lung provides a large absorptive surface area, a thin alveo-capillary membrane, and a large vascular bed through which the entire cardiac output flows with every heart beat. Additionally drugs administered by the pulmonary route avoid the challenges associated with transiting the gastro-intestinal tract.

Given these characteristics and the desire for rapidly absorbed drug products provided in patient-friendly formats, MannKind Corporation has developed an inhaled drug delivery technology based on dry-powder formulations delivered through discrete, breath-powered inhalers. Additionally, MannKind's proprietary inert excipient, FDKP (fumaryl diketopiperazine), the primary component of these Technosphere® dry-powder formulations, has the ability to deliver drugs in a cost-effective manner that is well-tolerated by patients.

MannKind has utilised this drug delivery technology during the development of Technosphere Insulin (Afrezza®), an innovative and patient-friendly orally inhaled insulin, to establish a formulation/device/development system with the potential to change the paradigm for inhaled drug delivery.

Going forward, systemic delivery by inhalation will have a dramatic impact on the market as more active agents are shown to benefit from this route of administration. However, the real impact will be realised when patients are given the opportunity to self-administer therapies in easy-to-use, patient-friendly delivery systems. MannKind's technology system meets all these requirements and offers the additional advantage of providing unique pharmacokinetics characterised by ultra-rapid drug absorption.

FORMULATION TECHNOLOGY

MannKind's dry-powder formulations are based on the novel excipient, fumaryl diketopiperazine (FDKP), shown in Figure 1.

FDKP is a substituted diketopiperazine that forms the Technosphere particle matrix and is the primary component of Technosphere dry-powder formulations. The particles can be either crystalline or amorphous (Figure 2). Crystalline particles are prepared by a controlled, pH-induced crystallisation process in which FDKP nanocrystals self-assemble into microparticles.[1-6]

A crystalline Technosphere particle can be envisioned as a three-dimensional sphere constructed from a deck of playing cards. Each card represents an FDKP nanocrystal and the sphere constructed from the cards represents a Technosphere particle. The back and front faces of the cards provide the sphere with a large surface area. The spaces between the cards provide the sphere with a high internal porosity resulting in low density and suitable aerodynamic properties for deposition in the distal airways.

These crystals provide a large surface area onto which drugs can be adsorbed to make an inhalation powder.[7] Amorphous particles can be formed from a salt of FDKP and the drug. Such particles are a homogenous composite of the FDKP salt and drug. Once the crystalline or amorphous Technosphere particles are formed, they are not processed further. Particle size is fixed during particle formation (either

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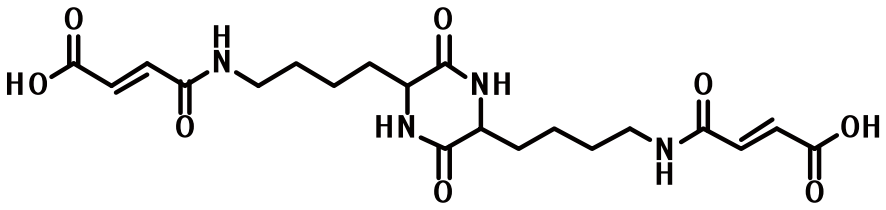

Figure 1: Chemical structure of FDKP.

crystallisation or spray drying) eliminating the need for milling, sizing, or blending.

Upon inhalation, Technosphere particles carry the drug to the lungs, dissolving immediately at the prevailing physiological pH in the lungs due to FDKP's high solubility at pH ≥ 6. Here, the drug is absorbed into the systemic circulation.

Drugs inhaled as Technosphere powders are often characterised by pharmacokinetic profiles that mimic intravenous injection. Absorption begins almost immediately after inhalation and circulating drug concentrations peak within minutes of administration. Duration of drug exposure is determined by the inherent circulating half-life of the drug itself. Drugs ranging in molecular weight from 300 to 100,000 Da are absorbed readily. Drugs having molecular weights >100,000 Da can be formulated for local lung delivery, but their systemic absorption is limited by their large molecular size.

The fumaryl diketopiperazine (FDKP) is absorbed but not metabolised, and is excreted intact, primarily in urine. FDKP does not directly facilitate drug absorption, but functions solely as the particle matrix.[8] Taken together, these unique features contribute to the distinctive pharmacokinetic profiles of drugs administered as Technosphere powders.

DELIVERY BY INHALATION

Technosphere powders are inhaled using small, high-resistance, breath-powered inhalers (see Figure 3). The Dreamboat™ inhaler is a re-usable device designed for 15 days of use. To take a dose of medication, the patient simply opens the device, inserts a unit-dose plastic cartridge containing the Technosphere powder formulation, closes the device, and inhales the powder through the mouthpiece in a single breath. The powder is expelled from the device by the patient's inhalation; no other activation is required. After dosing, the patient opens the device and then removes and discards the emptied cartridge.

Alternatively, the Cricket inhaler is a single-use disposable device comprising two components. To take a dose of medication, the patient simply removes the pre-loaded, single-use device from the package, activates by depressing the purple button, and inhales the powder through the mouthpiece in a single breath. The powder is expelled from the device by the patient's inhalation, no other activation is required. After dosing, the patient discards the used device. It is intended for indications that are short in duration or time of need.

COMBINATION PRODUCT DEVELOPMENT, DEVICE DESIGN

Successful delivery of dry-powder formulations requires careful consideration of many factors. Human anatomy dictates that particles with aerodynamic diameters of 1-10 µm have the highest probability of reaching and depositing in the deep lung.[9] Larger particles may be filtered by the tortuous path from mouth to alveoli and smaller ones may not settle or impact and can be exhaled.

As a result of the need for micrometer-sized particles, the normally insignificant static and van der Waals forces cannot be ignored and can begin to affect the "dispersability" of the powder leading to cohesion and agglomeration. Therefore, for a breath-powered inhaler to work effectively it must maximally harness the energy contained in an inhalation to lift and separate individual particles, but not impart too great a velocity onto any one. Particles with high momentum cannot change direction quickly enough to avoid inertial impaction in the conducting airways and may never reach the distal lung tissue.

An effective inhalation system must also consistently deliver the same mass of powder and adequately protect it from deleterious environmental factors prior to use. Moisture, for example, can quickly change a particle's morphology or permanently link it to neighboring particles to form large agglomerates.

Finally, users of inhalation systems vary in age, dexterity and cognitive ability. The most limited of users must still be able to co-ordinate the steps required for operation, or else the device is rendered useless.

These aspects of device design were evaluated in developing the Dreamboat inhalation system to deliver Technosphere powders (see Figure 4). A breath-powered mode of delivery offers advantages because patients are not required to synchronise an activation step with a sequential inhalation step. Instead, activation occurs by the patient's inhalation alone. In addition, several key features including re-usability and high resistance were incorporated. While the device itself is re-usable, the cartridge containing the powder formulation is single-use and is prefilled with a discreet quantity of powder. Other

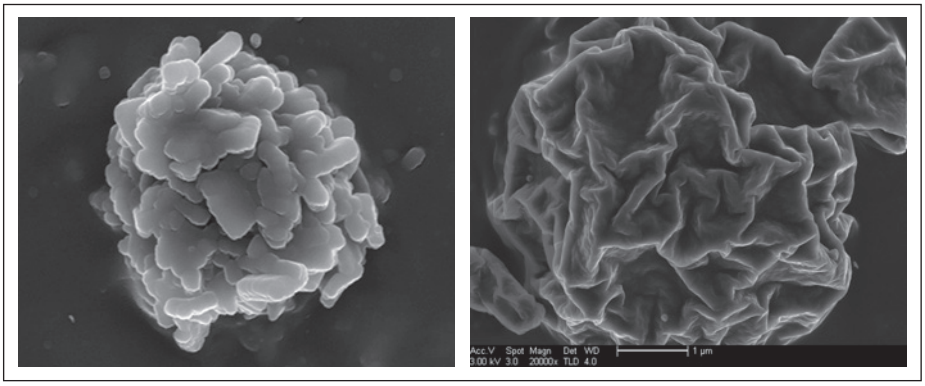

Figure 2: Crystalline particle (left) and amorphous particle (right).

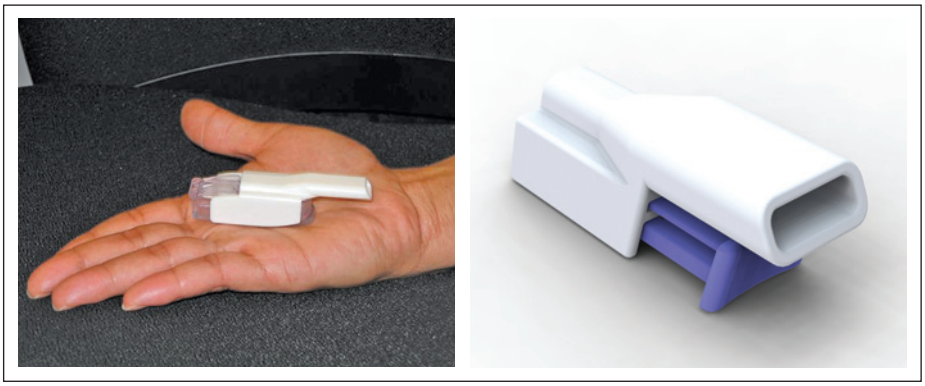

Figure 3: Dreamboat (left) and Cricket (right) inhalers.

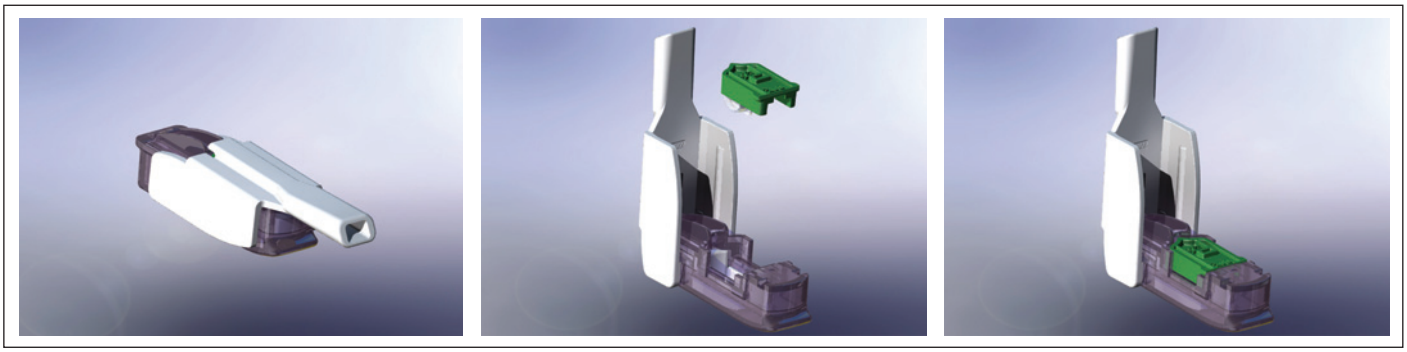

Figure 4: Technosphere powder inhalation system showing device (left panel), device with single-use, pre-metered cartridge containing drug powder (centre panel), and device with cartridge installed (right panel).

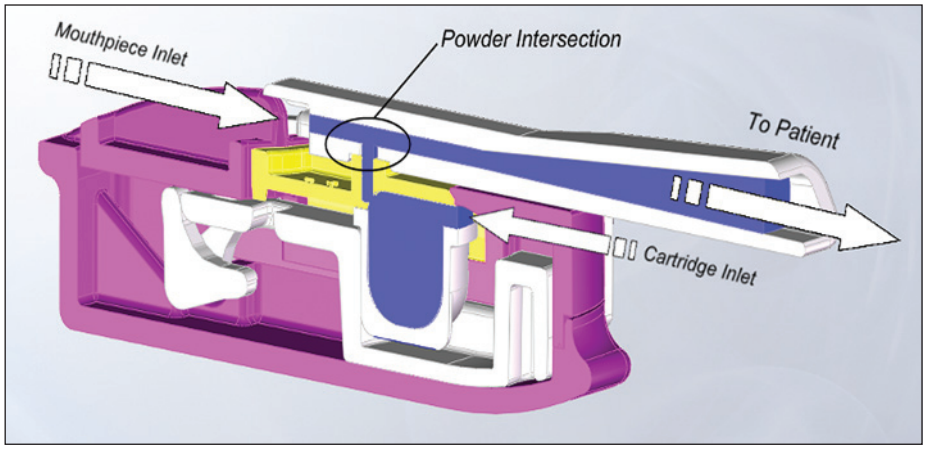

Figure 5: Inhalation system flow path.

desirable characteristics included in the design were small size for portability and discreetness, and simple, intuitive operation.

A concept called "flow balance" was employed in the design to provide effective dispersion and de-agglomeration of the powder. Air flow moving through the cartridge initiates de-agglomeration and lifts the powder from the bottom of the cartridge to the top exit port. By-pass air flow moving down the mouthpiece intersects air flow moving from the cartridge exit. Here it is sheared to complete the de-agglomeration process before exiting the mouthpiece (Figure 5). This air-flow balance allows complete discharge of the cartridge contents as well as providing forces that are sufficient to de-agglomerate the powder into particles sized within the respirable range.

The contributors to the flow balance including inlet/outlet areas, feature geometries, and proximities define the principle characteristic of the system called flow resistance. Based on the inhalation pressure supplied by the patient, the resistance determines the available air flow that drives powder delivery/performance. Importantly, pressure differentials across the inhalation system produce flow rates that are consistent with the Bernoulli principle, shown by the equation:

$$\Delta P^{1/2} = \Phi R$$

where ΔP is pressure drop, Φ is flow rate, and R is resistance. [10,11]

According to the equation, device system resistance is defined as the slope of the line produced by the relationship between the square root of pressure and flow (Figure 6). A high resistance was established to help increase flow turbulence at critical de-agglomeration points within the device system while simultaneously effecting slow average plume velocities to minimise throat deposition. Other researchers have found similar benefits from high resistance in delivery via dry-powder inhalers.[12-14]

Figure 7 shows the cumulative geometric particle size distributions for a range of fill masses and pressure drops (air-flow rates) in the device system. The inhalation system demonstrated consistent performance across the range of fill masses and applied flow rates. This consistent performance across a diverse range of pressure drops shows that this inhalation system is suitable for broad patient populations including pediatric, geriatric and populations with compromised pulmonary function.

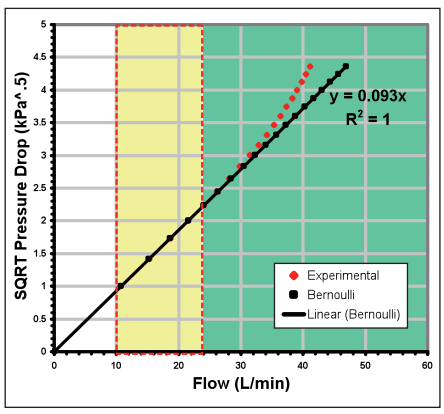

Figure 6: Experimental (measured) and predicted (Bernoulli) behavior of inhalation system resistance: Square Root of Pressure Drop vs Flow Rate.

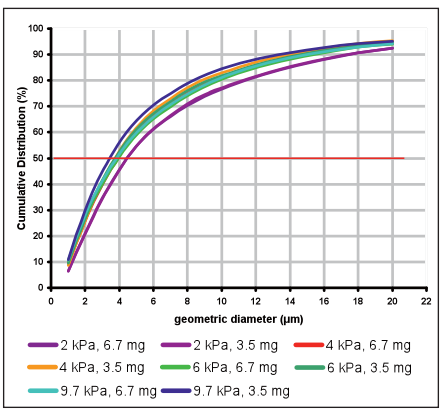

Figure 7: Cumulative geometric particle-size distributions over a range of cartridge-fill masses and pressure drops in the device system.

ADVANCING COMBINATION PRODUCT DEVELOPMENT THROUGH PATIENT PROFILING

The breath-powered mode of delivery and the high resistance within the Dreamboat design were carefully considered and selected. However, it was vital to understand how these attributes interfaced with patient abilities.

During use, pressure applied to the delivery system is the driving force imparting energy to the system (inhaler plus cartridge plus powder) and the product of pressure and time is a measure of the impact of this force

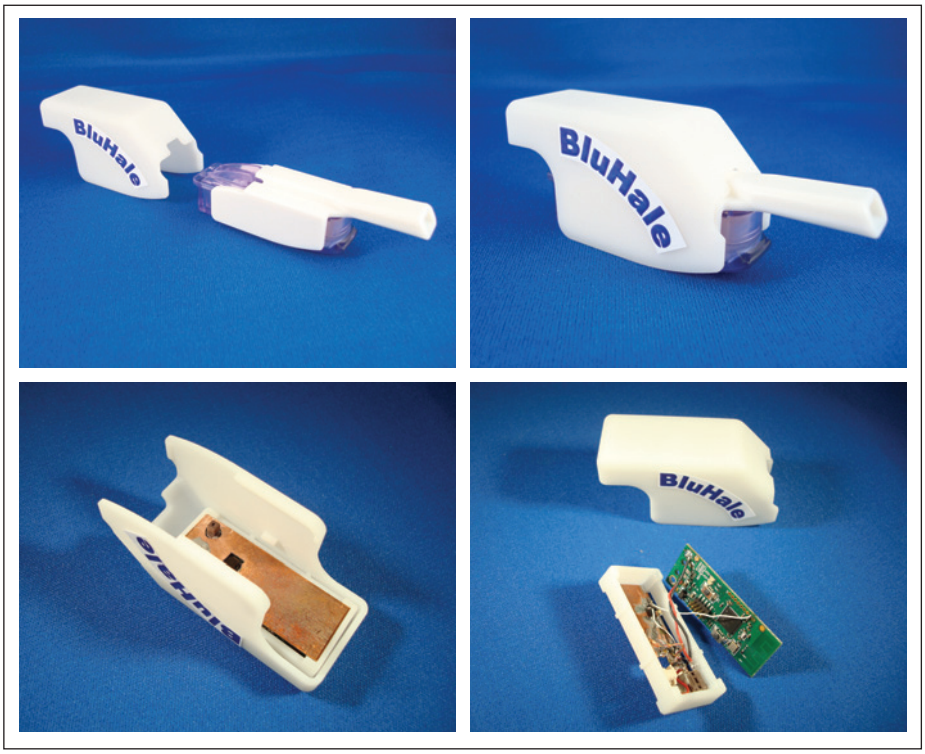

Figure 8: BluHale Jacket Technology

on the powder. These two parameters, peak inspiratory pressure (PIP) and area under the pressure-time curve (AUC), indicate utility of an inhalation effort.

Sensitivity of delivery performance to inhalation effort can be assessed by probing PIP and AUC values during the powder discharge. Since this generally occurs early in the development of the inhalation effort, PIP in the first two seconds ($PIP_{0\text{-}2\ sec}$) and AUC in the first second ($AUC_{0\text{-}1\ sec}$) are more specific and useful measures.

Recognising the criticality of these parameters, MannKind developed a compact and wireless pressure profiling technology, called BluHale®, to rapidly advance and understand the patient/delivery system interaction.

A small, discreet electro-acoustic sensor was used to measure the sound emitted by air flow through the system. Since higher flows (and greater sounds) result from higher pressures, the sensor output was calibrated to applied pressure.

Sound is a unique characteristic for inhalation devices because it generally emanates from the system in all directions. This allows it to be measured remotely unlike traditional pressure/flow sensors that must be located within the flow path. Data can be easily collected during dose administration without affecting sensor integrity or changing airflow dynamics through the device. Additionally, the inhaler interface with the subject is unchanged because of the compact nature of the electro-acoustic sensing technology and its simple adaption onto the device. The sensor, along with circuitry, is housed within a jacket-like frame that is easily affixed onto a dry-powder inhaler (see Figure 8).

Pressure-time profiles are captured and transmitted in real time to a graphical user interface. This enables subjects to achieve prescribed inhalation effort parameters successfully by watching the user interface during the inhalation.

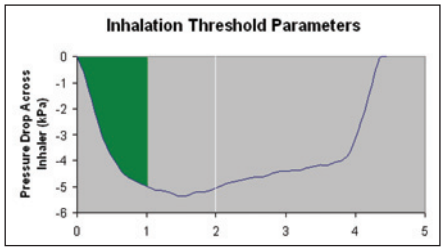

Figure 9: Parameterised BluHale pressure time profile

During clinical use, BluHale pressure-time curves were collected and parameterised for $PIP_{0\text{-}2sec}$ and $AUC_{0\text{-}1sec}$ (shown in Figure 9). In various clinical trials during which Technosphere formulations were administered to healthy subjects, $PIP_{0\text{-}2sec}$ values of ~4 kPa and $AUC_{0\text{-}1sec}$ values of ~3 kPa.sec were demonstrated.

An inhalation profile exhibiting these nominal values was then reproduced in the lab with an inhalation simulator to test delivery device performance attributes such as geometric particle-size distribution and mass percent emitted from the device. Based on this testing, design iterations were made to optimise the median geometric particle size of the emitted aerosol and maximise mass percent emitted.

Median geometric particle sizes of 3-4 µm with 97% emitted masses were realised in the final design. Variants of this nominal inhalation effort were then explored with the goal of establishing an effort threshold for performance as defined by minimum $PIP_{0\text{-}2sec}$ and $AUC_{0\text{-}1sec}$ values. In other words, it was desired to understand which inhalation efforts caused performance deterioration.

To this end, deterioration was defined by median geometric particle sizes above 4.9 µm (33% greater than the smallest achieved median size) or cartridge emptying below 87% (10% less than the nominal 97%), either condition resulting in failure. The threshold $PIP_{0\text{-}2sec}$ was found to be 2.0 kPa and the threshold $AUC_{0\text{-}1sec}$ was found to be 1.2 kPa.sec (see graphical depiction in Figure 10).

Thus, by recording subject inhalation profiles with a novel sound sensing system, MannKind was able to advance the development of its device delivery system rapidly. The design was accelerated and the difficult tasks of device characterisation and specification development were simplified. The end result was a high resistance, breath-powered delivery device system with robust performance across a large spectrum of patient inhalation efforts.

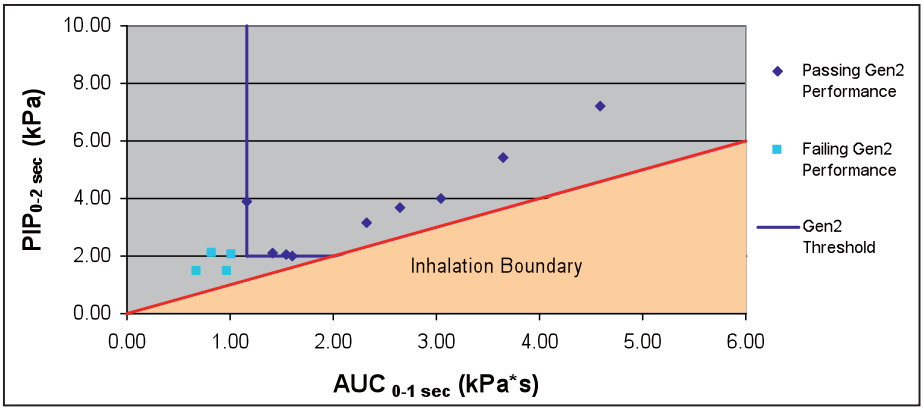

Figure 10: Threshold limits for the MannKind Gen2 Inhalation System

TECHNOLOGY EXEMPLIFIED IN AFREZZA™ (TECHNOSPHERE® INSULIN)

Insulin delivery by inhalation appears to be advantageous when compared against the other non-injected routes (oral, dermal, nasal).[15] Pulmonary insulin dosing was first reported in 1925 when Gänsslen described his investigation using a nebuliser.[16] While an effect on blood glucose was noted, the low bioavailability and constraints of the dosing apparatus made this route impractical.

However, the development more than 20 years ago of handheld inhalers and the accompanying technology for generating an aerosol with the requisite particle size distribution for lung deposition reignited the experimentation and development of pulmonary insulin administration. A number of inhalers (differing in the number of components, size, weight, and ease of use) that utilise solution or dry-powder formulations (with varying excipients) that entered clinical testing have been previously reviewed.[17,18]

Afrezza insulin is different from all other inhaled insulin products because it provides ultra-rapid insulin absorption with corresponding clinical benefits, as well as a number of novel formulation and device characteristics (described above) that appear to mitigate problems identified with earlier technologies.

CLINICAL TRIAL RESULTS

In a 12-week randomised, controlled trial in 110 patients with Type 1 diabetes, Afrezza insulin was administered at mealtime. The Afrezza-treated subjects demonstrated significantly reduced HbA1c concentrations from baseline (-0.83%), without experiencing weight gain. The control group, that received prandial treatment with injected insulin showed a similar statistically significant glycaemic improvement from baseline (-0.99%). However, the injected group experienced a weight change of +0.89 kg compared with -0.41 kg for the Afrezza group.[19]

Another study enrolled adult patients with Type 2 diabetes mellitus and poor glycaemic control in ten countries. Patients were randomly allocated to receive 52 weeks of treatment with prandial Afrezza plus bedtime insulin glargine (n=334) or twice daily premixed biaspart insulin (n=343) (70% insulin aspart protamine suspension and 30% insulin aspart injection [rDNA origin]). Over the 52-weeks, 107 patients on inhaled insulin plus insulin glargine and 85 on biaspart insulin discontinued the trial. The per-protocol analyses included 211 patients on inhaled insulin plus insulin glargine and 237 on biaspart insulin. Change in HbA1c with inhaled insulin plus insulin glargine (–0·68%, SE 0·077, 95% CI –0·83 to –0·53) was similar and non-inferior to that with biaspart insulin (–0·76%, 0·071, –0·90 to –0·62). The between-group difference was 0·07% (SE 0·102, 95% CI –0·13 to 0·27). As reported in previous studies, patients had significantly lower weight gain and fewer mild-to-moderate and severe hypoglycaemic events on inhaled insulin plus insulin glargine than on biaspart insulin. The safety and tolerability profile was similar for both treatments, apart from increased occurrence of cough. No statistically significant differences were noted between groups in the mean change from baseline in FEV1, FVC or lung diffusion capacity at week 52.[20]

Overall, these clinical data show that inhaled Afrezza insulin offers glycaemic control comparable to current injected insulin with less weight gain, reduced risk of hypoglycaemia, and reduced postprandial glucose excursion. These clinical data are correlated with the unique pharmacokinetics of Afrezza. Application of this technology to several other peptide and small-molecule drugs has the potential to deliver similar advantages.

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MannKind Inhaled Drug Delivery Technologies

Novel Technologies to Expedite Inhaled Drug Development

MannKind Corporation has developed a versatile inhaled drug delivery platform based on a formulation and device combination to provide patient-friendly self-administered medicines.

Integration of dry powder particle engineering, device innovation, and in vitro/in vivo system performance contribute to overall product development. For that purpose, MannKind has created several new techniques that allow efficient development of inhaled drug products. New drugs can be evaluated as inhaled products in preliminary feasibility studies in as little as 3-6 months.

Technosphere® Technology allows the pulmonary administration of therapeutics currently requiring administration by injection and offers several competitive advantages over other pulmonary drug delivery systems:

- Unique pharmacokinetic profile
- Applicability to a wide variety of drugs
- Rapid drug absorption with excellent bioavailability

MannKind's **Device Technology** concentrates on breath-powered, patient-focused dry powder inhalers, with adherence to several key principles:

- Consistency using high flow resistance
- Customizable for a variety of powders and user groups
- Modularity of a platform-based delivery technology
- Portability with a discreet system
- Scale-ability in high- and low-volume applications
- Sensitivity to environmental exposure

The MannKind device technology has been incorporated into multiple inhaler embodiments such as the multi-use device (above) and the single-dose, disposable device (right). Adjustments to meet the needs of specific API formulations and specific clinical indications can be easily implemented.

MannKind has also developed state-of-the-art **Delivery Technology** for the efficient development of inhalation products across a wide range of therapeutic areas. These systems can be used to understand and characterize patient inhalation parameters for rapid optimization of the formulation and device.

For more information on MannKind Corporation and its technology, please contact:
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CURRENT INNOVATIONS IN DRY POWDER INHALERS

The 3M Taper and 3M Conix are new dry-powder inhaler devices. In this article, Richard Sitz, Technical Manager, DPI Technology Platform Leader, 3M Drug Delivery Systems, describes these two latest products from 3M's inhalation group.

Recent advances in drug delivery via inhalation have created a number of interesting opportunities for inhalation devices. New developments have helped make this delivery route compatible with larger molecules, such as proteins and peptides, and inhalation delivery can be used for both local and systemic drugs. With the new capabilities made possible by recent advances, inhalation may soon become the therapy of choice for a variety of conditions.

As the pharmaceutical community is aware, administering drugs via the lungs offers a number of benefits. Compared with drugs that must travel through the patient's gastro-intestinal tract, inhalation can minimise systemic absorption and adverse effects. It also offers obvious benefits for treatment of respiratory diseases, including asthma and COPD. In addition, inhalation can play a role in delivering drugs for seasonal allergies and mass immunisations.

Within the field of inhalation technologies, dry-powder inhalers (DPIs) have seen a number of recent innovations, and they offer several advantages over aerosol-based inhalers. These devices can be used to deliver medicines that may not be compatible with an aerosol propellant formulation. Because the medicine in metered dose inhalers must be combined with propellants and other materials to work properly, this process may not be suitable for certain drugs. However, no propellant is necessary for drugs delivered via a DPI. Furthermore, DPIs have been shown to deliver more of the respirable-sized drugs deeper into the lung, enabling them to work more efficiently than other inhalation therapies. As they can be used with both lung-specific and systemic applications, DPIs give pharmaceutical developers valuable flexibility.

DPIs allow developers the ability to tailor the number of doses available, making them suitable even for single-use applications such as vaccines. Furthermore, they are convenient for particular patient needs. For example, a parent may be wary of giving a child a metered-dose inhaler with a hundred doses of an expensive asthma drug. However, with DPIs, the drug can be dispensed more carefully.

3M Drug Delivery Systems has a long-standing reputation as an innovator in inhalation technologies, having introduced the first metered-dose inhaler and the first CFC-free propellant pressurised metered-dose inhaler. Today, more than half of all metered-dose inhalers worldwide utilise 3M technology.

Figure 1 shows a selection of 3M's inhalation products, including 3M's two recently introduced technologies in the DPI category – the 3M™ Taper Dry Powder Inhaler and the 3M Conix™ Dry Powder Inhaler. Continuing the company's record of innovation, both products use unique design features to ensure efficient delivery of drugs and to simplify operations.

THE 3M TAPER DRY POWDER INHALER

The 3M Taper DPI (see Figure 2) has a proprietary design that stores active pharmaceutical ingredients (APIs) on a microstructured carrier tape (MCT). The inhaler uses 3M microreplication and extrusion technology to create a "dimpled" tape upon which one or more APIs are coated, enabling it to provide up to 120 pre-metered doses. This dimple design allows the use of API only, virtually eliminating the need for lactose or complex powder formulations.

The device works via a simple mechanical process: upon opening the mouthpiece, a dose is ready for use. The air flow of the patient's inhalation releases an impactor that strikes the tape and releases API into the airstream. API particles are further de-agglomerated as they pass through the device, helping to ensure effective delivery.

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Figure 1: A selection from 3M's inhalables product range, including on the left the new 3M Conix and 3M Taper DPIs.

DESIGNED WITH "DIMPLES"

Key to this device's method of action is the microstructured carrier tape. Prior to the delivery of a dose, a fixed length of the MCT is presented into the dosing zone within the device. The amount of API delivered with each dose is determined by the number of dimples on the tape, the volume of each dimple, and the density of API powder packed into the dimples; therefore, individual doses in the range from 100 μg to 1 mg are possible. The device can also be used to administer lower doses, but this may require blending the API with lactose.

The dimple geometry of the carrier tape is designed to provide a balance between API retention in the dimples throughout dimple filling and device storage, while promoting release of API from dimples during dosing. API is retained in the MCT dimples prior to delivery due to the high van der Waals forces and mechanical interlocking forces associated with cohesive micronised API. More than 90% of the API is released from the web during dosing.

MEETING NEEDS FOR PATIENTS AND PHARMACEUTICAL PARTNERS

To design the Taper device in a way that would meet the needs of patients and the medical community, 3M conducted patient use studies and interviewed healthcare providers in several global markets.[1,2] Findings from this research revealed a number of important factors. From the patient standpoint, an easily transportable device that is small enough to be concealed in the hand was desired. An audible or visual indication that the dose has been taken was also found to be important, as was an intuitive design with a comfortably shaped mouthpiece. Additionally, a device with a non-medical appearance, at an affordable cost, was requested.

These insights were incorporated into the final design of the Taper DPI, which was engineered to be intuitive and easy to use for patients, while meeting the needs of healthcare providers, pharmaceutical companies, and regulatory agencies.

The 3M Taper device incorporates these qualities into a single compact device which includes an intuitive three-step process to use (open - inhale - close), and has a ready-indicator feature in addition to a dose counter. Figure 3 shows the device in use.

The Taper's simple-to-use features also help encourage patient compliance. The ready indicator changes from green to red and makes an audible click to let the patient know the dose has been delivered. The dose counter is designed with a large, easy to read font size to make the patient aware of when to obtain a new device. As requested by patients in the market research, the device size is small enough to be easily carried in a pocket and discreetly held in the hand. The device's unique capability to deliver neat API, without the need to use large amounts of a lactose carrier, gives it the ability to hold up to 120 pre-metered doses in its small size.

The device has also been designed to withstand the rigors of real world use. Results of a vibration stress test show no statistical difference in the emitted dose between a pre-vibration device and a post-vibration one. In drop testing, all tested devices emerged intact and were fully mechanically functional after completion of dropping. Devices were confirmed to trigger upon exposure to inspiratory flow, proper web advancement was demonstrated, and the dose counters and ready indicators were fully functional, demonstrating the mechanical ruggedness of the device. Moisture protection has also been taken into consideration in the design of the product, to guard against moisture during both the device's shelf life and during its use.

Figure 2: The 3M Taper DPI device.

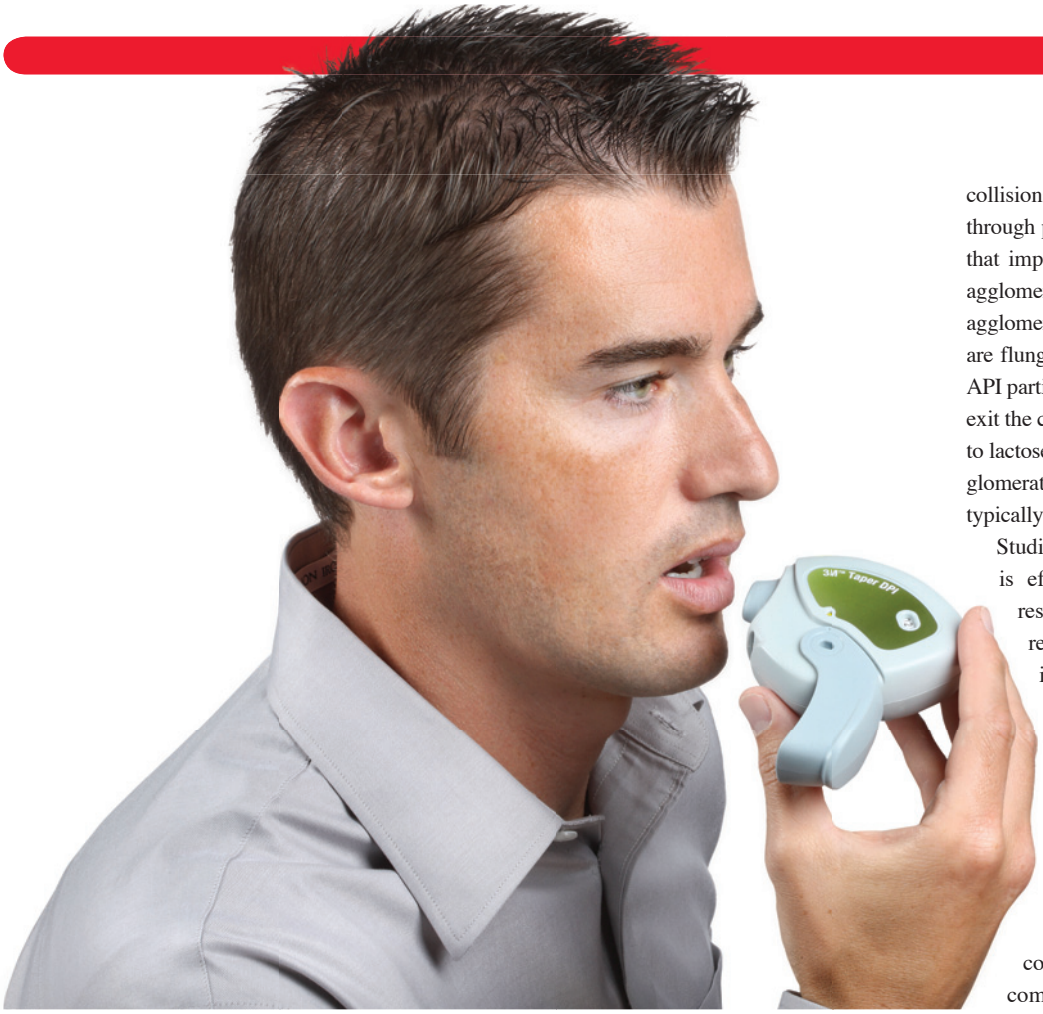

Figure 3: The 3M Taper in use

With its unique design and capabilities, the Taper DPI is designed to bring important new functionalities to DPI systems.

THE 3M CONIX DRY POWDER INHALER

In addition to the Taper DPI, the 3M Conix DPI provides pharmaceutical companies another tool to achieve high efficiency drug delivery to the lungs. The device uses an innovative reverse-flow cyclone design to offer effective drug delivery and simple operation. The technology is available in single-unit-dose designs (both disposable and reloadable) as well as multi-unit-dose designs to accommodate various therapeutic needs, including asthma, COPD and hayfever, as well as mass immunisations and vaccinations. The inhaler's design allows formulation flexibility and protection from moisture ingress, and is engineered to increase the effectiveness of energy transfer from the patient's inhalation to the drug formulation.

UNDERSTANDING REVERSE-FLOW DESIGN

Most dry-powder inhalers utilise a blend of micronised API and coarse carrier particles, typically lactose, to add bulk to the formulation. This approach is intended to make the metering and delivery of the API more reproducible. DPI devices are designed to separate the two types of particles through application of shear forces or induction of particle/particle and particle/surface impaction. These techniques generally result in separation, as the formulation leaves the device and the larger carrier particles subsequently impact on the patient's throat, while the smaller API particles are delivered to the lung.

The 3M Conix DPI system, however, uses a different approach to the de-agglomeration process. The aim of the Conix technology is to preferentially release small (API) particles that are potentially respirable while retaining larger lactose particles and lactose/drug clusters so that they can be further de-agglomerated. Using this technique, the emitted dose would be reduced while the fine particle fraction would be higher than a more traditional approach.

In the Conix device, deagglomeration and aerosolisation of the API occur through reverse-flow cyclone technology. As the patient inhales, air is drawn into the cyclone chamber, where a vortex is established. The base of the vortex cone is blocked such that when the vortex hits the bottom, the flow reverses and is forced through the center of the incoming air towards the exit orifice. This is known as a forced vortex.

The vortex produced by the reverse flow cyclone creates relatively high velocities – and therefore energy – in the air flow, which imparts the energy required for de-agglomeration through collisions with the cone wall, other particles and through particle shear. Previous work has shown that impaction events are more effective at de-agglomerating than airflow shear alone.[3] As de-agglomeration occurs, the large lactose particles are flung to the sides of the cone and the lighter API particles are carried along by the air flow and exit the cyclone. Therefore, any API still adhered to lactose particles are re-entrained into the deagglomeration process rather than being emitted, typically to impact in the throat.

Studies have demonstrated that the device is effective at holding on to large, non-respirable particles to improve the emitted respirable mass. Thus, Conix technology improves delivery to the lung as indicated by increased efficiency, and reduced throat and pre-separator deposition.

This technology brings high-efficiency API delivery to the passive DPI development arena using traditional "simple" formulations of API and lactose. The high efficiency of the device is promising for pharmaceutical companies that seek to deliver high-cost compounds while minimising waste, as well as those that utilise highly potent agents for which delivery to the lung needs to be maximised while systemic delivery is limited.

A PARTNER FOR GROWTH

The global market for DPI devices is large and rapidly growing, so 3M's business model allows it to partner efficiently with pharmaceutical firms to develop drug treatments and solve formulation challenges.

As data continues to mount on the unique benefits and capabilities made possible by inhalation therapy, 3M's innovative solutions and its ongoing research and development help make it a valuable partner for pharmaceutical firms. The Taper and Conix technologies represent the latest examples of 3M's robust capabilities in the inhalation field.

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PULMONARY DELIVERY & DRY-POWDER INHALERS:

ADVANCES IN HARD-CAPSULE TECHNOLOGY

Here, Fernando Díez, Business Development Manager at Qualicaps Europe, and Brian Jones, Scientific Advisor to the company, describe the development of capsules for dry-powder inhalers, and how the simplicity and efficacy of capsule-based dry-powder inhalers makes them an ideal delivery means for an increasing number of active pharmaceutical ingredients.

In the last decade there has been a significant change in the nature of the active pharmaceutical ingredients (APIs) that formulators have had to deal with. This has led innovator pharmaceutical companies to re-examine methods to deliver compounds other than by the standard, resulting in a renewed interest the in use of dry-powder inhalers (DPI) that use hard capsules as the dose container.

"THE MOST IMPORTANT PROPERTY FOR A CAPSULE USED IN A DPI IS ITS ABILITY TO BE CUT OR PUNCTURED IN A REPRODUCIBLE MANNER TO ENABLE THE POWDER TO BE EMPTIED FROM IT AS COMPLETELY AS POSSIBLE"

Originally this application was principally seen as a way of treating asthma and chronic obstructive pulmonary disease (COPD), but researchers have since realised that a whole range of other actives, including peptides and proteins, can be delivered by this route.

The attraction of using a capsule-based DPI is its simplicity. The powder formulation consists either of the API or a mixture of it with a carrier particle such as lactose or mannitol. A significant amount of research into particle engineering has enabled the manufacture of particles with the correct aerodynamic and carrier properties to ensure effective pulmonary delivery of the API. The small number of ingredients in the formulation reduces significantly the amount of analytical work required for the early development phases of a product compared with pressurised metered-dose inhalers.

Many types of validated DPI have been developed for delivering capsule-based products. They are reasonably cheap to manufacture, robust and effective in use. They have two roles; firstly to puncture or cut open the capsule shell so that the contents can be released; secondly to enable the patient's inspirational air flow to empty all the powder from the shell, detach the active from the carrier and guide the airstream into the patient's respiratory tract.

The first capsule DPI product, Sodium Cromolyn 20 mg (Intal Spincaps®), was developed in the late 1960s by Fisons in the UK.[1] This was a challenge for the empty gelatin capsule manufacturer because the shells in use then were not designed to be punctured by needles.

Capsules / Specification	Gelatin	Quali-V®	Quali-V®-I
Moisture Content % w/w	13.0 to 16.0	4.0 to 6.0	4.5 to 6.5
Microbial Level, cfu/g	$<10^3$	$<10^2$	$<10^1$
Triboelectrification potential	Higher	Lower	Lower

Figure 1: Table summarising specifications and properties of different hard capsules: Gelatin, Quali-V and Quali-V-I

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Qualicaps, then part of Eli Lilly, solved the problem by changing their gelatin blends to produce a capsule shell that could be punctured in such a way that the needles produced holes with flaps, which stayed open when the needles were retracted, and did not break off. This was the first breath-actuated inhalation device and it significantly improved patient treatment.

Gelatin is a very robust material and the capsules had all the correct properties for this application except for the fact that when exposed to low relative humdity they lose moisture and become brittle, because water acts as a plastizer for the shell.[2] The problem was minimised by careful control of the moisture content of the capsules and the use of suitable packaging. At that time hard capsules were only available made from gelatin.

In the late 1980s Qualicaps in Japan started a project to look for alternative shell materials whose mechanical properties were not dependent on moisture content. This resulted, in the 1990s, in a new type of capsule made from hypromellose, Quali-V®, whose mechanical properties do not change even when significant amounts of water are lost. This was the first non-gelatin hard capsule for oral use with the correct dissolution properties for pharmaceutical products.[3]

CAPSULE PROPERTIES FOR USE IN DPIS?

What are the special properties required of hard capsules for this application that standard capsules cannot supply? This is best illustrated by comparing Qualicaps special inhalation-grade hypromellose capsules, Quali-V®-I, with their standard pharmaceutical-grade gelatin and hypromellose capsules, Quali-V®. The inhalation-grade capsules differ from their standard capsules in several aspects, as shown in Figure 1.

The principal difference between the three is in the specification for the total aerobic count. The difference between gelatin and hypromellose capsules is a reflection on the manufacturing processes for the raw materials used. The lower count for the Quali-V-I capsules is achieved by a validated process for extra cleaning of the equipment used to manufacture the hypromellose solutions. This value is particularly important for inhalation capsules because unlike capsules that are swallowed the fill material from the capsule goes directly into the lungs in which there is no physiological trap like the acid environment of the stomach to prevent bacteria entering into the body.

The moisture content specification is derived from the equilibrium moisture content of the capsules between relative humidities of 35% and 55%. The hypromellose capsules both have a significantly lower moisture content than gelatin: gelatin = 13-16%, Quali-V = 4-6%; and Quali-V-I - 4.5-6.5%.

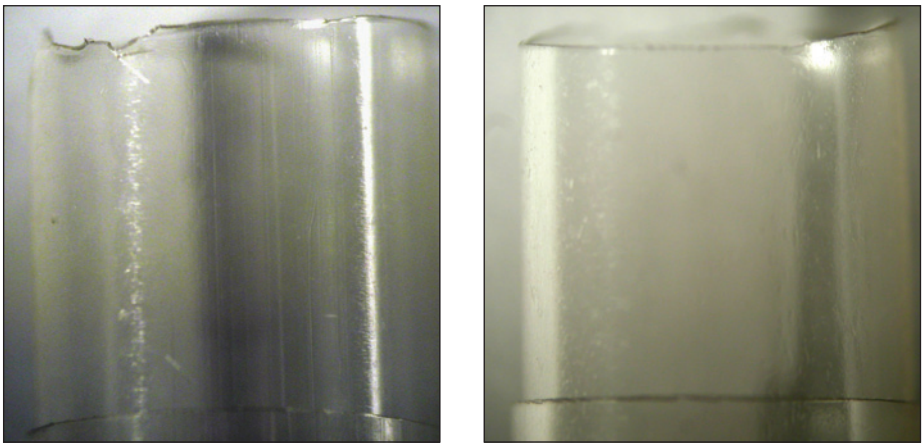

Figure 2: Capsule bodies cut open in an Aventis Eclipse® inhaler: A) Qualicaps gelatin capsule; B) Qualicaps Quali-V-I capsule. Capsules equilibrated at 35% relative humidity before testing.

The reason that the Quali-V-I capsules have a slightly higher moisture specification than the Quali-V is that they are made from a different blend of hypromellose types that are chosen for their mechanical/puncturing properties, whereas the blend used for the standard capsule is chosen for its dissolution properties. Their handling characteristics differ in that gelatin capsules are more prone to triboelectrification than hypromellose capsules.[4] This is relevant for inhalation capsules because this charge may attract powder to the shell wall and increase the amount retained in the capsule on emptying. The low moistures content of the hypromellose capsules provides a clear additional benefit with regard to moisture-sensitive APIs.

The most important property for a capsule used in a DPI is its ability to be cut or punctured in a reproducible manner to enable the powder to be emptied from it as completely as possible. The challenge in this process is to ensure a minimum amount of shell is broken off during cutting or puncturing. These particles could be inhaled – although they are too large to be deposited in the lungs.

Studies comparing gelatin and hypromellose capsules have shown the superior performance of hypromellose over gelatin in the production of these fragments particularly after storage at lower relative humidities.[5,6]

The quality of the cut can be assessed from the straightness of the edge produced (see Figure 2), which is also an indicator of the likelihood of fragments being generated. The quality of the punctures can by assessed by several factors: the shape of the hole determined by the shape of the pin head, and the nature of the flap formed, whether it is attached/detached and its angle to the shell wall – it must not have recovered and partly reclose the opening (see Figures 3 & 4).

CAPSULE POWDER FILLING

When inhalation products were first formulated in hard gelatin capsules they presented a

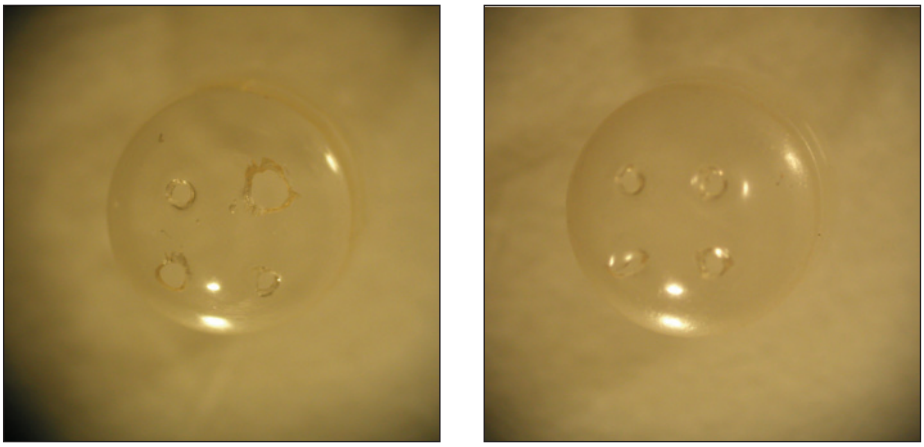

Figure 3: Capsule caps punctured in a Pharmachemie Cyclohaler® inhaler: A) Qualicaps gelatin capsule; B) Qualicaps Quali-V-I capsule. Capsules equilibrated at 35% relative humidity before testing.

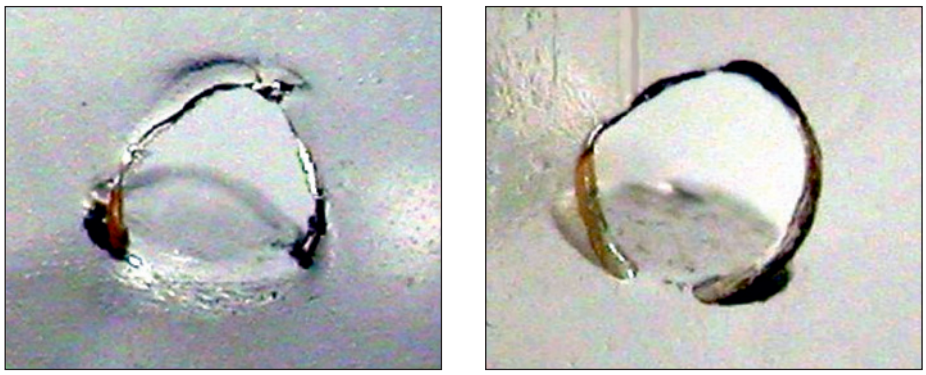

Figure 4: Capsules punctured in an Aventis Spinhaler®: A) Gelatin capsule; B) Quali-V-I, hypromellose, capsule. Capsules equilibrated at 35% relative humidity before testing.

completely different challenge to the control of filling. The powder-fill-weight of standard capsule products is typically four or five times the weight of the shell and because of this the filling operation can be monitored by measuring the gross weight of the filled capsules. This is because the total variance is equal to the square root of the sum of the squares of the individual variances, and thus the practical effect of the shell weight variance on the process in minimal.

However, in the case of the capsules for inhalation the reverse is true, because the fill weights are always less than the shell weights. The pioneer product, the Intal Spincap, had a fill weight of 40 mg in a size 2 capsule weighing 64 mg. The filling problem was solved initially by the adaptation of a manual filling machine, but the demand soon became too great for this process to keep up. Fisons then sponsored academic research studies into the relationship between powder properties and powder plug formation in a dosator-type filling and this led to the development of an automatic filling machine, by MG2 (Bologna, Italy) , that had a mini-dosator able to measure this small amount of powder at filling machine high-speeds.

Since then the fill-weights of formulation have become less and some formulation have fill weights of less than 10 mg. This problem has been tackled in two ways.[7] Firstly machines have been developed by both MG2 and Harro Höfliger (Allmersbach im Tal, Germany) that are able to weigh the capsule shell empty and then again after it has been filled. MG2, for example, developed the G100 machine which is capable of operating at speeds up to 90,000/hr at fill weights ≥ 3 mg/capsule. Secondly machines have been developed that can accurately measure even smaller amounts of powders. For example, Harro Höfliger has developed a vacuum-drum system that is able to operate at dose weights <1 mg, and which can be fitted on their Modu-C machine, which can also weigh capsules pre- and post-filling.

"THE SUITABILITY OF QUALI-V-I CAPSULES FOR DPI PRODUCTS HAS BEEN DEMONSTRATED BY ITS SUCCESSFUL USE BY VARIOUS MAJOR PHARMACEUTICAL COMPANIES"

LATEST PRODUCT DEVELOPMENTS

The initial use for this product type was for prophylactic treatment of asthma. There is still a demand for new products in the field of chronic obstructive pulmonary disease COPD. This disease affects 210 million people worldwide and it is projected that it will be the third leading cause of death by 2030.[8] The use of DPI systems has been expanded into the delivery of actives for systemic administration and this is demonstrated by the increasing numbers of papers published.[9]

The suitability of Quali-V-I capsules for DPI products has been demonstrated by its successful use by various major pharmaceutical companies and includes products in phase III clinical development as well as the registration phase.

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PULSATING AEROSOLS FOR SINUS DRUG DELIVERY: NEW TREATMENT OPTIONS & PERSPECTIVES IN CHRONIC RHINOSINUSITIS

In this article, Manfred Keller, PharmD, Executive Vice-President and Chief Scientific Officer of PARI Pharma together with PARI Pharma's Vibrent® Project Manager, Uwe Schuschnig, and Winfried Möller, PhD, Senior Scientist from the Helmholtz Zentrum München, Institute for Lung Biology and Disease (iLBD), outline how PARI Pharma has developed a novel pulsating aerosol delivery concept as a tailored version of its nebuliser technology platform, eFlow®, for the treatment of upper respiratory tract diseases, such as chronic rhinosinusitis (CRS). Furthermore, this device concept may also be an option for nose-to-brain drug delivery, offering new perspectives for instance in the treatment of migraine, Parkinson's and Alzheimer's disease.

Chronic sinusitis is one of the most commonly diagnosed chronic illnesses, and approximately 10-15% of the European and US population suffer from chronic rhinosinusitis.[1] Inflammation of the nasal mucosa (i.e. rhinitis), due to bacterial, fungal or viral infections, allergies, or exposure to inhaled irritants, leads to acute sinusitis and CRS.[2]

Chronic inflammation of the nasal mucosa results in trigger of defense reactions, mucosal swelling (including polyposis), increased mucus secretion, loss of cilia, airway obstruction and blocked sinus drainage. Under these conditions, bacteria and viruses may proliferate and cannot be removed from the nasal cavity and sinuses by normal ciliary function and clearance mechanisms. In addition, impaired mucociliary clearance in patients with primary ciliary dyskinesia (PCD) or cystic fibrosis (CF) also causes chronic sinusitis, and other chronic respiratory diseases, such as asthma and COPD, are linked to CRS.[3]

Due to the limited therapeutic success of both oral and of topical treatment regimes, functional endonasal sinus surgery (FESS) has been the primary approach for treating CRS. An effective topical therapy is an unmet need and may allow new therapeutic options treating upper respiratory diseases prior to or post surgery.

The sinuses are poorly-ventilated hollow organs, making topical aerosol based treatments complex and difficult since nebulised drugs do not penetrate into these areas. However, gas and aerosol transport into non-actively ventilated areas can be achieved by diffusion and flow induction caused by pressure differences,[4] and pulsating air-flows are generating such pressure gradients.

AEROSOL-BASED DRUG DELIVERY TO THE RESPIRATORY TRACT

Aerosolised drug delivery to the lower respiratory tract, either for topical or systemic therapy, has been used for a long time and is an established therapeutic concept using metered-dose inhalers (MDIs), dry-powder inhalers (DPIs) and nebulisers. Although these devices were adapted for nasal drug delivery, their approval is limited to the treatment of nasal hayfever and allergic symptoms.

The upper and lower airways exhibit many similarities since they are for instance ciliated and show mucus transport. Many upper and lower respiratory tract diseases are linked with each other supporting the concept of "united airways".[5] For example, recent evidence suggests that allergic inflammation in the

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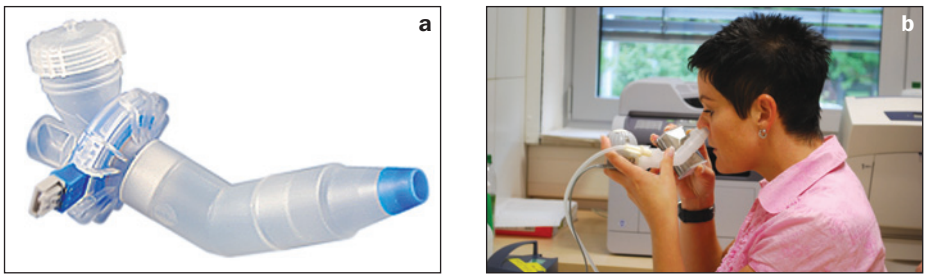


Figure 1: (a) PARI Vibrent®, a pulsating aerosol delivery prototype utilising a customised perforated vibrating membrane (eFlow platform nebuliser technology). (b) Use of the Vibrent during a deposition study using radiolabeled tracer. The nasal plug (resistance) was included in the output filter for capturing expelled aerosol.

upper and lower airways (asthma) co-exist, but their inter-relationship is poorly understood. In addition, chronic airway inflammation in CF patients is usually linked to the lower airways, but since mucus stiffening and mucus hyper secretion also occurs in the upper airways, CF patients suffer from CRS.[6] However, differences in anatomy implies specific requirements of topical drug targeting, which can be achieved in part by selecting aerosol particle sizes and breathing patterns, and by specific nebuliser device configurations including different modes of administration.

PARI GmbH, Starnberg, Germany, has outstanding experience and reputation in the field of pulmonary drug administration by jet nebulisers. PARI Pharma, a separate entity, is focusing on novel drug formulations, such as liposomal cyclosporine A, complexation and taste masking of antibiotics, as well as on device concepts such as the eFlow nebuliser platform technology.[7,8]

Recently, PARI Pharma has developed a pulsating aerosol drug delivery platform (PARI SINUS™ and Vibrent®) for the treatment of upper airway diseases by targeting drug delivery to the posterior part of the nose including the paranasal sinuses. The achievements obtained and future treatment perspectives are described in the following paragraphs.

CURRENT NASAL DRUG DELIVERY SYSTEMS

Standard medical nebulisers, such as jet nebulisers or vibrating membrane nebulisers, can be used for aerosol generation. The nose is an efficient filter for inhaled aerosols. For efficient penetration into the sinuses, the aerosol should penetrate into the posterior nasal cavity; therefore the aerosol should consist of smaller particles (droplets) with an aerodynamic diameter below 5 μm.[9] In addition, since the predominant deposition mechanism in the nose is impaction, the flow rate should be kept moderate.

One current topical treatment option of nasal disorders is the use of nasal pump sprays. These generate droplets between 50 μm and 100 μm diameter and volumes between 50 and 200 μl being administered by mechanical actuation in one nostril, each. Different drug formulations are available for use with nasal pump sprays, such as saline, decongestants, mucolytics or steroids. Although 100% of the administered drug deposits within the nose several studies have demonstrated that there is no significant aerosol access to the paranasal sinuses.[10,11] To address this unmet need new nasal aerosol delivery devices are being developed, like the ViaNase (Kurve Technology Inc, Lynnwood, WA, the US) and the Optinose (OptiNose AS, Oslo, Norway). However, these do not use pulsating airflow techniques.[10,12] These devices may be superior to nasal pump sprays and improve nasal drug delivery due to a smaller particle diameter of the aerosol and improved delivery techniques. Nevertheless, delivery of aerosol to the sinuses could not be proven and is unlikely since droplets or particles >10 μm can hardly travel and penetrate to the sinuses. This is supported by the limited ventilation of the sinuses and basic aerosol physics, as shown by investigations in a human nasal cast model and apparent from the operation conditions of these devices.[13,14]

Nasal irrigation with isotonic or hypertonic saline is an inexpensive and essentially risk-free treatment and is widely used as a non-aerosol-based nasal rinse and drug delivery method.[15] Although the overall fluid retention in the nose is very low, nasal irrigation with volumes of 20-250 ml via syringes, squeeze bottles and Neti pots have proven to be beneficial in removal of inflammatory cells and excess mucus, including wound cleaning after functional endoscopic sinus surgery (FESS).[2] However, drug delivery to the sinuses using nasal irrigation of such solutions containing drugs may only be possible post sinus surgery,[16] and lacks reproducible dosing and reliable treatment efficacy. Due to a lack of better alternatives, anti-inflammatory drugs, such as steroids were added to isotonic nasal rinse solutions and used as an anti-inflammatory treatment concept in CRS patients primarily post FESS.

DISCOVERY OF PULSATING AIRFLOWS FOR SINUS DRUG DELIVERY

The development of pulsating aerosols is based on discoveries by Hermann von Helmholtz, who found resonance conditions for gas exchange between secondary spaces (such as the sinus cavity) and the surrounding space.[17] These devices were called Helmholtz resonators and were used for instrument tuning. Based on this knowledge early pulsating aerosol studies for sinus drug delivery were done in the last century by Guillerm and colleagues.[18] Later Kauf systematically modeled and studied the penetration ability of aerosols into secondary spaces and performed first experiments on model cavities.[4] These studies were continued by Hyo *et al* and Sato *et al* using nasal casts and human cadavers, and they also could confirm deposition efficiencies between one and four percent.[13]

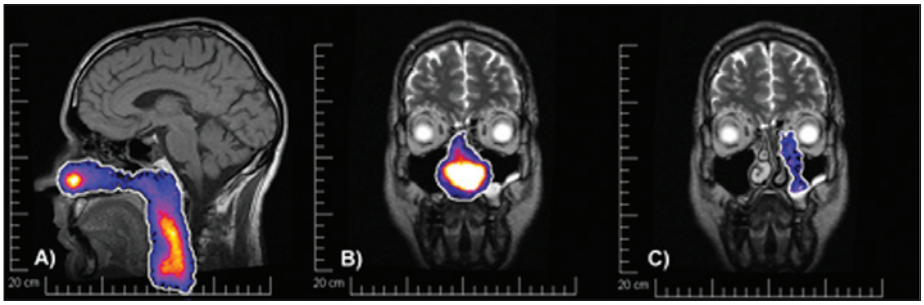
"THE VIBRENT IS ABLE TO GENERATE DROPLETS WITH A MMAD OF ABOUT 3 µM AND A FLOW RATE OF ABOUT 3 L/MIN CAUSING LESS IMPACTION. A FLOW PULSATION AT 25 HZ FREQUENCY IS SUPERIMPOSED ON THE AEROSOL STREAM."

PULSATING AEROSOL DELIVERY SYSTEMS

A pulsating aerosol is an aerosol stream superimposed by a pulsating airflow. The first commercial pulsating aerosol delivery device was developed in France by La Diffusion Technique Francaise (Atomisor Automatic Manosonique Aerosol, DTF, Saint Etienne, France), which is based on the early Guillerm studies.

In 2003, PARI GmbH, Starnberg, Germany, developed a commercial pulsating aerosol delivery device, the PARI SINUS, which has been approved in Europe via a CE marking

Metered Nasal Pump Spray



PARI Vibrent producing a pulsating aerosol

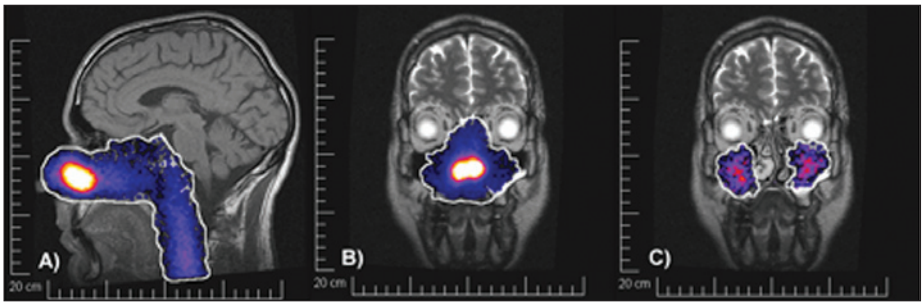


Figure 2: ^{99m}Tc-DTPA activity distribution image of a 100 µl metered pump spray (upper panel) versus the pulsating aerosol delivery for 20 seconds using the PARI Vibrent (lower panel) in lateral (A) and anterior view without a nasal shield (B) and with a nasal shield (C).

process and in the US most recently via a 510(k) clearance. The PARI SINUS is composed of a PARI LC STAR jet nebuliser with a mass median aerodynamic diameter (MMAD) of about 3 µm and a geometric standard deviation (GSD) of about 2.5. The output flow rate is 6 L/min, which is necessary to operate the nebuliser. A pulsation of 44 Hz is superimposed to the aerosol stream.

The PARI Vibrent is a more efficient electronic nebuliser utilising a customised perforated vibrating membrane as the aerosol generator (PARI eFlow)[8] coupled with an adjustable pulsation (PARI Pharma GmbH, Starnberg, Germany). The Vibrent (Figure 1a) is able to generate droplets with a MMAD of about 3 µm and a flow rate of about 3 L/min causing less impaction.[19] A flow pulsation at 25 Hz frequency is superimposed on the aerosol stream.

Administration of the pulsating aerosol is shown in Figure 1b. The Vibrent prototype handset is attached to one nostril and the nasal plug (flow resistor) in the other nostril. During delivery the subject is instructed to close the soft palate, which directs the aerosol from the delivery nostril to the output nostril, providing an aerosol pathway to the nasal airways only. Both, the output resistor and closing of the soft palate ensures optimal pressure transduction to the sinuses, inducing drug penetration to the paranasal cavities and prevents undesired lung deposition.

SINUS ^{99M}TC-DTPA AEROSOL DEPOSITION AND CLEARANCE

For testing nasal and sinus aerosol deposition and clearance, a pulsating aerosol was generated

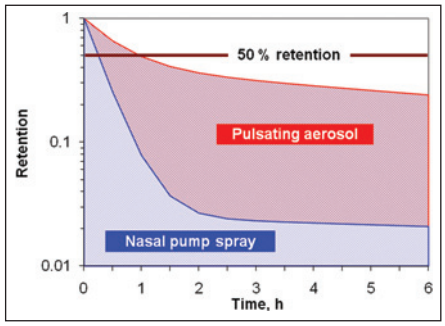


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Figure 3: ^{99m}Tc-DTPA nasal retention during six hours in one volunteer after delivery using a nasal pump spray or the pulsating aerosol device [11].

using the PARI Vibrent as described above. In the studies by Möller *et al*, a solution composed of ^{99m}Tc-DTPA (diethylene triamine pentaacetic acid) was delivered to each nostril for 20 seconds, and deposition distribution was assessed by gamma camera imaging.[11] The first image recorded immediately after aerosol delivery did not show aerosol deposition in the chest, confirming the tight closure of the soft palate during aerosol delivery.

Figure 2 shows anterior and lateral images of ^{99m}Tc-DTPA aerosol deposition distribution after nasal pump spray and after pulsating aerosol delivery (superimposed to coronal and sagital magnetic resonance tomography (MRT) scans of the subject). With both delivery methods the dominant fraction was deposited in the central nasal cavity. After suppressing the central nasal cavity activity using a lead shield, the ^{99m}Tc-DTPA aerosol deposition in the maxillary sinuses clearly appears.

There was 100% nasal drug deposition when using the nasal pump sprays and there was negligible drug penetration into osteomeatal area and the maxillary sinuses. With pulsating

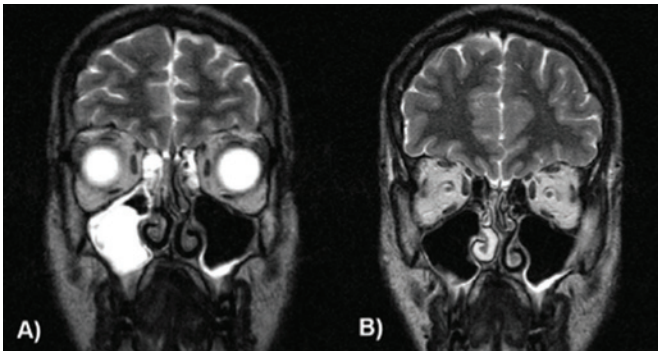

Figure 4: Coronal MRT (T2 weighted) slice of a patient before (left) and after (right) a three month once daily treatment with steroids (budesonide) using the PARI SINUS pulsating aerosol device.

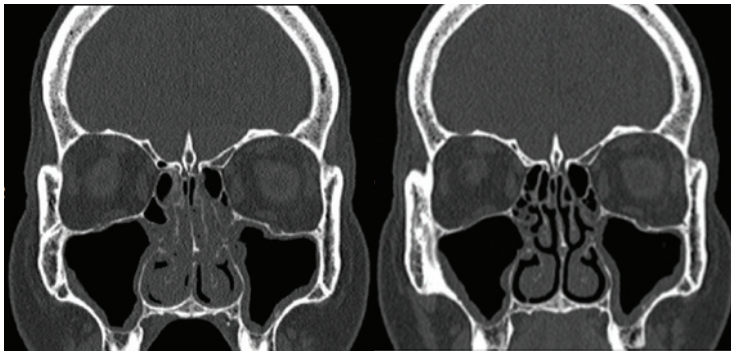

Figure 5: Computer tomography (CT) images of a CRS patient with polyposis before (left) and after (right) a six-week steroid treatment delivered using the PARI Vibrent.

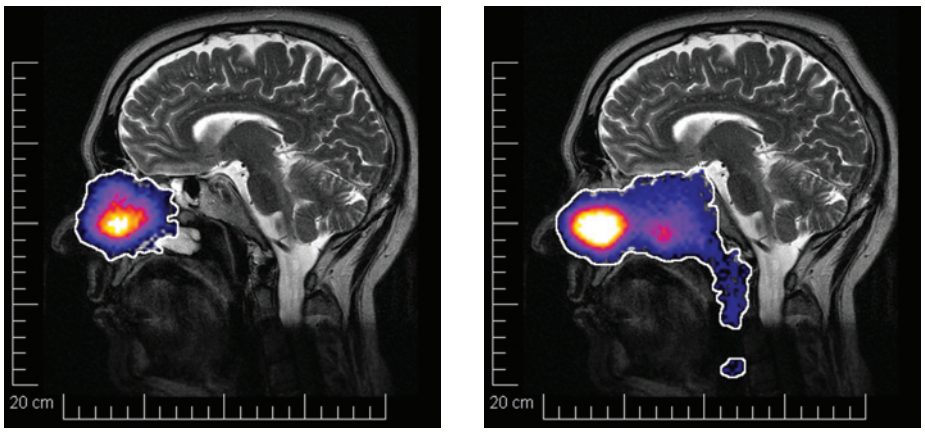

Figure 6: Lateral view of the deposition pattern of nasal spray (left) versus Vibrent (right) superimposed to a sagital MRI image of a patient after sinus surgery (ESS). The second deposition maximum after Vibrent administration (right) in the deep nose indicates activity access to the maxillary sinuses.

aerosol delivery total deposition in the nasal cavity (including sinuses) was 71 ±17 % of the nebulised dose and 6.5 ±2.3 % of the total nose activity penetrated to the sinuses.[11,20]

In addition, as shown in Figure 2, there is activity access to the posterior nose, including the ethmoid and sphenoid sinuses, when using the pulsating aerosols, but not after nasal pump spray delivery.

Compared with aerosol administration by nasal pump sprays, retarded clearance kinetics after pulsating aerosol delivery was reported: 50 % of the dose was cleared after 1.2 ±0.5 hours and more than 20 % of the administered dose was retained in the nose after 6 hours (see Figure 3). The cumulative retained dose 6 hours after delivery was obtained from the area under the retention curve and corresponds to 1.98 ±0.23 normalised dose units.hr for the pulsating aerosol.[11] Delayed clearance is of therapeutic advantage since drugs with a short half-life can be administered less frequently allowing a BID or once-daily dosing.

FIRST CLINICAL RESULTS

Case Studies Using the PARI SINUS and PARI Vibrent

Topical application of steroids using nasal pump sprays is a mainstay in allergic rhinitis and sinusitis therapy. There is evidence on polyposis that clinical symptoms are reduced when using intranasal steroids, but a complete cure can hardly be achieved, since the site and origin of inflammation is often located in the osteomeatal area and/or paranasal cavities. Two patients suffering from chronic polypose CRS inhaled budesonide for a period of 6-12 weeks using the PARI SINUS or the PARI Vibrent. Figures 4 and 5 show anterior MRT images of the two subjects before and after the steroid treatment period. After the treatment period the blocked maxillary and ethmoidal sinuses were completely cured and showed normal appearance.

The CT images of another patient before and after inhaling budesonide via a PARI Vibrent prototype over six weeks is shown in Figure 5. The previously almost entirely blocked nasal passage was free and the inflammation of the ethmoid sinuses reduced.

In both cases surgical interventions could be prevented.

Experience in CF Patients

Patients with dysfunctions of the ciliary transport apparatus, such as PCD or cystic fibrosis (CF), inhale mucolytics and other drugs to enhance mucociliary clearance (MCC) to remove mucus from the airways. Since the disease also manifests in the upper airways, patients will benefit when administering such drugs into the nose and paranasal sinuses using pulsating aerosols.

Preliminary clinical data in CF patients demonstrate improvements in the Sinonasal Outcome Test-20 (SNOT-20) after nasal administration of Dornase alpha (Pulmozyme) using the PARI SINUS.[6,21] The SNOT-20 is a quality of life measure (QoL) specific for patients with CRS symptoms, where psychological functions, sleep functions, rhinological symptoms, and ear and/or facial symptoms are assessed.[22]

Topical Treatment After FESS

Endoscopic sinus surgery (ESS) is an established method to improve ventilation of the paranasal cavities with the objectives that the innate immune system supported by medical treatment regimes will help to cure the disease. It is thought, that larger ostia may enable a better topical drug treatment.

To investigate this hypothesis, a subject who underwent ESS some years ago volunteered in a gamma scintigraphy deposition study. Surprisingly, no aerosol deposition could be detected in the paranasal cavities after administration of radiolabelled aerosol via a nasal pump spray whereas a deposition of about 24% was found when a comparable tracer was administered via the PARI Vibrent, as clearly shown in Figures 6 and 7.

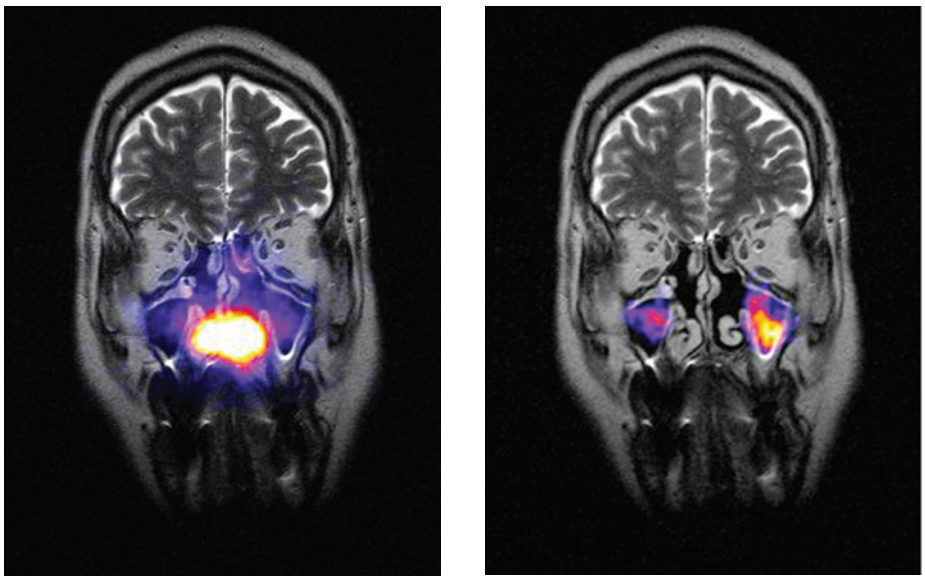

Figure 7: Anterior view of the deposition pattern of Vibrent without (left) and with nasal shield (right) superimposed to a coronal MRT image of a patient after sinus surgery (ESS).

SUMMARY AND CONCLUSION

Ventilation of the target site is a significant requirement for aerosol drug delivery. It was shown that aerosols penetrated paranasal cavities only in such cases when a pulsation was applied, causing efficient sinus ventilation of radiolabeled 81mKrypton gas.[23] In addition, pulsating airflow caused a sustained release of 81mKr-gas activity from the nasal cavity and the sinuses after switching off Kr-gas delivery.[14]

This aspect indicates towards an increased residence time of an aerosolised drug deposited to the sinuses. A substantial aerosol deposition of about 6.5% was only observed when aerosols were inhaled via Vibrent whereas paranasal deposition was below the detection limit upon administration of a radiolabeled aerosol via a nasal pump spray in 15 healthy volunteers.

The limited therapeutic success of topical treatments by nasal spray, irrigations and standard nebulised therapy may explain the high rate (about 500,000 annually in the US alone) of functional endonasal sinus surgeries (FESS). However, surgery does not usually effect a complete cure, but requires additional medicinal treatments, such as nasal irrigation with saline or saline with compounded drugs (such as steroids). Still, these treatment options are not very effective [15,24] as is apparent from a high rate of recurrent FESS.[2]

Thus, there is an unmet need to improve topical treatment options pre- and post-surgery. Current data support our view that the Vibrent may offer new therapeutic perspectives as an efficient topical treatment option in CRS. However, clinical studies delivering inhaled steroids, antibiotics, mucolytics, antiviral or antifungal drugs to CRS sufferers are needed to demonstrate if this assumption can be verified. There is no doubt that open nasal airways and ostia will be required to deliver drug into the posterior part of the nose.

There is also hope that deposition characteristics and nasal aerosol distribution patterns seen in the deposition studies support the expectation that systemic delivery may be possible for drugs and formulations having a good permeability via the thin epithelium separating the posterior nasal surface from the highly vascularised tissue. Furthermore, since aerosol was deposited in the olfactory area, delivery to the brain including the central nervous system could be considered as novel treatment options.[25,26] Hence, the design of future clinical studies including selection of primary and secondary endpoints must address such issues to obtain more information better to understand drug absorption, systemic uptake, and potential drug delivery opportunities and perspectives.

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SIMULATING DELIVERY OF PULMONARY (AND INTRANASAL) AEROSOLISED DRUGS

A key challenge in the development of a new therapeutic product is the characterisation of its ADME to help predict the human pharmacokinetics (PK). In this article, Siladitya Ray Chaudhuri, PhD, Senior Scientist, and Viera Lukacova, PhD, Team Leader, Simulation Technologies, both of Simulations Plus, Inc, outline the advantages of physiologically based PK (PBPK) models over traditional compartmental pharmacokinetics-based approaches, and describe how a mechanistic physiologically based pulmonary drug delivery model using the GastroPlus software can be of benefit in the development of novel inhalable formulations.

In the US, each year around 400,000 people succumb to ailments related to the lung, making these the third most frequent cause of death in the country.[1] In Canada, 16% of deaths are a result of respiratory illnesses,[3] whereas in the UK, one out of seven people suffer from chronic lung diseases.[2]

These statistics have catalysed an increased interest in improving our understanding of the pharmaceutical and pharmacological aspects of delivering drugs to the lungs. Traditionally, therapeutic ingredients have been delivered to the body (including the lungs) through oral and intravenous (IV) administration. There are many challenging factors in the oral administration of drugs that may preclude this possibility for a given compound. These factors include poor solubility and/or degradation (as a result of physicochemical instability) in the gastro-intestinal (GI) tract, poor permeability (and absorption), high carrier-mediated efflux, extensive gut and hepatic first-pass metabolism, or significant drug-drug interactions.[4] Similarly, for IV administration, the factors that may limit usage include high (possibly toxic) concentrations in non-relevant healthy organs (also relevant for oral doses), patient preferences (frequency of administration, needle phobia) and self-administration compliance issues.[5]

The possibility of avoiding some or all of these disadvantages, coupled with a very large absorptive surface area (approximately 140 m^2 in an adult human), make the lungs an attractive platform for aerosolised administration of a large variety of drugs,[6] such as bronchodilators, anti-inflammatory agents, mucolytics, antiviral agents, anticancer agents and phospholipid-protein mixtures for surfactant replacement therapy.[7]

One of the major challenges in the development of a new molecular entity (NME) is the characterisation of its absorption, distribution, metabolism and excretion (ADME) properties. An understanding of these properties helps us to predict the human pharmacokinetic (PK) behavior of the drug (concentration-time profiles in the plasma, lungs and other organs of the body). It may also help in choosing the optimal dosage form and dosing range for clinical trials and for predicting potential drug-drug interactions (DDIs) and population variabilities,[8] thereby speeding up the (Phase I) clinical studies by 1-6 months.[9]

"GASTROPLUS HAS BEEN ADOPTED BY PFIZER FOR ALL *FIRST IN HUMAN* PREDICTIONS." [21]

The traditional method for predicting human PK has been through allometric scaling of preclinical (animal) data.[10-11] However, this involves the use of compartmental pharmacokinetics, where the body is arbitrarily represented by one, two or three theoretical compartments with no relationship to anatomy and physiology. In addition, compartmental PK models require *in vivo* data to be collected first, which makes true prediction impossible. Mechanistic physiologically based PK

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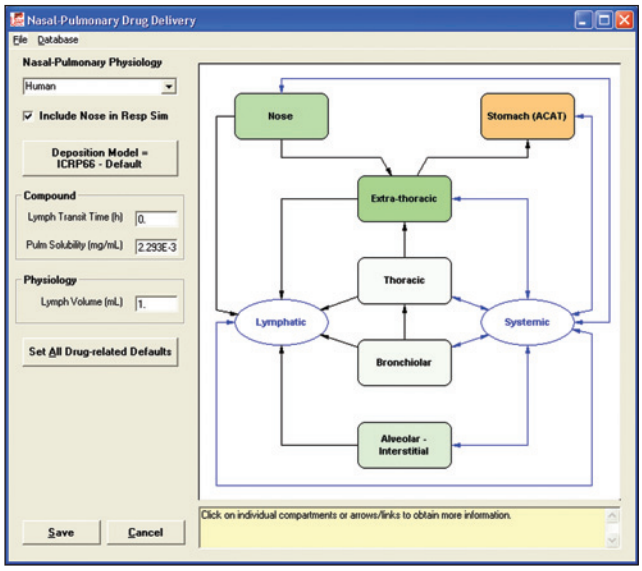

Figure 1: Nasal-Pulmonary Drug Delivery editor within the GastroPlus Additional Dosage Routes Module (ADRM).

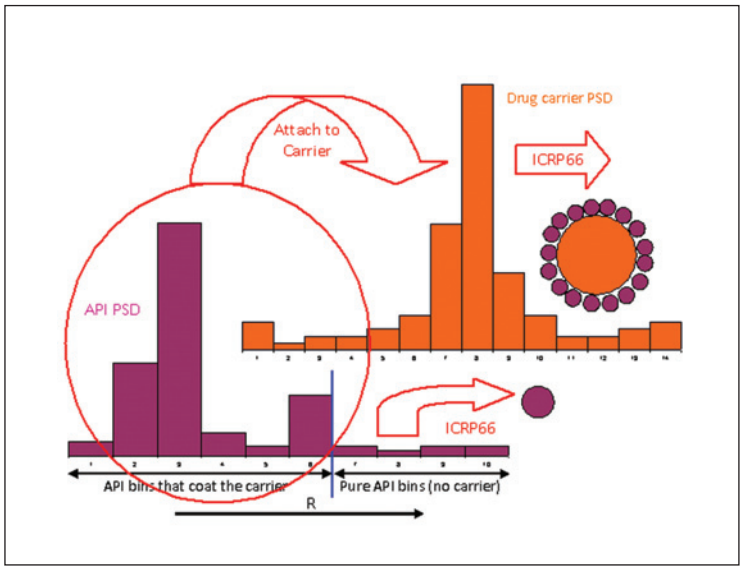

Figure 2: Combining API and drug carrier for distribution into different pulmonary compartments.

(PBPK) models can be predictive when parameterised with *in vitro* or *in silico* properties because the introduction of physiological and anatomical properties allows for the prediction of volume of distribution from molecular structure.[12] PBPK models can be used for early prediction of concentration-time profiles in the plasma and organs of the body. Thus, PBPK modeling [13] has become a powerful tool for predicting concentration-time profiles for NMEs and other drugs of interest.[8,14]

Unlike its compartmental counterpart, the complexity of the PBPK methodology (hundreds of differential equations and biopharmaceutical parameters) prevents its expression in a simple analytical form. As a result, variations of whole-body PBPK models have been incorporated in several commercially available software [15] products such as ChloePK,[16] PKSim,[17] Simcyp,[18] and GastroPlus™ .[19]

In a two-year prospective study to predict human exposure of 21 NMEs using *in vitro* and *in vivo* data from preclinical species, GastroPlus was shown to be more accurate than its commercial counterparts and more accurate than the method used previously at Pfizer.[20] As a result, GastroPlus has been adopted by Pfizer for all *First In Human* (FIH) predictions.[21]

Recently, the PBPK formalism of GastroPlus was extended to include a detailed, mechanistic multi-compartment physiological model of the lung and nose to describe the administration of inhaled and intranasal aerosolised drug molecules.[22] This model describes the lungs as a collection of up to five compartments: an optional nose (containing the anterior nasal passages; ET1); extra-thoracic (naso- and oropharynx and the larynx; ET2); thoracic (trachea and bronchi; BB); bronchiolar (bronchioles and terminal bronchioles; bb); and alveolar-interstitial (respiratory bronchioles, alveolar ducts and sacs and interstitial connective tissue; AI). The scheme is similar to that adopted in the ICRP 66 model [23] and is shown in Figure 1.

Immediately after administration, the drug is partly exhaled while the remainder is either swallowed or deposited in the mucus/surfactant layer lining the airways of the various pulmonary compartments in the model. The fractions of the administered drug in each compartment depend on the formulation characteristics (particle size, density, shape factor, etc) and can either be predicted by a built-in ICRP 66 deposition scheme[23] or specified by the user. The model accounts for various processes that the drug is subject to in the lung, such as mucociliary transit, dissolution/precipitation, absorption into pulmonary cells, non-specific binding in mucus/surfactant layers and the cells, metabolism, and transfer into the systemic circulation.

"RECENTLY, THE PBPK FORMALISM OF GASTROPLUS WAS EXTENDED TO INCLUDE A DETAILED, MECHANISTIC MULTI-COMPARTMENT PHYSIOLOGICAL MODEL OF THE LUNG AND NOSE."

The dissolution rate kinetics in the pulmonary mucus can be described by a variety of methods (including the traditional Noyes-Whitney equation,[24] taking into account the solubility of the compound at the pH of the mucus (pH = 6.9),[25] particle size and shape, particle density, and water diffusion coefficient. The passive absorption of drugs is driven by a concentration gradient with rates dependent on physiological (for example, surface area) and drug-dependent physicochemical properties (for example, permeability) for each compartment.

A large portion of the inhaled dose can be swallowed and this has been accounted for by connecting the lung compartments to the advanced compartmental absorption and transit ACAT™ (GI) physiological model[26] within GastroPlus. The lung compartments are also connected to systemic PK models in GastroPlus to simulate drug appearance in plasma after combined absorption from the airways and the GI tract. Human lung physiological parameters (surface area, thickness and volume for the mucus and cell) for each compartment were obtained from the literature.[23,27,28] The drug-dependent input parameters (including pulmonary permeability) were obtained from values reported in the literature [29] or correlations developed from them.

Among the most critical components in such pulmonary simulations are the characteristics of the aerosolised formulation. The current model allows for polydispersity in the active pharmaceutical ingredient (API). For polydisperse formulations, where the entire particle size distribution (PSD) for the drug is known, the comprehensive ICRP 66 scheme

is applied to a series of bins, each containing a fraction of API particles with equal particle radius. Equations describing the relevant masses across bins and compartments are shown in the boxed text below.

The relevant masses across bins and compartments are given as:

$$mass\ of\ \ drug\ in\ bin\ k = \omega_k \times\ Dose \quad (1)$$

$$mass\ of\ \ drug\ in\ bin\ k\ and\ compartment\ j = f^{dep}_{comp=j,bin=k} \times \omega_k \times Dose \quad (2)$$

$$mass\ of\ \ drug\ in\ compartment\ j = \sum_{k=1}^{no\ of\ \ bins} \left(f^{dep}_{comp=j,bin=k} \times \omega_k \times\ Dose \right) \neq f^{dep}_{comp=j} \times Dose \quad (3)$$

where ω represents mass fraction of API particles in each bin.

The API is often associated with a drug carrier/excipient (commonly lactose) having a different particle-size distribution. In such cases, the model assumes that the API particles will form a coating on the carrier if they are sufficiently small (less than a pre-defined minimum or cut-off value), otherwise there will be no interaction between the two. Small particles of the API bind onto the surface of the carrier particles (according to the ratio of surface area of particles in each carrier bin), then are distributed amongst the pulmonary compartments based on the composite radius of the API-carrier complex. Larger API particles will be distributed amongst the pulmonary compartments based on their own radius (independent of the carrier particles). Figure 2 is a graphical representation of this scheme for collective distribution.

EXAMPLE 1: BUDESONIDE

We employed the pulmonary drug delivery component of the ADRM within GastroPlus to simulate absorption and PK of inhaled budesonide in healthy human subjects, as reported by Miller *et al.*[22] The PKPlus™ module of GastroPlus was used to fit systemic PK parameters for budesonide from observed Cp–time profiles after IV administration of a 0.4 mg dose in healthy human subjects. The fitted three-compartmental PK parameters were then used without further modification to simulate systemic PK for all pulmonary dosage forms. Physicochemical properties were obtained from *in vitro* measurements [22] (where available) or *in silico* predictions.[30] For pulmonary doses, GI physiology used the default "fasted" state human ACAT model.

In an effort to highlight the predictive ability of the model, none of the parameters were fitted to the *in vivo* data from pulmonary administration. Deposition fractions in the lung compartments were predicted by the built-in ICRP 66 scheme assuming complete mouth breathing to mimic the inhalation from standard devices. The predicted plasma concentration-time profile is shown in Figure 3.

Figure 3 shows a good match between predicted and observed plasma concentration-time profiles. The C_{max} was overpredicted by about two-fold while the $AUC_{(0\to t)}$ and $AUC_{(0\to inf)}$ were within 3.5% and 2% of the observed values, respectively. There may be several reasons for these deviations, among them the input value for particle size. In the above simulation, we assumed the aerosol particles were 1.25 µm in radius, which is within the usual range for these formulations.

Nonetheless, to assess the effect of particle size of an inhaled formulation on the bioavailability of the drug, a parameter sensitivity analysis (PSA) was carried out. In this automated GastroPlus mode, multiple simulations were carried out by gradually varying particle size, while keeping all other parameters fixed, as shown in Figure 4.

Varying particle size affects the deposition fractions in the lungs as well as the rate of dissolution in the epithelial lining fluid. Variations in the deposition pattern (% drug deposited in each lung compartment) and bioavailability (reflecting the changes in both deposition pattern and dissolution rate) with varying particle size are shown in Figure 5.

Figure 5 indicates that variation in bioavailability follows a pattern very similar to the variation in fraction inhaled in the alveolar-interstitial compartment. A possible explanation is that any drug that is deposited in compartments other than alveolar-interstitial can be cleared by mucociliary transit and ultimately swallowed. Swallowed drug is subject to dissolution limitations in the stomach and GI tract as well as high (~ 85%) first-pass extraction in the liver; hence, it may not contribute significantly to the net bioavailability, in this case. In order to further differentiate between the effects of varying particle size on the deposition pattern and the dissolution rate, simulations were run with varying particle size but using a fixed deposition fraction (via the "User-Defined" option), pre-calculated for particles with radius 1.25 µm according to the ICRP 66 method (% of dose deposited: ET2 = 4.16, BB = 2.52,

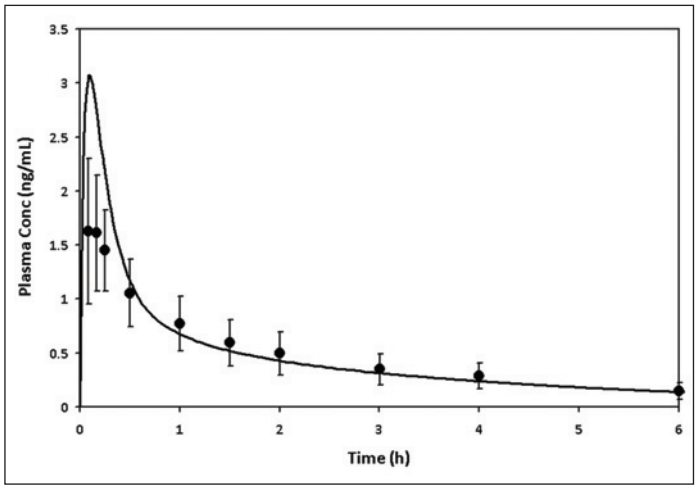

Figure 3: Predicted (line) and observed (circle) plasma concentration-time profiles for inhaled administration of 0.4 mg aerosolised suspension of budesonide with no fitted parameters.

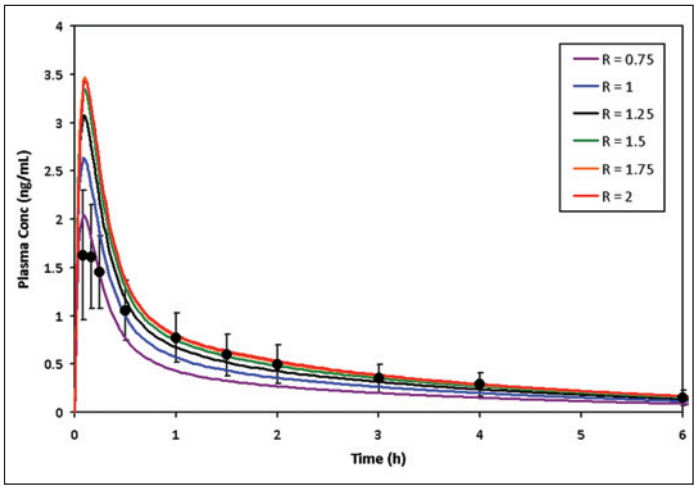

Figure 4: Variation of plasma concentration-time profile with changing particle size (0.75-2 µm). Deposition fractions were calculated for each particle size using the built-in ICRP 66 method.

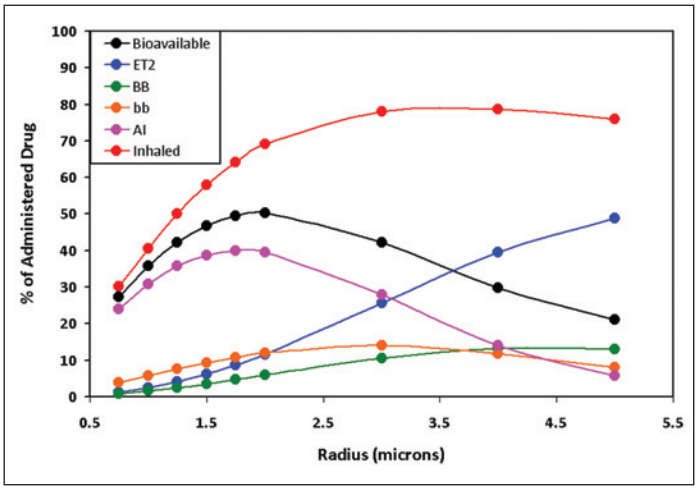

Figure 5: Variations in bioavailability, inhalability and % drug deposited in each lung compartment with changing particle size (0.75-5 μm). Deposition fractions were calculated for each particle size using the built-in ICRP 66 method.

"THIS NEW CAPABILITY OFFERS A VALUABLE TOOL FOR SCIENTISTS IN THE DEVELOPMENT AND UNDERSTANDING OF INHALED AND INTRANASAL DRUG CANDIDATES."

bb = 7.61, AI = 35.75). The results of this analysis are shown in Figure 6.

Figure 6 indicates that, in this case, changing particle size has no effect on bioavailability. Thus, the changes to the predicted bioavailability in Figure 5 are mainly due to changing deposition fractions in the lung.

EXAMPLE 2: TOBRAMYCIN

The case of Tobramycin further highlights the predictive ability of the pulmonary model as well as its scalability across dose levels and dosage forms. We also simulated the absorption and PK of inhaled aerosolised tobramycin in healthy human subjects as reported by Newhouse *et al.*[31]

Two dose levels and formulations were considered: an aerosolised suspension (Pulmosphere, 80 mg) and a solution (TOBI, 300 mg). We used a similar methodology as described previously: systemic PK was obtained from an independent source of IV data [32] and was used unchanged; GI physiology was the default "fasted" state human ACAT model. In this case, however, reported experimental values of deposition fractions were used in place of the ICRP 66 model. Also, none of the physicochemical or physiological parameters were altered from their pre-calculated default values. Figure 7 shows that there is good agreement between the observed plasma concentration-time points and the simulated profile.

CONCLUSION

Our mechanistic physiologically based pulmonary drug delivery model provides quite good agreement between observed and simulated plasma concentration-time profiles for both budesonide and tobramycin even with no *ex post facto* calibration of the model (that is, no input parameters were fitted). We believe this new capability offers a valuable tool for scientists in the development and understanding of inhaled and intranasal drug candidates.

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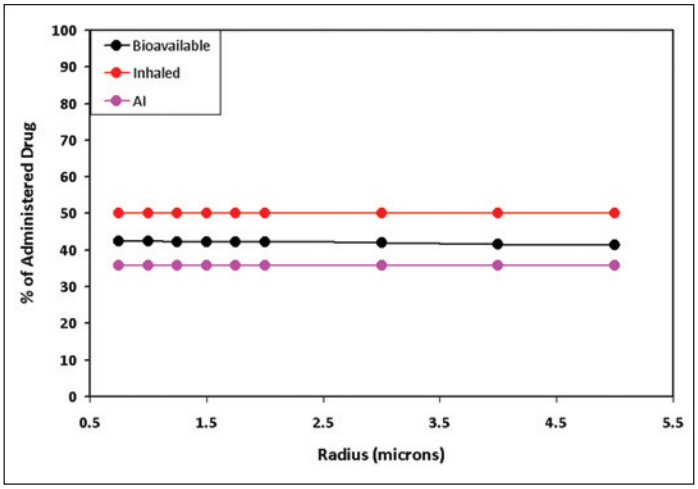

Figure 6: Variation of bioavailability with changing particle size. Deposition fractions were held constant.

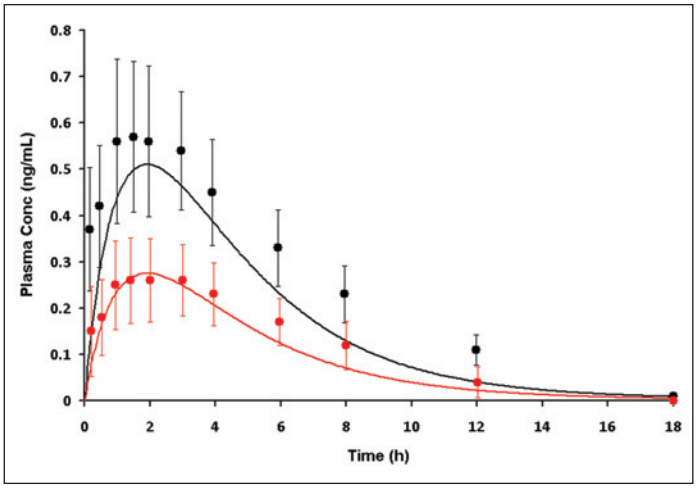

Figure 7: Comparison of unfitted simulations with observed plasma concentration-time data for inhaled aerosolised administration of 80 mg suspension (Black) and 300 mg solution (Red) of tobramycin. Dots represent observed values (with error bars) and lines represent simulated profiles.

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PRESSPART

MODIFYING MDI CANISTER SURFACES TO IMPROVE DRUG STABILITY & DRUG DELIVERY

Hydrofluoroalkane (HFA)-based propellants are widely used in modern metered-dose inhalers (MDIs), due to their lack of hazardous and environmentally-damaging effects. However, an HFA's active pharmaceutical ingredient can interact with the canister substrate, causing deposition of the drug to the canister walls, or interact with the solution, causing degradation and resulting in increased impurity levels. Over the past few years, a number of surface coatings have been developed that can be applied to MDI canisters and valve components, to protect the contents from deposition and degradation. More recently, plasma processes have been developed to modify and improve the surface energy performance of a MDI canister. This approach has a number of advantages to alternative coatings but requires careful optimisation to ensure the highest quality finish and MDI performance. Richard Turner, Business Development Director, Presspart Manufacturing Ltd, explains.

Metered dose inhalers are commonly used to deliver drugs for treating respiratory and nasal disorders. The drugs are administered by aerosol, in suspension or solution, with a liquefied gas propellant. For over 50 years, chlorofluorocarbons (CFCs) were the propellants of choice, but these were phased out and finally banned at the end of 2008, in line with the Montreal Protocol.[1]

> "THE RESULT IS A COATING TECHNOLOGY WITHOUT THE EXTRACTABLE ISSUES POTENTIALLY ENCOUNTERED WITH SOME POLYMER SYSTEMS."

Replacement propellants have been developed over the past two decades based on hydrofluoroalkanes (HFA), specifically HFA 227 and HFA 134a. These substances are not ozone-depleting, they are also non-flammable and chemically inert, making them ideal candidates for use in medical products. However, some properties of these compounds are substantially different from those of the CFCs traditionally used in MDIs.

The surface properties of a device can have an important effect on the device's interactions with its most immediate environment and substances with which it comes into contact. As a result, the device's surface chemistry has a vital role on the surface functionality and, therefore, overall performance of the device and drug.

When HFA-MDI drug formulations are in suspension, interactions with the canister substrate can cause deposition of the drug on the canister walls or on exposed surfaces of the valve components. Interactions with solutions more commonly cause degradation, resulting in increased impurity levels. In both cases the interaction leads to a reduction in the drug content in the formulation, resulting in the patient receiving less than the prescribed dose.

RANGE OF COATINGS

Applying a suitable surface coating to the MDI components improves the stability of the formulation as well as the product performance, and helps to extend the product's shelf life. A range of coatings have been developed that can be applied to both the canister and valve components to protect the contents from deposition and degradation.

Commonly used coatings include barrier coatings, such as anodisation of the canister, to change the surface characteristics and

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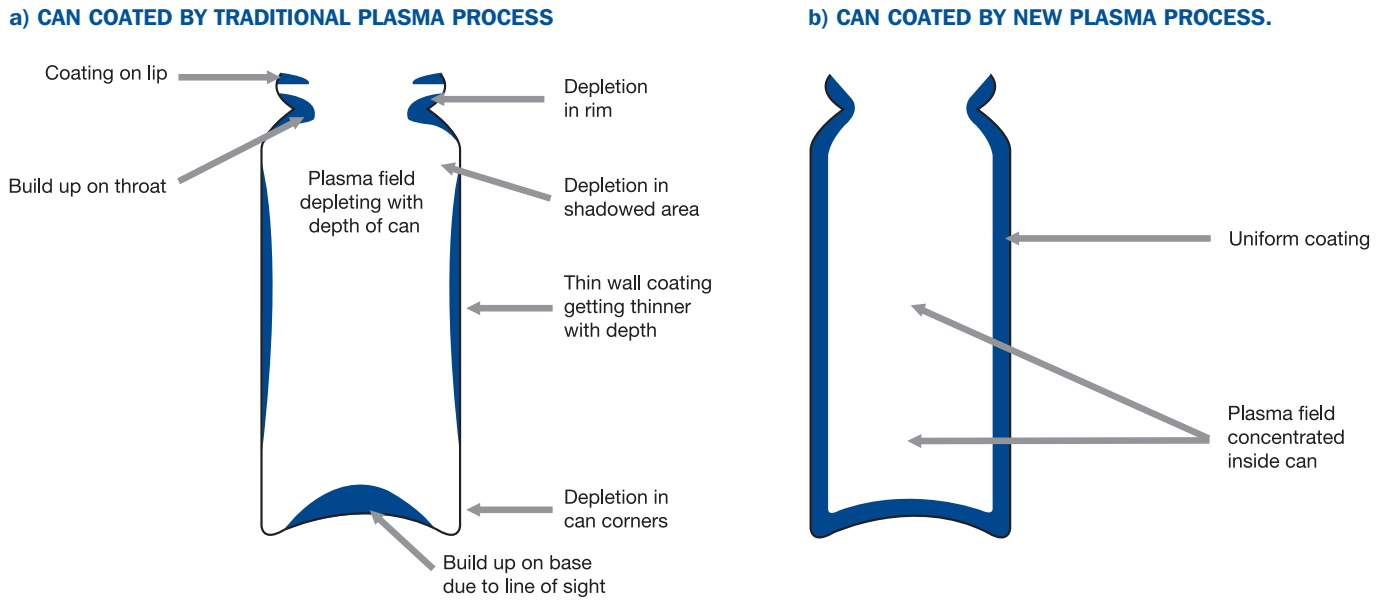

Figure 1: a) Traditional plasma processing does not ensure a uniform coating to the internal walls of the canister. b) The new plasma process gives a uniform coating to canisters.

ultimately act as a protective barrier for sensitive formulations. Various low-surface-energy coatings are available for suspension formulations. For example, a surface treatment has been specially developed for deep-drawn anodised 5052 aluminium canisters and is suitable for budesonide HFA; several new coating compounds such as E3 and E5 acrylic polymers have been developed that prevent certain HFA-containing drug formulations (for example, salbutamol) from interacting with the MDI and adhering to canister walls.

Fluorocarbon polymers are commonly used to coat the interior canister surfaces to eliminate adhesion or deposition of albuterol on canister walls; albuterol is widely used with MDI drugs, particularly beclomethasone diproprionate. Fluorocarbon polymers used in coatings are commonly made from multiples of one or more of a variety of monomers; particularly preferred coatings tend to be pure perfluoroalkoxyalkylene (PFA), and blends of polytetrafluoroethylene (PTFE) and polyethersulphone (PES), due to their relatively high ratios of fluorine to carbon. In addition, coatings that combine fluorcarbon polymers with non-fluorcarbon polymers (such as polyamides) are used for certain formulations to improve adhesion of the coating to the canister walls; other coating types include epoxy-phenol resins or even a thin film of glass.

COATING TECHNIQUES

Standard metal coating techniques can be used to pre-coat the metal substrate and cure it, prior to shaping the metal into the components (for example, through deep-drawing or extrusion). This pre-coating method has the advantage of being well suited to high-volume production.

Other coating techniques include: spraying the insides of preformed cans; dipping; or electrostatic dry-powder coating, followed by curing. Many of these processes require high temperatures (up to 400 °C when curing), which can create additional costs and complications. Furthermore, only the most robust canisters (that is, those produced through deep-drawing) should be subjected to such high temperatures, as less robust canisters can become unrolled or suffer other morphological changes under these conditions.

PLASMA PROCESSING TECHNOLOGIES

More recently, gas plasma-based processes have been developed to modify and improve the surface energy performance of an MDI canister. Gas plasma processing is an industrial technique that is carried out in a vacuum to coat a wide range of substrate materials. The process involves constant or pulsed excitation of gas by either radio frequency (RF) or microwave field to produce an energetic plasma.

The process creates an ultra-thin layer that protects against degradation, deposition and corrosion. It is a low-temperature process (<75°C for metallic substrates and <45°C for polymeric substrates), and is ideal for uniform treatments of components with complex shapes, including small components in large volumes. The coating adheres well to the component substrate, because the plasma process cleans the component surface while in the vacuum, resulting in an ultra-clean substrate-coating interface.

Using gas plasma to tailor the surface chemistry has the advantage of providing uniform surface treatment without changing the properties of the bulk material. The process can be used to change the outermost layers of the material only, without polymerising a coating, resulting in modifications to the functional chemistry. These modifications can be used "stand-alone" or with the addition of a subsequent surface coating through a single process cycle, depending on the application and desired properties.

OPTIMISING THE PLASMA PROCESS

Plasma processing of MDI canisters can bring multiple benefits to the MDI performance, helping to reduce drug deposition and also to improve the stability of formulations where interactions with the aluminium substrate would lead to product degradation and reduced shelf life. However, plasma processing for MDI canisters needs to be highly controlled to ensure complete consistency of treatment and uniformity of coating to the internal walls of the canisters.

Plasma chemistry is critical to the performance of the coated canisters – the right choice of precursor chemistry enables a robust process with excellent performance. A variety of plasma treatments have been tried in the past, including single- and dual-layer technologies with a range of monomers, but these have failed to penetrate the market due to poor scalablity and cost viability. However, alternative developments have become available that make plasma a real choice for MDI cans.

A cost-effective process has been established using an optimised plasma chemistry consisting of an intrinsically robust monomer, highly

ionised to form a high crosslink density. The ultra-pure gases and monomers do not contain any solvents, so do not produce any waste by-products. The result is a coating technology without the extractable issues potentially encountered with some polymer systems.

It is critical that plasma processing achieves complete and consistent coating across the entire surface of the inside of the canister. Traditional plasma processes, RF or microwave, are particularly difficult to control when internal surfaces are to be treated. Poor penetration of plasma ions with low energy results in non-uniform, thin or porous coatings with poor performance. Increased ion energy to aid depth of can penetration gives rise to ion etching at the can neck and a more "line-of-sight" process.

This partial "line-of-sight" process leads to non-uniformity/thickness variation in such geometries (see Figure 1a). For thin nanometre coatings on MDI cans this is observed as striations in colour or colour bands down the can. With the best compromise the coating builds up around the canister lip, throat and base, with depletion at the rim, shoulders and can corners.

More recently, an improved process has been developed that eliminates the issues associated with typical plasma system designs. Using proprietary gas/monomer delivery configurations and electric field control (designed specifically for can coating geometry), uniform coatings can be deposited (Figure 1b).

Dedicated system design configurations mean constant, high deposition rates with extreme reproducibility in terms of coverage, chemical speciation and product performance. The unique combination of process equipment design and precursor monomer means the technology is now scalable to handle the throughput and commercial demands of the MDI world market.

This process has been used to develop several different plasma coating options that successfully prevent drug deposition on the can walls, and prevent drug degradation in solution or suspension. Examples include surface treatments for budesonide, formeterol, fluticasone proprionate and beclomethane dipropionate, amongst others.

> "DEDICATED SYSTEM DESIGN CONFIGURATIONS MEAN CONSTANT, HIGH DEPOSITION RATES WITH EXTREME REPRODUCIBILITY IN TERMS OF COVERAGE, CHEMICAL SPECIATION AND PRODUCT PERFORMANCE."

CONCLUSIONS

Gas plasma processing offers considerable advantages in the coating and treating of MDI canisters for improving the stability of the formulation and extending product shelf life. In addition, the ability to plasma process high volumes of the canisters fulfils the high volume demand from the MDI market.

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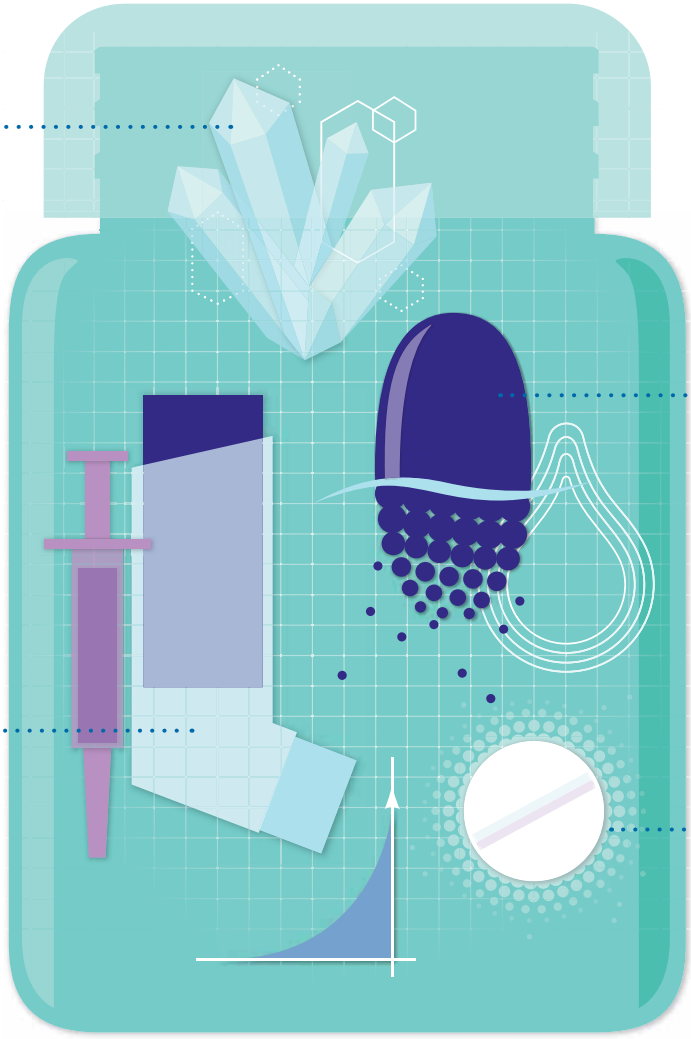

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