Inhaled medications have been around for decades, particularly in the treatment of respiratory disease like asthma and chronic obstructive pulmonary disease (COPD) (1). In addition, huge efforts have been made over the last two decades to use the enormous surface area of the lung to deliver small molecules, proteins and peptides (for example, insulin, growth hormone, interferons and calcitonin) to treat systemic diseases (2).

In the past, effective delivery through and to the lungs has presented severe limitations, mainly due to the limited consideration of one critical factor: the patient and their breathing behaviour. Another potential complication arises from the structure of the respiratory tract itself, which presents a succession of physiological filters aimed at preventing environmental aerosol pollutants from damaging the lungs. Unfortunately, this means that inhaled drugs also face these barriers. With such a wide variety of breathing patterns to consider, it is almost impossible to predict or maintain a consistent drug dose when using traditional low-tech nebulisers or inhaler technologies.

However, the pulmonary system still presents a potentially ideal means for topical therapeutic agents, since the lung would present a safer and more versatile organ for drug delivery than either oral or intravenous delivery.

FACTORS TO CONSIDER WHEN DESIGNING AN INHALATION SYSTEM

There are a number of biophysical and physiological factors that have to be considered when designing technologies for the delivery of inhaled aerosols. These include both physical properties of the drug formulation (particle diameter, particle density, hygroscopicity, electrical charge, chemical properties of the substance) and factors relating to the patient themselves (age, pulmonary diseases and breathing patterns). Variations in any of these factors can result in a substantial change of particle deposition in the lung. For example, large particles (>10µm) are not able to penetrate into the lung because they are deposited by impaction in the upper respiratory tract. On the other hand, small particles (0.1-1.0µm) are inspired into the alveoli, but are also expired without significant deposition. Particles of diameters between 2-5µm show the ideal pulmonary deposition behaviour and are able to transport a substantial mass of compounds into the lung.

THE IMPORTANCE OF PERSONAL BREATHING PATTERNS

Major pharmaceutical companies have been optimising the physical properties of drug compositions for many years in order to maximise uptake into the lungs. Despite this, it can be very difficult to design an optimal pulmonary delivery system when trying to accommodate variability in the breathing patterns of patients. Both age and illness can have major effects on a person’s style of breathing – factors that can then result in the ineffective administration of aerosolised drugs.

Breathing patterns are of paramount importance in inhaled particle deposition because the location of deposition can dictate the percentage of the compound that is absorbed, and this has obvious implications for dosing and drug effectiveness. One recent study found that the total respiratory tract deposition of patients with pulmonary disease varied between 20 and 95 per cent when using a standard inhalation device (see Figure 1) (3). Such a discrepancy can mean that some patients are not receiving doses adequate for a therapeutic response, while others are taking doses in excess of the therapeutic window.

By Gerhard Scheuch and Axel Fischer at Activaero GmbH

Intelligent Inhalation Technology

A novel inhalation system incorporating a smart card enables the breathing patterns of patients to be controlled, thereby ensuring consistent and optimal pulmonary drug delivery that can be tailored to the individual.

Figure 1: Controlled inhalations lead to a simultaneous high drug deposition and decreased variability
With such significant variability, inhalation schedules often require the patient to inhale for long periods of time in order to ensure adequate dosing. Long treatment schedules are not only inconvenient for the patient, but also have obvious implications for treatment compliance. More importantly, such schedules may not be applicable to treatments that have toxicity problems at higher doses over sustained periods of time (for example, corticosteroids).

It becomes apparent then that breathing patterns have to be controlled in some way to ensure adequate and efficient dosing that is simple, safe and quick to complete. The importance of controlled inhalation is shown in Figure 2. Figure 2A shows the deposition pattern of spontaneous breathing after inhalation of a radio-labelled drug; most of the drug became impacted in the patient’s throat and was subsequently swallowed into the stomach. Figure 2B shows how controlled inhalation with a slow flow rate leads to homogeneous distribution of the drug in the lungs (3).

**CONTROLLED INHALATION**

Research in recent years has, therefore, sought to develop technologies to control the breathing patterns of patients and thereby ensure consistent and optimal dosing. At Activaero, we have developed the first commercially available technology (AKITA) to meet these objectives; AKITA breathing systems allow individualised, controlled inhalations in combination with proven nebulisers (LC SPRINT® and APIXNEB® from Pari (4)) (see Figure 3). The technology comprises a patient-tailored controlled breathing system with a smart card that records patient inhalations, thereby enabling the most precise and efficient patient-tailored pulmonary delivery.

Using the systems, patients do not have to concentrate on the right breathing technique because the device induces the optimum breathing pattern for them. In effect, the device takes control of inhalation and provides the patient with status information on a display. This breathing control is achieved by using a patient- and drug-specific smart card, which predetermines the inhalation flow rate and inhaled volume based specifically on the patient’s respiratory condition. The systems also make it possible to precisely target different regions of the lung. To target the larger airways, for example, a small bolus of aerosol is introduced in the middle of an inspiration to prevent systemic uptake of an inhaled drug.

The smart card contains a drug’s optimised delivery information and is inserted into the AKITA device before the first inhalation. The predetermined inhalation flow rate of aerosol is then delivered to the lung by a compressor unit through the nebuliser in the device; this takes control of inhalation once the patient initiates a breath and begins ventilating the lung at a constant, comfortable rate. The patient can view the inhalation progress and the number of inhalations left on a small screen. The smart card also records the progress of each inhalation session, providing valuable compliance data on each treatment. This information is important in the clinical trial setting, especially when patients use the inhalation device at home.

Because breathing is controlled to induce optimal aerosol drug delivery, overall treatment times can be significantly shorter than traditional methods. In the clinical setting, results show that the system is well accepted in patients with cystic fibrosis (CF) due to the reliable dosing (5), which ultimately leads to greater compliance (6).
EARLY CLINICAL TRIALS FOR PULMONARY DRUG DELIVERY

In the clinical development of pulmonary drugs, the decision as to which device should be used is very important. In large patient population indications such as asthma, the target formulation of a drug may favour the use of a dry powder inhaler (DPI); however, such a decision involves tremendous formulation effort with obvious cost and time implications. At the same time, it is crucial to demonstrate clinical feasibility as soon as possible. For these reasons, it is usually best to conduct early clinical trials using a liquid formulation.

The risk of selecting a ‘wrong’ or highly variable device can endanger the success of the entire drug development project and lead to a premature ‘no go’ decision. The AKITA systems represent a good starting point in the initial pulmonary drug delivery trials, because only the precise knowledge of lung dose and risk/benefit ratio of the drug can lead to the best commercial formulation strategy. A comparison of the risks/benefits of different formulations and device strategies is given in Table 1.

CLINICAL VALIDATION

The AKITA technology has been validated in a clinical setting in multiple indications such as alpha-1 antitrypsin (AAT) deficiency (6,7), cystic fibrosis (8,9) and asthma (10). Potential further indications under investigation include COPD, lung metastases and idiopathic pulmonary fibrosis (IPF), as well as pulmonary hypertension (PAH).

In a recent study conducted by Talecris Biotherapeutics, the AKITA2 APIXNEB™ nebuliser system was used to deliver the missing AAT protein into the lungs of patients with AAT deficiency and cystic fibrosis. In the past, the success of this approach was hindered by several factors including: a high variability of deposited material; poor total and peripheral deposition in patients with advanced lung disease; and long nebulisation times.

The nebuliser system provided controlled breathing patterns for a total of 20 subjects who participated in the study (seven patients with AAT deficiency, seven with cystic fibrosis and six healthy volunteers). The regional deposition of the protein was then measured in comparison with the healthy volunteers. The results showed that the total lung deposition in all subjects was between 70 and 73 per cent of the drug amount in the nebuliser, with approximately nine per cent of the drug remaining in the device (see Figure 4, page 64).

Based on these results, the nebuliser system efficiently delivered AAT into the lungs and provided a

Table 1: Comparison of risks/benefits of different formulations and device strategies

<table>
<thead>
<tr>
<th></th>
<th>Standard Jet Nebuliser</th>
<th>Standard DPI</th>
<th>AKITA2 APIXNEB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung dose (% filled dose)</td>
<td>10-16%</td>
<td>10-25%</td>
<td>70-80%</td>
</tr>
<tr>
<td>Inter-subject variability</td>
<td>Very high (SD &gt;45%)</td>
<td>High (SD = 35-45%)</td>
<td>Very low (SD = 10-15%)</td>
</tr>
<tr>
<td>Medication needed for 100mg lung dose</td>
<td>600-1,000mg</td>
<td>400-1,000mg</td>
<td>120-140mg</td>
</tr>
<tr>
<td>Patients needed to identify dose effect of 33%</td>
<td>15-20</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Time required for formulation issues</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Costs for formulation development</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Target different lung regions</td>
<td>Difficult</td>
<td>Difficult</td>
<td>Very precise</td>
</tr>
<tr>
<td>To change formulation after Phase II study to DPI or MDI inhaler</td>
<td>Costs</td>
<td>No costs</td>
<td>Costs</td>
</tr>
<tr>
<td>Qualification studies for Phase II</td>
<td>Easy</td>
<td>Difficult</td>
<td>Easy</td>
</tr>
<tr>
<td>Dose escalation studies</td>
<td>Medium</td>
<td>Difficult</td>
<td>Easy</td>
</tr>
</tbody>
</table>

Figure 3: AKITA inhalation devices (Activaero GmbH) are inhalation systems that control compliance and medication dose. Different variants of these systems are available to cover a broad range of molecules (devices shown with Pari nebulisers)
consistently high deposition with a large proportion of the drug deposited in the peripheral airways in a short period of time.

CONCLUSION

With a large surface area (up to 140m²), good vascularisation, low thickness of the alveolar epithelium (0.1µm, 0.2µm) and an immense capacity for solute exchange, the pulmonary system presents a safer and more versatile option for improved drug delivery. Developed with these characteristics in mind, AKITA technology has proven to be a truly novel method for the effective delivery of precise aerosol doses to different regions of the lungs. The technology presents reproducible deposition patterns across a variety of different implications and severities, meaning that all patients are capable of performing the controlled breathing patterns. In addition, the technology has strong potential for home treatment, specifically in indications such as cystic fibrosis, severe asthma and COPD.

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