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Highly reproducible powder aerosolisation for lung delivery using powder-specific electromechanical vibration

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Dry powder inhalers (DPIs) have been in use since the 1970s, but it is only within the past few years that their use has constituted > ~ 10% of the inhaler units sold worldwide. Similarly, active DPIs have been in development for more than a decade, but no active device has yet been approved. Oriel is developing an active DPI technology that uses a very simple physical design coupled with a complex knowledge of powder flow and dispersion characterisation. The DPI uses electromechanical vibration with frequencies determined through the analysis of powder flow properties. Results so far have shown highly reproducible, efficient performance. The technology lends itself to both unit-dose and multidose platforms in a targeted cost-effective DPI.

Keywords: active dry powder inhaler, powder flow characterisation

Expert Opin. Drug Deliv. (2005) 2(3):579-585

1. Overview of the market

Asthma and chronic obstructive pulmonary disease (COPD) have traditionally been treated by the use of inhaled β-agonists (such as salbutamol) and by a mixture of oral theophyllines and oral steroids. The advent of the use of inhaled steroids, which allowed delivery of the drug directly to the site of action (i.e., the lung), thereby reducing the unwanted side effects of steroids and allowing much lower doses to be used, was a major advance in the control of asthma. In recent years the concomitant use of long-acting β-agonists and inhaled steroids has been seen as the optimum in controlling both the bronchoconstriction and inflammation associated with asthma. The use of inhaled anticholinergic agents (such as ipratropium) is now well accepted in the treatment of COPD [1].

The typical method of delivery of these medications is via metered-dose inhalers (MDIs) or dry powder inhalers (DPIs) [2,3]. The former have been used for > 40 years and have recently been undergoing reformulation efforts because the propellants that are used to expel the drug from the canister are, due to environmental concerns, being phased out. This has led to an increase in the use of DPIs, which contain no gases and are driven by the patient's own inhalation effort.

Early forms of DPIs were introduced in the 1970s (e.g., SpinHaler™ [Rhône-Poulenc Rorer], RotaHaler™ [GlaxoSmithKline]; both unit-dose devices). These consisted of the drug being placed in a capsule that the patient broke open and the contents of which were inhaled.

Recently, research into optimal approaches for delivering drugs to the lungs has expanded and increased, focusing on the evolution of DPIs from unit dose to true multidose. Multidose devices package a number of doses, ideally 1 months therapy, into a convenient single package. In a multidose device, the patient indices a new dose into position in a limited number of steps (e.g., index, inhale, close device), as compared with the multiplicity of steps required to load a unit-dose device (e.g., remove dose from overwrap, open device, load dose into device, puncture dose to

open, inhale, remove spent dose, clean, close device). Multi-dose devices require the patient to carry a single item rather than carrying the device and doses separately.

DPIs provide drugs to the lungs in a powder form. The process of converting a powder dose into an aerosol requires that the powder be fluidised before being delivered to the patient's airflow during inhalation. Powder fluidisation and aerosol delivery can be provided by passive or active means.

Passive DPIs depend on the patient's inhalation to provide the energy needed for dispersing the powder, which often requires the patient to inhale at a maximum rate for the inhaler to work properly. The strength of the patient's inspiratory flow rate, therefore, determines the dose that is administered [4,5]. Furthermore, the amount of drug delivered to the lungs (particles < 5 µm) depends on the inhalation flow rate generated by the patient and the inhalation profile [6]. This can be particularly problematic for the elderly, for children or for patients with severely compromised lung function. The current limitations of existing DPIs are that, unlike the MDIs that use propellants to expel the drug, they require the patient to provide energy. The passive devices have a tendency to show variability in delivery of the drug to the patient. These devices and their performance are highly sensitive to powder formulation [7]. All MDIs utilise similar components (i.e., can, valve, actuator/mouthpiece). No equivalent to the MDI exists for DPIs, with DPI designs and components varying drastically [8]. Regulatory agencies are striving to provide a minimum standard for inhaled products; this has resulted in some products not gaining regulatory approval and others being approved only in a limited number of countries because the device could not meet the required global standards.

Active DPIs use an energy source to generate powder dispersion, which means that the dosage is less dependent on the patient's efforts than in the case of passive DPIs, and the range of patients that can use these devices is, therefore, broader. Although no active device has yet been approved, a number of active devices are in development [3,9]. However, the complexity of active devices has, so far, limited their development to expensive therapies where a high device cost can be tolerated.

Historically, the global use of DPIs has accounted for < 10% of all inhaled drug delivery units (< 50 million units/year), but in the past several years the market has altered dramatically. In Europe, the percentage of DPI use has grown to > 35%; a similar picture is seen in Japan. In the US, with the recent successful launch of GlaxoSmithKline's Advair™ Diskus™, the use of DPIs continues to grow strongly.

Oriel's technology is a potential step forward in the evolution of inhalation drug delivery systems. This technology, which is built on knowledge of the physics of powder flow, can be incorporated into a DPI that has its own source of energy. The technology has multiple benefits of decreasing dependence on powder formulation effects and patient inhalation efforts. The resulting Oriel inhaler could, therefore, ultimately replace MDIs as a platform technology for pulmonary drug delivery.

2. Oriel's delivery technology

Oriel's DPI delivery technology was developed to address limitations, particularly related to reproducibility and thus regulatory approvability, of existing DPIs [2,9]. The technology is based on principles involving the mathematical interpretation of the flow and dispersion properties of powdered medications. Anthony Hickey, Oriel's Chief Scientific Officer, whilst working in the area of powder cohesion, found that an understanding of how drug powders flowed was predictive of their aerosolisation [10]. In research conducted in his laboratories at the University of North Carolina, a rotating drum tool was used to measure flow properties of various dry powder drug formulations [11]. A variety of mathematical descriptors was determined for the formulations, including Fourier, fractal and chaos analysis, stochastic and percolation models [12]. These descriptors were all based on describing flow data as irregular oscillations around a mean value. The degree of irregularity was shown to be predictive of performance of the formulations in a passive DPI device. *In vitro* performance was further correlated with *in vivo* brochodilation effects of the formulations [13]. Taken together, the method demonstrated an ability to predict inhaler performance for a given blend through physical flow characterisation, providing a valuable screening tool for formulation development.

Principles of control theory stipulate that for a system to be controlled, a model of the system must be generated so that the state of an output variable from the system can be predicted from the measurement of the appropriate input variables [14]. As the work described above provided a predictive capability, additional work was conducted to turn prediction into control in an active DPI.

2.1 Powder characterisation

Initial research was conducted on better understanding the rotating drum system and its relationship to DPI control. The rotating drum is one of the most frequently cited dynamic systems for studying the flow of granular materials. In this system, powder is placed in a circular drum mounted with its primary axis parallel to the horizontal. The drum is then rotated around its axis, causing the powder to rise and then cascade down in an avalanche as its angle of repose is exceeded. The powder angle relative to the horizontal as a function of time, or the time elapsing between avalanches are the two most commonly recorded parameters [15]. This seemingly simple system exhibits complex patterns of flow that are highly dependent on the material in the drum. In addition to its utility as a platform for studying granular flow, the rotating drum is relevant to powder processing applications. Mixing and milling are also examples [16-18]. The system can also be used for dynamic powder characterisation. A number of studies of both theoretical and practical interest have been published.

When the first thorough studies of the rotating drum were reported [19,20], an attempt was made to use the theory

of self-organised criticality (SOC), which was discovered a few years earlier [21]. In this theory, individual grains of sand added to a pile build until a critical state is reached and an avalanche is initiated. According to SOC, the distribution in the sizes of avalanches follows a power law relation. However, Evesque did not observe SOC for avalanches in the rotating drum [19]. Instead, he described the dynamics of the system using soil mechanics concepts dependent on the pile inertia, friction and gravity. SOC could only be observed under the more controlled conditions of bidisperse drum fillings [22]. In an alternative theoretical description, the distribution of avalanche angles and time between avalanches was determined according to a stochastic Markov process [23]. In other words, avalanches and their relationship between subsequent avalanches occurred according to a statistical distribution. The future state of the system could then be predicted by choosing the time to the next avalanche from the distribution. This author believes that this description is compelling. Models that correlate to pharmaceutical powders have been generated to support the hypothesis [15].

Other authors have described the state of the system as determined by chaotic dynamics with complex periodicity [11,24]. In fact, for a model system with a monodisperse distribution of particle sizes, there was perfect temporal periodicity in the powder angle [25]. Evesque stated that the size of a particular avalanche was dependent on the previous 60 avalanches. Kaye and Hickey found that the complexity of the dynamics were dependent on the environmental conditions [24] and material properties [11] of the powder in the drum. Temporal periodicity, even if highly complex, is a key parameter in the use of the rotating drum for powder flow prediction.

The rotating drum has practical application both for the information it provides relative to rotary processes and for its use in powder flow characterisation. A commercially available rotating drum characterisation instrument (TSI Aero-Flow™, TSI-Amherst) was used to compare the performance of a number of powder blends [26]. Analysis of the time between avalanches was predictive of tableting performance for two optimal formulations. However, the method was unable to distinguish between different, poorly flowing powders. Variations in the time to avalanche were correlated with surface energetic properties of micronised and unprocessed salbutamol sulfate [27]. The method was suggested for use in quality control analysis of batch variability for the micronisation process. Other data analysis methods have been used with success for the rotating drum. Statistical analyses of the size of avalanches were found to distinguish between powders of both similar and varying powder types [15].

2.2 Powder dispersion control

The principles of two of the models discussed above were combined for the control of powder dispersion in the Oriel technology. The first was the observation of a statistical relationship between avalanche initiation and termination angles and the second was the observation of temporal periodicity in avalanching. The technique further assumes that characterisation performed in the rotating drum is relevant to powder formulation in a DPI. It has been shown that the avalanches in the drum are determined by the first few monolayers of powder [28] (i.e., a small mass of powder). This demonstrates the relevance to smaller unit doses of powder in a DPI. Also important is the determination that the distribution remains constant, shifted in time according to the rotation rate of the drum, up to the point at which the rotating enters a centrifugal regime [29].

Based on the principle of the statistical relationship of angles, it was hypothesised that the system could be forced to a given angle through the addition of energy at an appropriate time using that relationship. This would entail monitoring the instantaneous angle of the powder and the application of energy through some form of actuator. Extending this hypothesis to the control of flow in a DPI, a fluidised powder could be made to flow more uniformly by the application of energy at the appropriate frequency or frequencies. As a fluidisation sensor would not be practical in a cost efficient DPI, an open-loop control method was selected that draws on the second principle, that there is a temporal periodicity of powder flow in the rotating drum governed by the physical properties of the powder. This open loop control uses the observed distribution of frequencies of powder avalanching and applies vibration at these frequencies to a fluidised powder in the DPI. In summary, the Oriel DPI dispersion control technology uses the application of frequencies of vibration, determined through physical characterisation, to drive an initially fluidised powder into a very uniform fluidisation state. This, in turn, provides very consistent aerosolisation and drug delivery as described below.

2.3 Oriel dispersion engine

The principles of dispersion control have been incorporated into various prototypes based around an 'engine' concept. The dispersion engine uses an actuator to provide vibration: a signal source that provides the powder-specific vibration frequencies and an amplification stage. Each of these can be incorporated into a unit-dose or multidose platform. The actuator consists of a piezoelectric polymer material: polyvinylidene fluoride (PVDF). The piezoelectric properties of PVDF were discovered more than three decades ago and the material has been used in medical devices, primarily as a sensor [30,31]. When PVDF is metallised and electrically stimulated, the dimensions of the material are changed through the principle of the piezoelectric effect. By placing an alternating electric field on the material, the PVDF changes shape repeatedly. The design of the PVDF into blisters, in which the drug formulation is placed, ensures that the change in shape results in a vibration of the powder. Extensive optimisation has been performed on blister shape and its effect on powder fluidisation. The shape of the PVDF blister determines both its frequency response and output [32]. Curvature of the blister provides mechanical

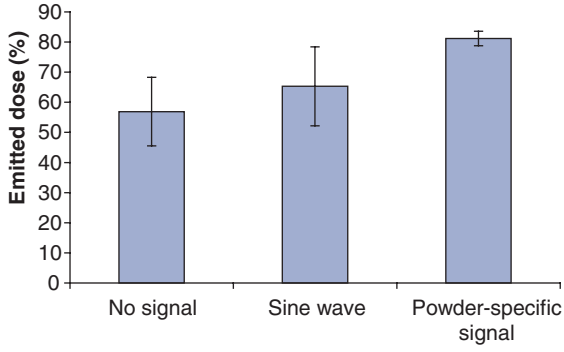

Figure 1. Emitted doses for three test conditions using 1% albuterol/lactose blend.

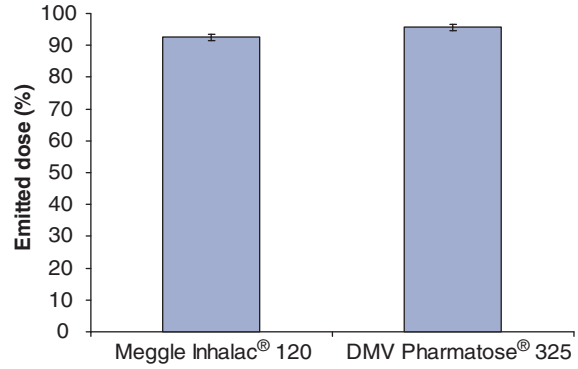

Figure 2. Emitted dose delivery as a function of lactose supplier and size fraction.

amplification of the dimensional change induced by the electrical excitation.

3. *In vitro* results

The *in vitro* performance of the Oriel dispersion technology has been investigated over a wide range of powder formulations. These include active pharmaceutical ingredients produced by the full range of available production techniques (e.g., jet milling, spray drying, supercritical fluid recrystallisation). Effective delivery has been achieved for each of these techniques. The dispersion engine technology has been developed across multiple prototypes of both unit and multidose. Selected *in vitro* studies are described below.

3.1 Proof of principle

Initial experiments performed at the University of North Carolina demonstrated that the application of a powder-specific vibration frequency could be used to improve powder dispersion and reproducibility. Model drug formulations were produced by blending micronised salbutamol and lactose. Lactose powders were Pharmatose® 325M (DMV International) and Inhalac 120 (Meggle). A 1% (weight by weight [w/w]) blend of salbutamol sulfate was created with each of the excipients. A simple inhalation tube was attached to a small section of curved PVDF to provide an entrainment conduit for testing purposes. The tube had a very low resistance (less resistant than RotaHaler) so that dispersion performance would be dictated primarily by the vibration, rather than by pneumatic effects. Dispersion tests were conducted at 60 l/min into an Andersen eight-stage impactor. Vibration frequencies for the formulation were determined using the methods described in the previous section.

Three conditions were tested using the 1% salbutamol Inhalac 120 blend: the entrainment tube with no excitation signal on the polymer; a sine wave signal; and the nonlinear, powder-specific signal (n = 4 for each signal condition). Emitted doses (EDs) were determined for each of the three signal conditions. Pneumatic entrainment effects (no excitation vibration) in the conduit accounted for ~ 55% of the dose emission, but were highly variable (standard deviation [SD] = 11%) as shown in **Figure 1**. The addition of energy through nonspecific vibration (sine wave) increased the overall dose emission, but did not decrease the ED variability. With the application of the signal derived from characterisation of the powder flow, the dose could be increased and, perhaps more importantly, the variability decreased significantly (SD = 2.4%).

In a second proof of principle experiment, vibration signals were calculated for drug/lactose blends formulated with differing suppliers and size fractions. **Figure 2** shows ED results for each of the formulations as dispersed from the entrainment conduit using the vibratory signal calculated for the formulation (n = 3 for each). In both cases, EDs were > 90% and variability was < 1% SD. The small batch blends had a blend uniformity of 1% so the blend was dispersed with a variability equal to the blend variability. Increased ED values relative to those presented in **Figure 1** can be explained by the use of new piezopolymer material for the data shown in **Figure 2** (whereas a piezo element that had been used for > 50 dispersions was employed for the previous data).

3.2 Signal and prototype improvements

The preceding data were used to demonstrate the ability of the powder-specific vibration to improve dispersion performance. The fine particle fraction (FPF) was examined using an initial prototype. Initial experiments showed low FPF. One strength of the technology is the ability to improve performance through 'software' changes by modifying the vibration frequencies. It was observed in the previous experiments that powder-containing blisters were too deep, so that even when fully fluidised, not all of the powder was entrained in the airflow. Therefore, the flow path was modified slightly to bring the airflow into proximity with the blister. Initial results showed good fluidisation (88% ED) but inefficient deaggregation (11.5% FPF). The signal improvements increased the FPF to 27.3% while actually decreasing the ED to 80%. Flowpath modifications brought the ED back to initial levels and increased the FPF further to 38.5%. These results are

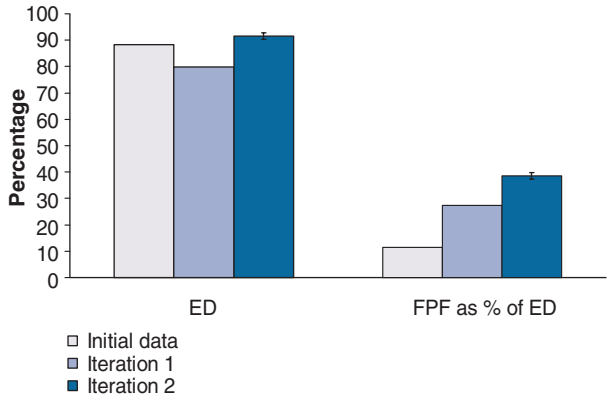

Figure 3. Effect of modification of signal and flowpath on ED and FPF.
ED: Emitted dose; FPF: Fine particle fraction.

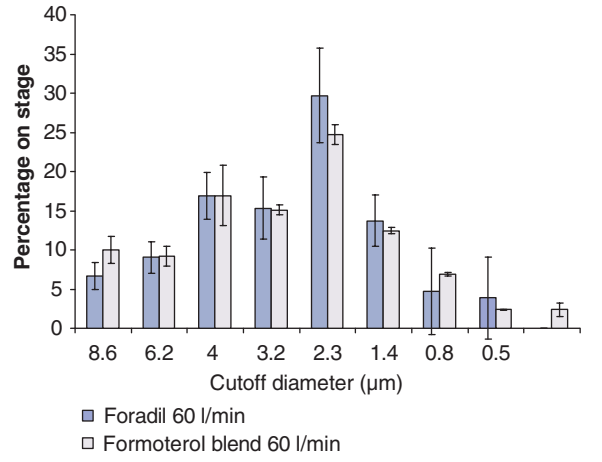

Figure 4. Cascade impaction stage-by-stage comparison of the deposition percentage for the Aerolizer® and the Oriel engine. Note the close correlation on a stage-by-stage basis but with relative standard deviations decreased to ~ 2% from ~ 8%.

shown in **Figure 3**. No formulation changes were required to achieve the performance increase.

3.3 Performance matching

The experiments described in the previous section suggest an ability to tailor dispersion performance to a given target. For a platform inhaler, this would be advantageous in that the DPI could be matched to an existing product. A more recent prototype of the Oriel engine was compared with an existing product for the delivery of formoterol fumarate. Formoterol is a long-acting bronchodilator used in the treatment of asthma and the prevention of bronchospasm. Formoterol fumarate was blended with inhalation-grade lactose at 0.5% w/w. The blend uniformity was assayed via high performance liquid chromatography (HPLC) and determined to have a relative SD of 1.8%. Supplies of Foradil® Aerolizer® (Novartis Pharmaceuticals; formoterol fumarate 12 µg) were purchased. The Aerolizer is a unit-dose, capsule-based DPI. A vibration signal was determined for the lactose powder.

Aerosolisation performance was measured by cascade impaction using an Andersen eight-stage, non-viable impactor operated at a flow rate of 28.3 and 60 l/min. The 60 l/min modifications (preseparator, stages -1 and -0) were used for that flow rate. For the Oriel inhaler, 5-mg powder doses were used (25 µg/dose) with three shots per impaction. The Aerolizer impactions were performed with three capsules per impaction. All impactions were performed in triplicate. Impaction plates were rinsed and formoterol content determined by HPLC. The Oriel inhaler, the Aerolizer and Aerolizer capsules were rinsed to achieve mass balance. As different doses were used (25 versus 36 µg) the particle size distribution was determined as a ratio of the mass on each stage to the total ED with a goal of matching performance of the Aerolizer. A representative plot of the percentage mass distribution on each stage is shown in **Figure 4**. The Oriel inhaler produced highly reproducible results on a stage-by-stage basis with a distribution that matched the Foradil distribution.

4. Expert opinion and conclusion

The Oriel dispersion technology is based on fundamental physical principles of powder flow and control. Extensive research and development effort has been conducted in the powder characterisation on which the technology is based. The DPI 'engine' uses a novel approach to an actuator for an active inhaler wherein the drug packaging material forms the actuator. Proof of concept studies demonstrated that the use of powder-specific vibration provided significant improvements to reproducibility of dispersion. Further development of the technology has demonstrated an ability to quickly meet *in vitro* performance targets without reformulation efforts. This ability to target performance allows the technology to be used to match existing products. Extensive optimisation of blister and flow path design have provided an efficient prototype DPI.

Oriel is developing two platforms that use its powder-specific vibration technology. The first to the market will be a unit-dose platform. The unit-dose platform will enable rapid product development and be appropriate for drug compounds that are more appropriate for unit-dose packaging. The second platform to the market will be a premetered, multidose format. One month's therapy in the DPI is targeted. The multidose platform will be applied to small molecules for the treatment of asthma and COPD.

Other active devices in development address a number of the key features that are important in inhaled delivery: mainly active administration of drug, consistent dose delivery and a high proportion of dose getting to the lung. These are all important and so far some companies have been technically successful, but this comes at a high price per dose delivered to the patient. It is unlikely that these devices will be

competitive in the respiratory (asthma/COPD) field where cost of the device has traditionally been very low. Oriel envisions achieving these same targets with much simpler, and, therefore, less expensive, approaches. The Oriel device requires a low part count that will help achieve cost targets in the order of existing multidose devices. Although no electronics-based inhaler has yet been approved, and the inclusion of a stored power source will subject them to additional regulatory scrutiny; it is anticipated that electronic inhalers will eventually reach the market.

In addition, Oriel's development of a multidose platform will be targeted to better patient acceptance. It is expected that patients, when given a choice between unit-dose products, which require carrying multiple components and complex operations to use, and multidose products, which provide 1 month's therapy in a simple package, will choose the multidose product. Multidose, premetered products are more difficult to develop as they require the design of dose indexing and opening systems. Oriel has produced prototype designs that address these systems. In addition, the mechanical design complexities will be offset by the ease of formulation development in the Oriel DPI. Oriel's active system will enable rapid matching of a given performance specification without repeated reformulation of the active pharmaceutical ingredients and excipient. From this standpoint, the Oriel DPI can be developed as a true platform technology. Finally, the reproducibility observed so far suggests the potential to obtain rapid regulatory approval.

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