Delivery of formoterol from a novel multi-dose inhaler Airmax™

X.-M. ZENG*, S. JONES*, D. O'LEARY*, M. PHELAN† AND J. COLLEDGE‡

*IVAX Pharmaceutical U.K. Ltd, Royal Docks, London E16 2QJ, U.K., †IVAX Ireland, Waterford, Ireland and ‡Pharmaceutical R & D, Yamanouchi Europe BV, Leiderdorp, The Netherlands

Abstract  Using a proprietary technology known as the X-ACT™ system—Active-metering, Cyclone-separator Technology, a novel multi-dose inhaler (Airmax™) was developed to provide accurate and consistent dosing and a high-fine particle fraction of the drug. Formoterol, present as a blend with lactose monohydrate was delivered from Airmax™ to obtain a nominal formoterol dose of 6 or 12 mg. The devices were tested using a five-stage liquid impinger and a unit dose sampling apparatus, operated under conditions specified in European Pharmacopoeia (2000). Fine-particle dose (FPD) was defined as the dose of the aerosolized drug particles with an aerodynamic diameter < 5 μm and fine particle fraction (FPF) was the ratio of FPD to the total recovered dose. Dose per actuation was found to be 970 ± 11.5% label claim (LC) or 5.8 ± 0.7 μg (n=140), and 100 ± 94% LC or 12 ± 1.1 μg (n=440), for the 6 and 12 μg strengths, respectively. The mass median aerodynamic diameter was 2.4 ± 0.1 μm (n=14), the geometric standard deviation 2.1 ± 0.1 (n=14), and FPF 44.4 ± 2.4% (n=14) for both strengths. Thus, the combination of active metering and cyclone separator produces highly consistent doses of formoterol that have a large respirable fraction.

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Keywords  Airmax™; active metering; cyclone separator; dry powder inhalers; formoterol.

INTRODUCTION

Drug delivery to the lung by inhalation has long been regarded as the preferred route for the treatment of lung diseases since it maximizes therapeutic effects and minimize any side effects by targeting drugs directly to the sites of actions. Pressurized metered dose inhalers (pMDI) are still the dominant devices but the Montreal Protocol and its consequent environmental legislation have urged the pharmaceutical industry to develop alternative devices since the chlorofluorocarbon (CFC) propellants used in conventional pMDI contribute to the depletion of atmospheric ozone layer. Another problem plaguing pMDI is the requirement of coordination between actuation and inhalation. Many patients are unable to operate the devices correctly even after training. Although such a problem has, to some extent, been solved by the use of spacer devices and breath-actuated mechanism, pMDI still have other problems such as time-dependent dose variation (shaking, priming, dose tailing) and variable deposition depending on inhalation manoeuvre (I). There is still environmental concern with the use of replacement propellants hydrofluoroalkanes (HFAs) specifically for HFA-134a due to its degradation product, trifluoroacetic acid which is not environmentally friendly (2). Also, HFAs are known to be 2000 times as potent as carbon dioxide as a “greenhouse” gas. If the Kyoto Protocol is ratified, then the reduction in greenhouse gases may affect the use of HFA propellants in medicinal aerosols.

Without the use of any propellants, dry powder inhalers (DPIs) are environmentally friendly. These are breath-operated devices and thus overcome the coordination issue. The dose is released and subsequently dispersed by the patient’s inspiratory airflow. Single-dose DPIs (Spinhaler®, RPR and Rotahaler®, Glaxo Wellcome), were introduced approximately 30 years ago but these have been considered inconvenient and difficult to use (3). More recently, development has taken place of devices holding multiple pre-metered unit doses (Diskhaler® and Diskus®, Glaxo Wellcome), and reservoir-type devices, where each dose is metered from bulk during use (Turbuhaler®, Astra Zeneca; Clickhaler, Innovata Biomed and Easyhaler®, Orion). Each device has its strength and weakness. For example, Turbuhaler® typically delivers up to twice as much of the metered dose to the lungs as Diskus® (4,5). Conversely, lung delivery has been found to be more consistent at different flow rates with Diskus® than Turbuhaler® (3,6). The dose indicator
on Diskus® gives an exact reading of the number of doses remaining, whereas that for Turbuhaler® only gives an approximate indication that the inhaler is close to empty. Both devices require the patient to open a dust cover and then prime the inhaler before taking a dose (7,8). Currently, there is hardly any DPI that delivers consistently high doses to the lung. Therefore, it is the aim of the present work to develop a device that is consistent in delivering a dose and efficient in generating deeply inspirable drug particles.

**METHODS**

**Design concept**

Two key mechanisms are involved in the delivery of drugs from multi-dose dry powder inhalers (MDPI) and these are metering and dispersion. In broad senses, metering mechanism governs the delivered dose whilst the dispersion mechanism determines the amount of drug that can reach the lower airways. Therefore, in the development of Airmax™, special attention has been given to these mechanisms, leading to the invention of an active metering and a cyclone-separator Technology.

Unlike other inhaler devices that rely on gravity for dose metering, Airmax™ uses an air pump to meter out the precise dose of medication. The dry powder (a blend of medication and the lactose carrier) is contained in a funnel-shaped bulk powder drug reservoir, which lies beneath the air pump. The action of patient’s opening the mouthpiece cover activates this pump, which in turn exerts a constant air pressure on the powder in the drug reservoir (Fig. 1). The controlled air pressure on the powder ensures that the same volume of the blend enters the dose cup below the drug reservoir, from one dose to the next. This precise, consistent filling of the powder into the dose cup then determines the amount of powder available for inhalation—and thus assists in accurate and consistent dose delivery.

After dose metering, the next stage is to ensure that the drug is separated from the carrier, and dispersed into primary particles that are small enough to reach the site of actions in the small airways of the lungs. This is achieved by Airmax™’s unique cyclone separator. When the patient inhales, air enters Airmax™ through two tangential inlets above the mouthpiece; this creates the cyclonic flow within the separator in the direction shown by the arrows in the diagram (Fig. 2). The cyclone separator is designed to maximize the dispersion and deaggregation of the drug by means of cyclonic flows within the separator. Ramps on its roof are precision manufactured to induce turbulence and prolong the length of time while the air-borne powdered drug blend remains in the cyclone. As the drug blend is spun round inside the separator, the centrifugal and drag forces that are generated on the particles, the turbulence of the airstream and collisions of particles with the cyclone walls all act together to maximize break-up of drug agglomerates and separation of the drug from the lactose carrier.

Once the particles in the blend have been separated, the smaller drug particles are released into the mouthpiece first, while the larger lactose particles remain in the cyclone separator. The separated dose leaves the cyclone and is delivered to the user via the mouthpiece, from where the fine particles are delivered to the lungs. The larger lactose particles are emitted from the cyclone next; they stay mainly in the mouth and throat, from where they are swallowed. The total metered dose is

**Fig. 1.** Schematic drawing of the active metering principle of the Airmax™ device.
emitted. In this way, the cyclone separator technology ensures effective drug dose delivery to the lung.

The air pump and dose metering are triggered by a sequence controller inside Airmax™, operated by the patients' opening the mouthpiece cover. The sequence controller also automates the transfer of the metered dose from the “metering position” to the “inhale position”, and the indexing of the dose counter. The mechanism has been designed to be robust and resistant to mishandling. This simple automated system means that Airmax™ is easy to use.

Measurement of air resistance

Air resistance is an important characteristic for DPI since it determines the inspiratory flow rate achievable by patients. The air flow rate in turn governs drug delivery from the device to the lung. It is therefore essential to control device air resistance so as to produce adequate air flow rate by the majority of patients after inhalation with “comfortable” effort normally corresponding to a pressure drop of 4 kPa (40.8 cmH₂O) across the device (9). In order to quantify air resistance, air flow rates from Airmax™ at different pressure drops between 1 and 5 kPa were determined by attaching Airmax™ to a dose uniformity sampling unit (DUSA, Copley, U.K.) that has a manometer (RS, U.K.) attached to its port to measure pressure drop. After the pressure drop was adjusted to the pre-determined value, the flow rate across the DUSA was measured by a digital flowmeter (Copley, U.K.). Ten devices were tested ad the mean flow rate at each pressure drop was utilized to calculate the air resistance of the device.

Formulation development

Formoterol, a long acting beta-2 agonist bronchodilator, has been delivered by a unit-dose, capsule-based DPI (Foradil®️, Novartis Pharma S.A.) to deliver a nominal dose of 12 µg formoterol fumarate (10). In order for the drug to gain access to the lower airways, a prime requirement is that the drug particles have an aerodynamic diameter between 1 and 5 µm (11). Particles of such a size range are notoriously difficult to flow and disperse due to its highly cohesive nature (12). The micronized drug is often mixed with a coarse carrier such as lactose to improve powder flow and dispersion properties (13). Thus, for administration via Airmax™️, micronized formoterol was blended with lactose. During development, various grades of lactose were evaluated to obtain formulations with optimal pharmaceutical performance.

Emitted mass

The through life emitted mass from Airmax™️ was assessed gravimetrically using the Emitted Dose Collector System (EDCS, the Technology Partnership). The performance of Airmax™️ was also compared to that of a conventional multi-dose dry powder inhaler (Oxis Turbuhaler®️️). For both inhalers, single dose was drawn into a collection filter at an airflow rate of 60 l/min for 4 s. The increase in the weight of the filter was taken to represent the mass delivery of each actuation.

Dose content uniformity (DCU)

Dose per actuation (DPA) was tested using conditions as specified in European Pharmacopoeia (2000). Thus, 10
doses, three at beginning, four middle and three at end of device life, were fired separately into a Dose Uniformity Sampling Apparatus (Copley, U.K.) at $Q$, a flow rate that generated a pressure drop of 4 kPa across the device (ca. 69 l/min). After 4 litres of air had been drawn through the device, the drug that was collected was recovered and analyzed using a validated high performance liquid chromatography (HPLC) method. Whilst DPA results have routinely been assessed using European Pharmacopoeia (2000) specifications for DCU, content uniformity results have been re-calculated as percentage of label claim.

**Aerodynamic particle-size distribution**

This was assessed using a five-stage liquid impinger (MSLI, Copley, U.K.) operated at European Pharmacopoeia (2000) conditions. A number of doses (20 for 6 μg devices but 10 for 12 μg devices) were actuated into an MSLI, each drawn by 4 l of air at $Q$. The dose number was determined by the sensitivity of assay methods. Each device was tested at beginning and end of device life. The drug deposited at each stage of MSLI was then recovered separately and assayed by a validated HPLC method.

Total recovered dose (TRD) was the sum of drug collected from the induction port and at all five stages of the impinger. Fine particle dose (FPD) was defined as the dose of the aerosolized drug with particle size < 5 μm. Fine particle fraction (FPF) was the percentage ratio of FPD to TRD. Results were also expressed as Mass Median Aerodynamic Diameter (MMAD) and Geometric Standard Deviation (GSD) of the particles collected in the MSLI. It is again impossible to report all aerodynamic data but great caution has been taken to include data that best reflect the performance of these products.

**RESULTS**

**Air resistance**

Plotting the square root of pressure drop ($P$) against volumetric flow rate ($Q$) resulted in a straight line with intercept of 0, a slope of 0.0924 and $R^2 = 0.996$. Since $P_{0.5} = RQ$ (4) where $R$ is the air resistance. The air resistance takes the value of the slope, i.e. 0.0924 (cmH$_2$O)$^{0.5}$ min/l.

**Emitted mass**

Figure 3 shows typical mass-delivery profiles from the formoterol Airmax$^\text{TM}$ and OxisTurbuhaler®. Clearly, the Airmax$^\text{TM}$ has a highly consistent delivery of drug with a RSD of mass delivery of ca. 2%. In comparison, Oxis Turbuhaler® appears to be less consistent and has an RSD of ca. 12% in mass delivery.

**Dose content uniformity**

The overall mean DPA ($\pm$ SD) of 6 μg formoterol Airmax$^\text{TM}$ was $970 \pm 11.5$% label claim (LC) or $5.8 \pm 0.7$ μg ($\pm = 140$). Each individual device produced mean DPA within 85–115% LC. The majority of DPAs (95%) were within 80–120% LC. Five DPAs (3.6%) were outside of 80–120% LC, but within 75–125% LC. Two DPA (1.4%) fell out of 75–125% LC, but within 65–135% LC. The spread of DPA values is shown in Fig. 4.

![Fig. 3](image-url) Mass delivery from a 12 μg formoterol Airmax$^\text{TM}$ and a 12 μg OxisTurbuhaler®.
The overall mean DPA (± SD) from 12 µg formoterol Airmax™ was 100 ± 94% LC or 12.0 ± 1.1 µg (n=440). Each individual device produced mean DPA, which was within 85–115% LC. The majority (98%) of DPA’s were within 80–120% LC. Seven DPA’s (1.6%) were outside of 80–120% LC, but within 75–125% LC. Two DPA’s (0.4%) were marginally higher than 125% LC, but less than 135% LC. The spread of DPA values is shown in Fig. 5.

**Aerodynamic particle-size distribution**

From Table I, it can be seen that fine-particle fraction measured between 41 and 49% for both strengths, and there was no difference in the performance at the start and end of device life. The mass median aerodynamic diameter varied between 2.2 and 2.6 µm and the geometric standard deviation between 1.9 and 2.0. Total recovered dose was close to LC, and all devices delivered in excess of the nominal number of actuations.

**Stability studies**

Extensive stability studies are being performed on these products under International Conference on Harmonisation (ICH) conditions. Devices are stored at several orientations, under various conditions including 25°C/60% RH, 30°C/60% RH and 40°C/75% RH, either in their final packaged form or completely unpacked to mimic the conditions when the devices are used by patients. Data from these studies support a shelf life of at least 24
months for inhalers packed in moisture-proof foil pouches and in-use life of at least 3 months after packaging has been removed.

**DISCUSSION**

Airmax™ demonstrated reproducible mass delivery of the blend, leading to consistent delivery of the drug. Thus, the active metering principle has successfully produced precise and repeatable delivery of the drug. Drug delivery from Airmax™ is close to the LC and the performance is maintained throughout life.

The second element of the technology is the cyclone separator. This is constructed to efficiently disperse the drug in order to provide a high lung delivery. Formoterol would be expected to be a difficult molecule to disperse due to the small dose compared to the mass of lactose carrier. However, for both strengths fine-particle fraction measured over 40% with an MMAD of 2.2–2.6 µm. Thus, almost half of the delivered dose had an aerodynamic particle size < 5 µm, suggesting that Airmax™ is highly efficient in generating deeply inspirable drug particles. Moreover, there was little difference in the intra- and inter-device performance, an indication of consistent pharmaceutical performance.

The Airmax™ exhibited a moderate resistance to inhalation airflow with specific resistance similar to that of Turbuhaler® (Table 2). As expected, it has also been shown that the air resistance through Airmax™ is independent of the type and mass of the blends in the hopper. The air resistance of Airmax™ is close to the range of 0.06–0.09, which is preferred by the patients (9).

As well as delivering a good technical performance, it is important that an inhaler is attractive, convenient, robust and as simple and foolproof in use as possible. Airmax™ has been designed to have a familiar shape, not unlike the pMDI that most patients will have used. It is compact, and simple and intuitive to operate: opening the mouthpiece cover is all that is necessary to prepare a dose for inhalation, and after taking the dose closing the mouthpiece cover again makes the device ready for the next use. A dose counter with a generously sized display provides a clear and precise indication of the number of doses remaining and gives extra warning as the inhaler approaches empty. All of these functions are operated from the movement of the mouthpiece cover by a sequence controller inside the device, which coordinates metering of the dose, transfer to the inhalation position and advancement of the dose counter. Testing demonstrated that the sequence controller is unaffected by operation to five times the normal device life.

In conclusion, active metering and cyclone separator technology are the keys for the excellent performance characteristics of Airmax™, including a highly accurate and consistent dose of formoterol and a large proportion of the delivered dose consisting of fine (respirable) particles.

**Acknowledgements**

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**REFERENCES**


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**Table 1.** Aerodynamic particle-size distribution of formoterol from Airmax™ at Q (ca. 69 l/min)

<table>
<thead>
<tr>
<th>Test parameters</th>
<th>Device strength/no. of actuations (device no.)</th>
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<tr>
<td></td>
<td>6 µg/60 (n=4)</td>
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<tr>
<td></td>
<td>12 µg/60 (n=3)</td>
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<tr>
<td><strong>Start of inhaler</strong></td>
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<tr>
<td>TRD (µg)</td>
<td>6.22 ± 0.67</td>
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<tr>
<td>MMAD (µm)</td>
<td>2.40 ± 0.14</td>
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<td>GSD</td>
<td>2.20 ± 0.06</td>
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<tr>
<td>FPD (µg)</td>
<td>2.90 ± 0.41</td>
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<tr>
<td>FPF (% TRD)</td>
<td>46.5 ± 2.5</td>
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<tr>
<td><strong>End of inhaler</strong></td>
<td></td>
</tr>
<tr>
<td>TRD (µg)</td>
<td>5.87 ± 0.05</td>
</tr>
<tr>
<td>MMAD (µm)</td>
<td>2.35 ± 0.06</td>
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<tr>
<td>GSD</td>
<td>2.13 ± 0.05</td>
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<tr>
<td>FPD (µg)</td>
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<tr>
<td>FPF (% TRD)</td>
<td>43.3 ± 2.6</td>
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**Table 2.** Air resistance of Airmax™ compared with other commercial DPIs (9)

<table>
<thead>
<tr>
<th>Inhalation devices</th>
<th>Air resistance (cm H₂O)0.5 min/l</th>
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<tbody>
<tr>
<td>Rotahaler</td>
<td>0.040</td>
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<tr>
<td>Spinhaler</td>
<td>0.051</td>
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<tr>
<td>ISF inhaler</td>
<td>0.055</td>
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<tr>
<td>Diskhaler</td>
<td>0.067</td>
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<tr>
<td>Airmax</td>
<td>0.092</td>
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<tr>
<td>Turbuhaler</td>
<td>0.100</td>
</tr>
<tr>
<td>Inhalator M</td>
<td>0.180</td>
</tr>
</tbody>
</table>


8. van der Palen J, Klein JJ, Schildkamp AM. Comparison of the new multidose powder inhaler (Diskus/ Accuhaler) and the Turbuhaler regarding preference and ease of use. *J Asthma* 1998; 35: 147–152.


