Expert Opinion

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Adaptive Aerosol Delivery (AAD®) technology

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Jet nebulisers have, since the 1920s, been used for delivery of inhaled drugs for the treatment of asthma, chronic-obstructive pulmonary disease and pulmonary infections. During the last two decades, recognition of the shortcomings of conventional nebulisers has led to the development of new 'intelligent' nebulisers such as the Adaptive Aerosol Delivery (AAD®, Profile Therapeutics, a Respironics company) systems. Diseases of the airways have traditionally been logical candidates for treatment with inhaled drugs. The introduction of the 'intelligent' nebulisers has, however, broadened the possibilities for inhaled treatment to include drugs targeted for systemic diseases. These nebulisers offer the possibility to deliver more precise doses of drug, maximise lung deposition, enhance adherence to treatment and compliance with the device through feedback to the patient, and last but not least, offer the possibility to reduce nebulisation times.

Keywords: AAD® system, Adaptive Aerosol Delivery, HaloLite®, I-neb, nebuliser, Prodose™

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1. Introduction

The inhaled route for therapeutic aerosols is a common practice in the treatment of diseases such as asthma or chronic-obstructive pulmonary disease (COPD). Pulmonary drug delivery for these diseases limits exposure to systemic drug effects. The inhalers used are relatively inefficient conventional pressurised metered-dose inhalers, dry powder inhalers or jet nebulisers, which deliver drugs with a broad therapeutic window. The development of new pulmonary drug delivery systems that deliver more precise and reproducible doses of drug has, however, broadened the range of drugs that could be delivered to, or through, the lungs.

The forces driving the pharmaceutical industry to consider pulmonary drug delivery of new molecules include ever increasing competition, pricing pressures, drug patent life, life cycle management, and patient demands. The main customers for pulmonary drug delivery are the patients, healthcare payers and investors. This means that new pulmonary drug delivery systems, such as the Adaptive Aerosol Delivery (AAD®, Profile Therapeutics, a Respironics company) systems, need to provide a sustainable competitive advantage by creating a technical solution that meets the patient's demands, is cost effective, in order to meet the payer's demands, and generates a new market or extends the commercial life of the drug, in order to meet the demands of the investor.

Numerous types of inhalation devices are available, but the nebuliser can provide a faster and more cost-effective route to the market for many new drug delivery applications. Conventional nebulised therapy, however, is a rather inexact method of drug administration, and wastes a large amount of aerosol during exhalation to the environment [1]. An inhalation device that is efficient, and delivers a precise amount of aerosol with minimal environmental or care giver exposure will be required for the delivery of expensive drugs with the potential to cause adverse reactions. The main reason for the inexact drug delivery is the constant drug output of the conventional nebuliser, which makes the amount of drug inhaled directly dependent on the breathing pattern of the patient. The duty cycle of the patient's breathing pattern is

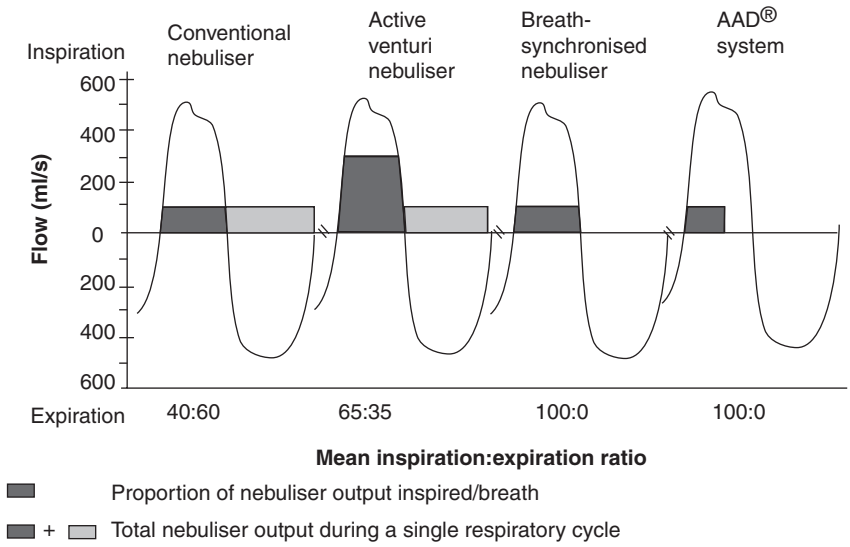

Figure 1. A schematic representation of the tidal volume and inspiration/expiration ratios of four different types of jet nebuliser. The drug available for inhalation is indicated by the dark shaded areas, whereas the lightly shaded areas indicate losses to the surrounding air. These two areas are used to calculate the mean inspiration/expiration ratios for the aerosol output of the different types of nebuliser. Modified from [29] with permission of AstraZenaca, Lund, Sweden.
AAD: Adaptive Aerosol Delivery.

typically 40:60 [2], which means that the time of inspiration is ~ 40% of the single respiratory cycle and the time of expiration ~ 60% (**Figure 1**). This means that at least 60% of the drug delivered from the nebuliser will be wasted to the environment and potentially be inhaled by those caring for the patient. Active venturi jet nebulisers were developed to increase the amount of drug inhaled and decrease the amount wasted [3]. Breath-synchronised nebulisers have further improved the amount inhaled by delivering aerosol only during inhalation. As the aerosol is delivered during the whole inspiration, filling the entire anatomical deadspace, some of it will be exhaled. Pulsed aerosol drug delivery during only part of the inhalation could minimise the amount lost during exhalation, and provide the basis for delivery of precise preset doses of drug.

An important feature required in a new inhalation device would be feedback from the device to the patient on how to inhale, and information on when the preset dose of drug has been delivered. Published data on patient adherence to nebulised treatment indicates that a large proportion of the prescribed doses are never used [4]. There is a lack of published data on how patients comply with the instructions on nebuliser use, as conventional nebulisers lack any data-recording features. As a consequence, there are limited data available on the patient's true adherence, that is, the product of adherence to treatment × compliance with the device.

2. The Adaptive Aerosol Delivery technology

The AAD technology was developed by Profile Therapeutics to minimise the variability of the delivered dose, to minimise the waste of aerosol to the environment and to improve the patient's adherence to their treatment and compliance with the correct use of the device [5,6]. On 1 July, 2004, Respironics, Inc. aquired Profile Therapeutics Plc, the developers of AAD technology. The AAD systems have been designed to adapt delivery of aerosol to the patient's breathing patterns, eliminating the greatest source of variability in drug delivery associated with conventional nebulisers. It also provides the patient with feedback on how to effectively use the AAD system during the treatment. When the preset dose is delivered, the device switches off and a buzzer indicates completion of treatment.

The AAD systems use electronics and sensors within the device to constantly monitor and adapt to individual breathing patterns, and pulse aerosol during the first part of the inspiration. The AAD systems have been designed to analyse the breathing pattern of each individual patient. The timing of the pulse of aerosol to be delivered is determined by this analysis. The AAD systems analyse the pressure changes of the airflow of the first three breaths, to ascertain the correct starting point for aerosol delivery. The monitoring of the preceding three breaths continues throughout the treatment, and the AAD systems continually adapt to the breathing patterns of the patient.

2.1 The HaloLite® AAD system

In 1997, HaloLite® (**Figure 2**) became the first AAD system to be made commercially available [6]. It was designed on active venturi jet nebuliser technology to aerosolise formulations typically used for the treatment of asthma patients. The HaloLite AAD system consists of a handpiece, including a mouthpiece, a medication chamber and an electronic control unit. The compressor is operated from mains electricity. The HaloLite AAD

Figure 2. The HaloLite® AAD® system. Copyright of Profile Therapeutics, a Respironics company.
AAD: Adaptive Aerosol Delivery.

Figure 3. The Prodose™ AAD® system. Copyright of Profile Therapeutics, a Respironics company.
AAD: Adaptive Aerosol Delivery.

algorithm enables precise pulses of aerosol to be delivered into each inspiration by monitoring the flow characteristics of each breath in a breathing pattern. A flow sensor monitors the flow of the inhalation and exhalation through the mouthpiece. The signal is then transferred to the processor running the AAD software, via an analogue-to-digital converter, to enable analysis of the breathing pattern. Once the trend of the breathing pattern has been established in the first three breaths, the start of each subsequent breath can be identified rapidly and accurately. This allows aerosol to be pulsed into the very beginning of each inspiration, ensuring maximum opportunity for the aerosol bolus to penetrate deep into the lung. Aerosol pulse times have been set to 50% of inspiration time, based on the rolling average of the last three inspirations. The amount of medication delivered during each pulse is calculated by the AAD software, and the total sum over the course of the treatment is determined. The patients are given both audible and visual feedback to inform them of a successful treatment. Depending on the volume of drug in the vial used, a significant amount of drug will remain as residual, as HaloLite is preset to deliver only 0.25 ml/preset dose.

2.2 The HaloLite® Paediatric AAD system

The HaloLite Paediatric AAD system is a version of HaloLite designed expressly for use by children aged 6 months to 5 years. This age group breathe with much lower tidal volumes than adolescents and adults, and therefore, the minimisation of the equipment deadspace is important. Deadspace becomes an issue when the tidal volume approaches the combined anatomical and equipment deadspace. With a low deadspace:breath ratio, aerosol will be inhaled into the deadspace, and then exhaled before it reaches the target deposition site. HaloLite Paediatric incorporates a number of features to address the deadspace issue, as well as utilising an inflatable cuff facemask to ensure adequate sealing of the nebuliser–patient interface. These features called for the introduction of inhalation and exhalation valves to the facemask connection to minimise equipment deadspace, and the incorporation of a deadspace correction within the AAD algorithm, to ensure an accurate calculation of the delivered dose. The device is not available at present.

2.3 The Prodose™ AAD system

The Prodose™ AAD System (**Figure 3**) is a second-generation AAD system, based on the HaloLite design. However, it offers significant improvements in convenience and flexibility over HaloLite. The Prodose AAD system consists of a compressor connected to a self-powered handpiece fitted with a liquid crystal display. Prodose uses improved versions of the AAD algorithms designed for HaloLite. The length of the aerosol pulse into the inspiration is entirely dependent on the breathing pattern of the patient, up to a limit of 8 s pulse time. Patients with tidal volumes < 1 l will continue to have aerosol pulsed into 50% of their inspiration. A minority of patients with tidal volumes > 1 l [2] will reduce the treatment times as the aerosol is pulsed into a greater percentage of the inspiration. These improvements have been shown to lead to faster and more accurate dose delivery for Prodose compared with HaloLite [7].

2.4 The AAD Disc™ technology

The main difference between the HaloLite and the Prodose AAD systems is that instead of using a factory-programmed

Figure 4. The I-neb AAD® system. Copyright of Profile Therapeutics, a Respironics company.
AAD: Adaptive Aerosol Delivery.

Figure 5. The Spacer AAD® system as a concept. Copyright of Profile Therapeutics, a Respironics company.
AAD: Adaptive Aerosol Delivery.

preset dose, Prodose utilises the AAD Disc™ (Profile Therapeutics) to control drug delivery. The AAD Disc is a plastic disc containing a microchip and an antenna, which, when inserted into Prodose instructs the device about the dosage, the dosing frequency, and the number of doses which may be delivered, together with various control data, including drug lot number and expiry date. The AAD Disc is programmed to a specific drug formulation, and can be packaged with the drug as part of the pharmaceutical packaging process.

The Prodose AAD system with the AAD Disc technology is presently approved in Europe for delivery of colistimethate sodium and iloprost.

2.5 The I-neb AAD® system

I-neb AAD system (**Figure 4**) is the third-generation AAD system, currently under joint development with Omron Healthcare (Kyoto, Japan). I-neb will be a device combining a new, proprietary vibrating mesh technology, and the AAD system with the AAD Disc technology. The third-generation 'intelligent' I-neb AAD system will be a small (150 × 65 × 45 mm), lightweight (210 g), virtually silent and fast drug delivery device that is designed to significantly reduce the inconvenience of conventional nebuliser/compressor therapy, while delivering a precise, reproducible dose. I-neb can deliver a preset volume in the range 0.25 – 1.4 ml depending on the size of the I-neb metering chamber, which has a residual volume of ~ 0.1 ml. The vibrating mesh has a variable power range for the optimisation of the aerosol output. The previous generations of the AAD systems have incorporated audible patient feedback at the end of a completed treatment. I-neb will include continuous feedback on the device functions through the liquid crystal display, along with tactile patient feedback at the end of a completed treatment. The I-neb AAD system will include the AAD algorithm used in the Prodose AAD system. New algorithms that will guide the patient to a slow and deep inspiration could also be included (target inhalation mode; see Section 6). The I-neb AAD system will be available in Europe from early 2005.

2.6 The Spacer AAD® system

The Spacer AAD system (**Figure 5**) is applicable to, for example, pressurised metered-dose inhalers with valved holding chambers (pMDI VHC). The incorrect use of a pMDI VHC can lead to a large variability in the delivered dose. Creaming and/or sedimentation of the drug within the pMDI, the sedimentation of drug within the VHC and the efficiency of the facemask seal will determine the delivered dose. The Spacer AAD system is based on an algorithm which takes into account the creaming and/or sedimentation within the pMDI and the sedimentation in the VHC. Patient feedback on delivered dose will guide the patient or parent in achieving a facemask seal against the face and to deliver the correct dose. The device is under development.

3. *In vitro* results

The *in vitro* performance of the AAD systems has been extensively investigated. As the AAD systems are breath-actuated, a breathing simulator (MiMiC Breathing Emulator, Profile Therapeutics) was developed for simulation of different human breathing patterns [2,8,9]. In the following section, the main results from some of the *in vitro* studies are reviewed.

3.1 Impact of pulse time

The early *in vitro* studies performed with the HaloLite AAD system showed a linear relationship between drug delivery and pulse times, in the range 0.1 – 1.0 s [6]. The linear relationship was important for accurate drug delivery of the preset dose. The particle size was also measured for pulse times in the range 0.1 – 1.0 s. The results showed that ~ 80% of the output was in particles < 5 µm in diameter, irrespective of pulse time [6].

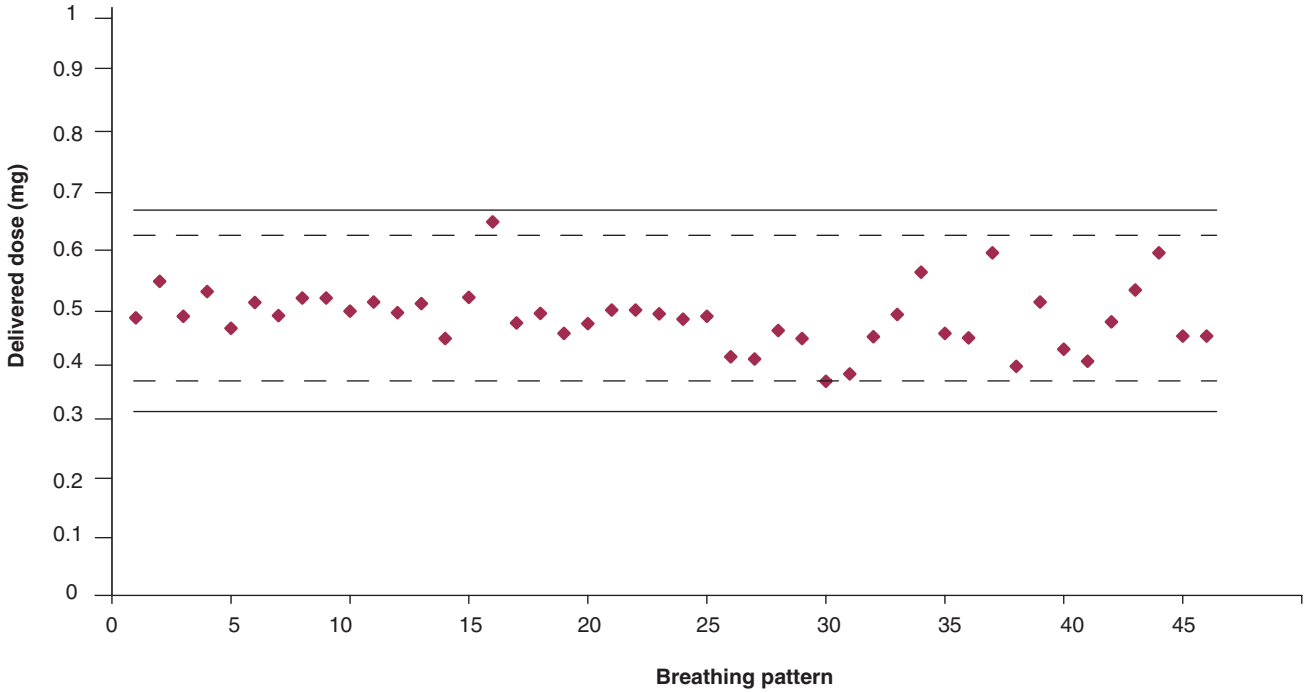

Figure 6. The mean delivered dose of salbutamol has been plotted against 46 simulated adolescent and adult breathing patterns, which were used for the test of the Prodose™ AAD system. The dashed lines represent ± 25% and the solid lines ± 35% of the nominal dose.
AAD: Adaptive Aerosol Delivery.

3.2 Drug delivery

The HaloLite AAD system targets aerosol delivery into the first 50% of a patient's inhalation, and is designed to deliver a preset dose of 0.25 ml/actuation. In order to test the accuracy of the preset dose, 50 adult/adolescent/paediatric breathing patterns (tidal volume [V_T] 0.1 – 1.24 l, peak inspiratory flow [PIF] 9 – 89 l/min, inspiration:expiration [I:E] ratio 1:0.6 – 1:1.97) were selected to be used on the MiMiC Breathing Emulator [2,10]. The mean delivered dose was 97% (0.244 ml) of the preset dose with a coefficient of variation (CV) of 17%, and with 92% of doses within ± 25% of the nominal dose.

The Prodose AAD system has been tested in a similar test set-up [7]. A total of 46 'real life' adult/adolescent breathing patterns (V_T 0.24 – 1.24 l, PIF 18 – 89 l/min, I:E ratio 1:0.6 – 1:1.97) were selected. The mean amount of marker on the filters was equal to a liquid volume of 0.243 ml (s.d. ± 0.026), with 98% of the doses delivered within 0.25 ml ± 25% (**Figure 6**). The mean treatment time was 264 s. The results for Prodose are similar to those for HaloLite, but the mean treatment time was somewhat shorter (i.e., 264 versus 293 s). Thus, Prodose delivers a preprogrammed dose consistently across a wide range of human breathing patterns in a shorter treatment time than HaloLite.

3.3 Flexible dosing

The AAD Disc is an important feature of the new Prodose AAD system. The accuracy of Prodose to deliver an accurate amount of drug was tested using five AAD Discs [11]. The five AAD Discs were programmed to deliver 35, 56, 250, 500 and 625 µl volumes of salbutamol (2 mg/ml). In the test set-up, Prodose was connected to a breathing simulator, a AAD Disc was fitted to Prodose, and the device was activated. The mean delivered volumes of salbutamol were 37, 61, 263, 547 and 686 µl, respectively. The highly linear results (r^2 = 0.9998; **Figure 7**) showed that the AAD Disc can be programmed with

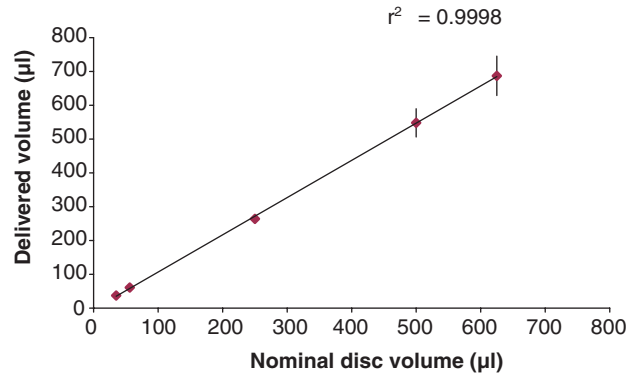

Figure 7. The mean delivered volume of salbutamol has been plotted against the programmed (AAD Disc™) volume of salbutamol. The Prodose™ AAD® system was used in the study.
AAD: Adaptive Aerosol Delivery.

different dosages of drug, which the Prodose AAD system can deliver accurately during inhalation.

In conclusion, these *in vitro* studies have shown that the AAD systems can deliver a range of doses of drug reproducibly within different patient breathing patterns.

4. Adaptive Aerosol Delivery systems in clinical studies

Some of the AAD systems have been included in clinical studies of lung deposition, adherence and compliance, and clinical efficacy and safety. In the following section, the main results from these studies will be reviewed.

4.1 Lung deposition

The HaloLite AAD system was used in a study designed to determine the delivered dose, lung deposition and exhaled dose of ^{99m}Tc–DTPA in 10 adult asthmatic patients and 9 adult healthy subjects [12]. HaloLite was filled with 2.5 ml of radiolabelled saline, and was preset to deliver 315 mg of aerosol. Lung deposition was measured using a gamma camera. The results showed a mean delivered dose of 315 mg (s.d. ± 50 mg, CV 17%), a mean whole lung deposition of 60% of the preset dose, and a mean exhaled fraction of ~ 3%. There was no significant difference in the drug distribution profile between the asthmatic patients and the healthy subjects.

One Australian and three British research groups have compared the HaloLite AAD system with active venturi jet nebulisers in terms of lung deposition. Devadason *et al.* [13] determined the lung deposition of radiolabelled recombinant human DNase in 15 children with cystic fibrosis (CF) aged 3 – 16 years, using, HaloLite and a conventional active venturi jet nebuliser (Pari LC Plus®, Pari Medical Ltd, UK). The fill volumes were 1.25 mg/1.25 ml with HaloLite, and 2.5 mg/2.5 ml with Pari LC Plus. The results showed a significantly higher peripheral lung deposition with HaloLite compared with the Pari LC Plus nebuliser (right lung $p = 0.015$, left lung $p = 0.040$). The mean lung deposition was 115.3 µg (s.d. ± 47.2) for each actuation with HaloLite and 230.2 µg (s.d. ± 103) with Pari LC Plus. The lung dose in 7 children after two actuations of HaloLite was 246.5 µg (s.d. ± 72.4). There was no drug lost to environment with HaloLite, whereas a mean of 600 µg was lost with Pari LC Plus.

Byrne *et al.* [14] compared the HaloLite AAD system with the Pari LC Plus nebuliser in terms of lung deposition of colistin in 15 CF patients > 6 years of age. A standard 1 mega unit of colistin in a 3 ml diluent – labelled with ^{99m}Tc-DTPA – was used to measure the lung deposition. The Pari LC Plus nebuliser was run to dryness and HaloLite was used with a single dose. The patients inhaled colistin twice-daily for 7 days with both devices. As a smaller amount of colistin was delivered with HaloLite due to the single dose strategy, the total lung dose of radiolabelled colistin was significantly higher with Pari LC Plus (2.96 MBq versus 9.0 MBq; $p < 0.0001$). The lung dose was, however, significantly higher for HaloLite when calculated as a percentage of the amount of drug used (30.79 versus 19.75%; $p < 0.04$).

Kastelik *et al.* [15] compared the HaloLite AAD system with the Pari LC Plus nebuliser in terms of lung deposition in a scintigraphy study in 10 healthy adult subjects and 6 adult CF patients. Lung deposition of the ^{99m}Tc–DTPA radiolabelled aerosol was measured using planar scintigraphy. HaloLite delivered, on average, 2.1 times ($p = 0.003$) as much aerosol to the lungs as Pari LC Plus. Aerosol deposition with HaloLite had higher central distribution than that obtained with Pari LC Plus. Two subjects had higher lung deposition from Pari LC Plus than from HaloLite. There was marked inter-individual variation in the lung deposition pattern in the CF patients. The overall inter-subject variability of the delivered dose was 56% with Pari LC Plus and 24% with HaloLite ($p < 0.05$).

Coldham *et al.* [16] recently presented a lung deposition study comparing the Prodose AAD system with the Pari LC Plus nebuliser in 8 adult patients diagnosed with CF. The nebulisers were charged with 150 MBq of ^{99m}Tc–DTPA in 3 ml of saline and the nebulisation time was 6 min. γ-Scintigraphy was performed immediately after nebulisation. Anterior and posterior images of the lungs were taken simultaneously, after which images of the nebuliser chambers, mouthpieces and exhalation filters were taken. The mean total dose delivered to the lungs was 3.31% with Pari LC Plus and 5.12% with Prodose. The mean amounts deposited in the mouthpieces and exhalation filters were ~ 38 and 4%, respectively. The mean residual volumes were 59.6 and 84.5% with Pari LC Plus and Prodose, respectively. The images showed a greater lung deposition for Prodose, but with a higher level of radiation in the stomach and central airways than with the Pari LC Plus (data on file).

The results of these studies show consistently that the lung deposition achieved with the AAD systems tested was superior to that of conventional active venturi jet nebulisers. This means that when switching a patient from a conventional nebuliser to an AAD system, the clinician should consider the dosage of the drug used. The results also highlighted how efficiently the pulsed aerosol delivery minimised the amount of drug released to the environment during nebulisation. This is, however, not the case with conventional nebulisers, which may expose those caring for the patient to the risk of inadvertent topical or inhaled drug exposure.

4.2 Adherence and compliance

Adherence to treatment and compliance with the nebuliser used are some of the keystones in successful domiciliary nebuliser therapy. The HaloLite AAD system supplied with a patient logging system (see Section 6) was used in a 4-week, open-label, multi-centre study assessing adherence to treatment and compliance with HaloLite [17]. A total of 121 patients with asthma, COPD and emphysema, who used HaloLite for the administration of salbutamol or terbutaline and/or budesonide, completed the study. Of the patients, 38% also continued to take another nebulised

medication using their standard conventional nebuliser. The adherence was 51% for patients using only HaloLite, and 30% for patients using HaloLite and another nebuliser. A total of 4801 treatments were recorded with HaloLite, and in 96% of these the patients took their preset doses of drug. The co-efficient of correlation between the total number of treatments and the dose received over the study period was 1.00 ($p < 0.001$) for HaloLite and 0.67 ($p < 0.001$) for the patients' standard nebuliser.

The HaloLite Paediatric AAD system has been compared with a pMDI and a valved holding chamber (pMDI VHC, Aerochamber, Trudell Medical, London, ON Canada) in terms of drug delivery, adherence to treatment, compliance with device, true adherence, and acceptability [18]. A total of 14 children aged 11 – 36 months, diagnosed with asthma and on regular treatment with inhaled corticosteroids, were enrolled into an open-label, randomised, crossover study. They received budesonide for 2 weeks with each delivery system. The HaloLite Paediatric device was supplied with a patient logging system (see Section 5), whereas the pMDI VHC incorporated a data-logger, which recorded information on how the device was used. HaloLite Paediatric was preset to deliver budesonide 25 µg to the patient. A single actuation of budesonide 200 µg was used with the pMDI VHC. The median delivered dose of budesonide was 36 µg (range: 31 – 45 µg; CV 15%) with HaloLite Paediatric and 53 µg (range: 17 – 85 µg; CV 47%) with the pMDI VHC. The median adherence was 68% (range: 11 – 96%) with HaloLite Paediatric and 71% (range: 11 – 100%) with the pMDI VHC. The median device compliance was 30 and 51%, and the median true adherence was 23 and 36%, respectively. The size of the HaloLite Paediatric was generally less acceptable than the size of the pMDI VHC with a data-logger.

The first long-term proof of concept study of the use of the AAD system in children was performed in 10 centres throughout Spain with a modified active venturi Ventstream jet nebuliser (Profile Therapeutics), which incorporated an AAD system [19]. The study was of a 24-week, double-blind, randomised, parallel-group design, with budesonide inhalation suspension delivered twice-daily by parents to 125 young children with mild-to-moderate asthma. Data on the parents' adherence to their child's prescribed nebuliser treatment regimen and compliance with the demands of the nebuliser, the face mask and the AAD system, was recorded through a prototype patient logging system [20]. A total of 35,481 treatments were recorded and analysed together with a study questionnaire regarding the parents' and childrens' acceptance of the AAD system. The adherence to the treatment regimen was 91.3% and the compliance with the AAD system was 90.4%. True adherence, the product of adherence and compliance, was 82.5%. Approximately 90% of the parents found the face mask easy to seal and the equipment easy to use, and > 90% of the children accepted it within 1 week. These results show that the AAD system could be of real clinical advantage for delivery of reproducible doses of drug to young children.

The results of the studies indicate that the level of adherence to treatment and compliance with the AAD system was relatively high. The high level of true adherence indicates that when a patient had started the treatment, the procedure was followed until the feedback system indicated completed drug delivery. This positive effect of the AAD system on adherence/compliance over the conventional nebuliser is supported by the results of a study conducted in CF (see Section 4.4). It is, however, difficult to put these results fully into context as there is little comparable information published on conventional nebulisers as these lack the features required to collect the necessary data.

4.3 Asthma

In the above described paediatric 24-week double-blind, randomised, parallel-group study, budesonide inhalation suspension was delivered with the AAD system to 125 young children with mild-to-moderate asthma [19]. The initial delivered dose was 100 µg b.i.d. and the maintenance delivered dose was 25 µg b.i.d. These doses were delivered in an initial:maintenance ratio of 2:22, 6:18 or 12:12 weeks. There was a clear improvement in the overall health score as assessed by a visual analogue scale with all three treatment regimens and a marked reduction in daytime and night time asthma symptom scores (range: 0 – 3), but no statistically-significant differences between the treatment regimens (**Figure 8**). The incidence of oral candida was low throughout the study, indicating low drug deposition into the upper airways. Improvements in the mean daytime asthma score for the different treatment regimens averaged ~ 1.0 (2:22), 0.8 (6:18) and 0.9 (12:12). It is difficult to evaluate the clinical impact of the changes in symptom scores as the ethics committees did not approve of the inclusion of a placebo group in the study. One can, however, compare the magnitude of change with those of a paediatric, 12-week, double-blind, randomised, parallel-group study with budesonide inhalation suspension delivered with the Pari LC Plus nebuliser to 480 young children with moderate persistent asthma, performed in 38 centres throughout the US [21]. Patients in this study were started on one of five treatment regimens receiving either placebo, or budesonide in nominal doses of 0.25 mg/q.d., 0.25 mg b.i.d., 0.5 mg b.i.d. or 1.0 mg q.d. Both day and night-time asthma symptom scores were recorded on a diary card (range: 0 – 3). The improvements in the mean daytime asthma symptom score for the different treatment regimens averaged 0.19 (placebo), 0.28 (0.25 mg q.d.), 0.4 (0.25 mg b.i.d.), 0.46 (0.5 mg b.i.d.) and 0.37 (1.0 mg q.d.). The difference in improvement of the symptoms scores in the two studies is remarkable. Assuming a lung deposition of 5 – 10% of the nominal doses in the study by Baker *et al.* [21], the relevant lung doses of budesonide should have been 12 – 25 µg (0.25 mg q.d.) to 50 - 100 µg (1.0 mg q.d.). Thus, the lung doses of budesonide should have been comparable to those of the Spanish study. The differences in improvement could only be related to the type of patients included, to the parents' appreciation of the child's asthma status, and to the drug delivery systems used. As the delivery sys-

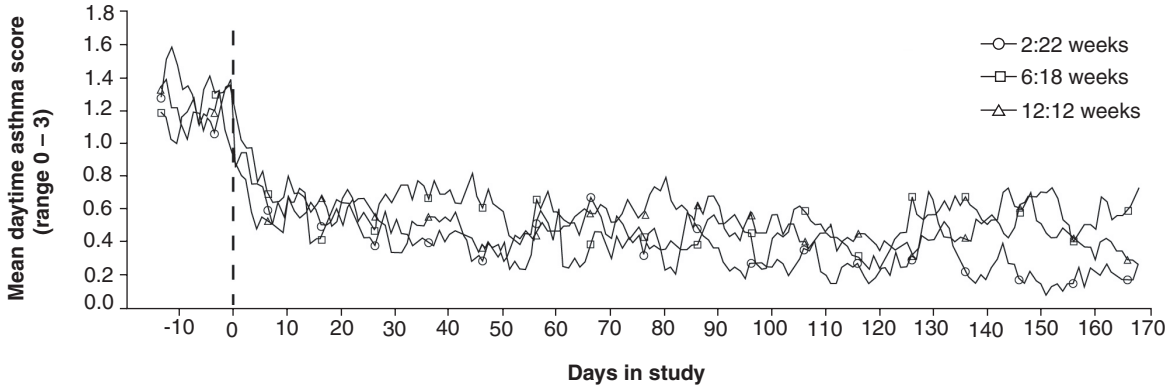

Figure 8. Mean daytime asthma score over 24 weeks for three groups of children who received nebulised budesonide in an initial:maintenance ratio of 2:22, 6:18 or 12:12 weeks. The initial delivered dose was 100 µg b.i.d. and the maintenance delivered dose was 25 µg b.i.d. Reproduced with kind permission from *Respiratory Disease in Practice* and AstraZeneca, Lund, Sweden.

tem was the most significant difference between the studies, the results indicate that the AAD system might play an important role in the treatment of young children with asthma, and that the device is effective and safe for long-term delivery of budesonide inhalation suspension to young children.

4.4 Cystic fibrosis

The performance of the HaloLite AAD system was compared with that of conventional jet nebulisers in a 6-month, multicentre, randomised, open-label study in 259 patients with CF using nebulised antibiotics for the management of pulmonary infections with *Pseudomonas aeruginosa* [22]. During the study the patients were maintained on the same treatment that they had used prior to enrolment. Study end points were change in pulmonary function, adherence to treatment, compliance with the nebuliser used, true adherence, and response to a study questionnaire regarding any preferences for the HaloLite AAD system compared with the patients' original nebulisers. Of the 259 patients, 133 were randomised to HaloLite and 126 to conventional nebuliser usage. The results showed no statistically significant differences in pulmonary function between the groups. A total of 30 patients using HaloLite and 20 patients using conventional nebulisers provided data for evaluation of adherence and compliance. The mean adherence to treatment was 62% for patients using HaloLite and 47% for patients using conventional nebulisers. The mean compliance was 84% for patients using HaloLite and 43% for patients using conventional nebulisers. These differences were not statistically different. The difference in true adherence was, however, statistically significantly different in favour of HaloLite ($p = 0.006$) (**Figure 9**). The questionnaire showed that there was a statistically significant ($p < 0.0001$) preference for the HaloLite AAD system compared with the patients' original nebulisers. An unplanned subgroup analysis of patients using the study devices for inhalation of both

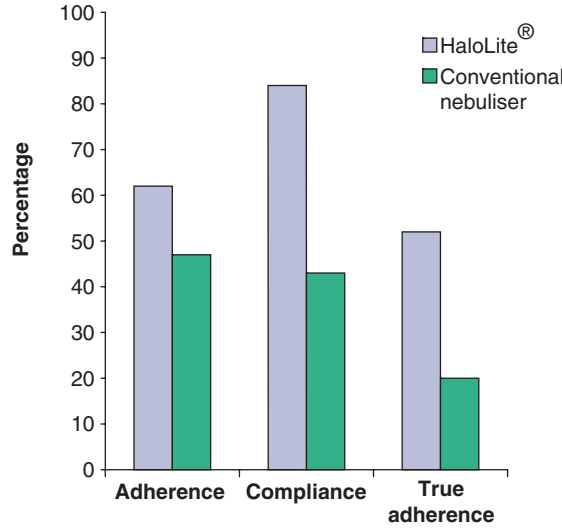

Figure 9. The mean adherence to treatment, compliance with device and true adherence recorded for 30 patients using the HaloLite® AAD® system, and for 20 patients using conventional nebulisers.
AAD: Adaptive Aerosol Delivery.

anti-biotics and bronchodilators showed an increased effect in FEV_1 (forced expiratory volume in 1 s) for patients using HaloLite [23]. This interaction between device and bronchodilator was statistically significant ($p = 0.001$) (**Figure 10**). The results indicated that in the treatment of patients with CF, the HaloLite AAD system is as effective and safe as conventional jet nebulisers in terms of pulmonary function, but superior in terms of true adherence.

4.5 Pulmonary hypertension

The HaloLite AAD system has been compared with Ilo-Neb/Aerotrap (Nebu-Tec, Germany) and Ventstream jet

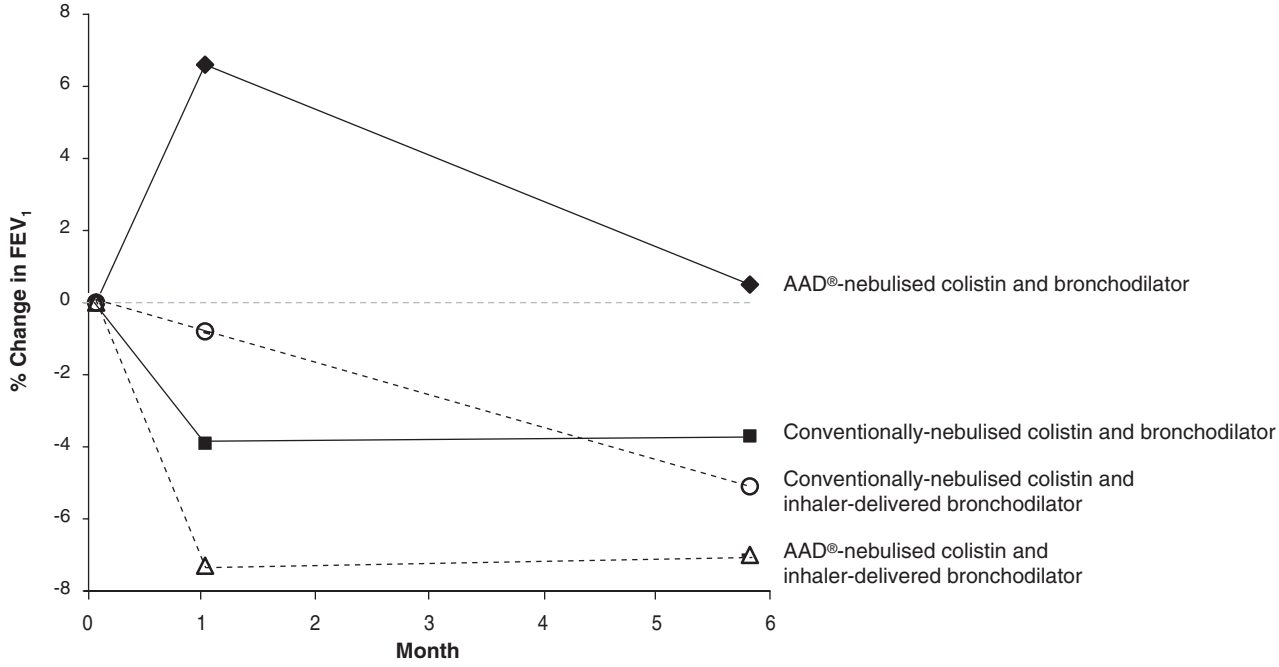

Figure 10. The change in FEV_1 has been presented for 189 patients participating in the cystic fibrosis study. The patients used the HaloLite® AAD® system or conventional nebulisers. The division into subgroups was made depending on which device the patients used for administration of the antibiotic and the bronchodilator.
AAD: Adaptive Aerosol Delivery; FEV_1: Forced expiratory volume in 1 s.

nebulisers in patients with severe pulmonary hypertension [24]. The study end points were arterial iloprost plasma levels and hemodynamic effects. The concentration and volume fill of iloprost was adjusted for each device to deliver a 5 µg dose of iloprost at the mouthpiece during ~ 10 min nebulisation. The standardised dose of iloprost was inhaled from each nebuliser by 12 patients in a crossover study design. During inhalation of iloprost, both the pulmonary vascular resistance and pulmonary arterial pressure decreased substantially, whereas the systemic arterial pressure was largely unaffected. Cardiac output, and mixed venous and arterial oxygen saturation increased. The pharmacodynamic profiles with the three devices were superimposable. Iloprost entered the systemic circulation rapidly and peaked immediately after termination of nebulisation, with similar maximum serum concentrations (158, 155 and 157 pg/ml), and half-lifes of serum levels (6.5, 9.4 and 7.7 min) for the three nebulisers, respectively. The results indicated that HaloLite was as efficient as the other two jet nebulisers in the delivery of aerosolised iloprost to patients with severe pulmonary hypertension. To adjust the conventional nebuliser to deliver iloprost 5 µg at the mouthpiece would be quite a problem in clinical practice. The delivery of a preset dose is, however, one of the main functions of an AAD system, such as HaloLite.

The HaloLite AAD system was selected as the device of choice in a large, European, 12-week, randomised, parallel-group, multi-centre study including patients with selected forms of severe pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension [25]. The study compared repeated daily inhalations of either iloprost 2.5 or 5.0 µg – administered either six- or nine-times daily with a median inhaled dose of 30 µg/day – or placebo. Iloprost or placebo was diluted with saline to a concentration of 10 µg/ml, and HaloLite was charged with a 2 ml volume fill. The geometric median aerodynamic diameter of the particles was 4.3 µm. A total of 203 patients were included. The primary end point was met if the New York Heart Association (NYHA) functional class and distance walked in 6 min were improved by at least one class and at least 10%, respectively, in the absence of clinical deterioration. The combined clinical end point was met by 16.8% in the iloprost group compared with 4.9% in the placebo group ($p = 0.007$). The distance walked in 6 min increased by 36.4 m in the iloprost group as a whole ($p = 0.004$) and by 58.8 m in the subgroup with primary pulmonary hypertension. Hemodynamic values improved significantly at 12 weeks after iloprost inhalations ($p < 0.001$), were largely unchanged before iloprost inhalations, and were significantly worse in the placebo group. There were improvements in the NYHA class ($p = 0.03$), dyspnoea ($p = 0.015$), and quality of life ($p = 0.026$).

Inhalation of iloprost with HaloLite and Prodose, for the treatment of primary pulmonary hypertension (PPH), was recently approved in Europe.

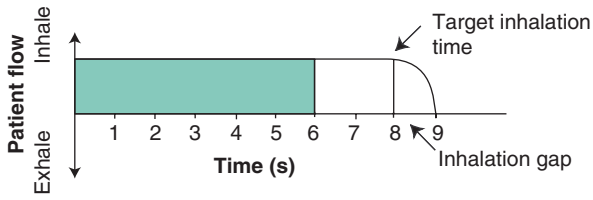

Figure 11. A schematic diagram of a slow and deep inhalation, the 'target inhalation mode', provided by the new I-neb AAD® system. The aerosol is pulsed into the first 6 s of the 8 s target inhalation mode, after which a tactile feedback informs the patients that they can stop the inhalation of the aerosol. The inhalation gap represents the patient's reaction time in response to the feedback.
AAD: Adaptive Aerosol Delivery.

5. Conclusion

The AAD system is the first commercialised technology that adapts the timing and volume of aerosol delivery to match the patient's breathing pattern. The *in vitro* evidence suggests that the AAD system can deliver relatively precise and reproducible doses of aerosol. The clinical evidence indicates that the AAD systems are superior to conventional active venturi jet nebulisers in terms of lung deposition and true adherence. The AAD systems have been successfully used in relatively large clinical studies involving patients with asthma, CF and pulmonary hypertension.

The Prodose AAD system with the AAD Disc technology is approved in Europe for delivery of colistimethate sodium, and the HaloLite and Prodose AAD systems are approved for delivery of iloprost. The new small and portable I-neb AAD system will be available shortly.

6. Expert opinion

Future developments of the AAD system could include features that guide the patient in how to inhale the aerosol for optimised drug delivery and lung deposition, enable the patient to follow the progress of the disease, and provide healthcare professionals with the tools to monitor the progression of the patient's status, adherence and compliance on a daily basis.

6.1 The 'target inhalation mode'

The potential of slow deep breathing to increase lung deposition of aerosol was recently presented [26]. A total of 11 healthy volunteers inhaled radiolabelled aerosol using three different breathing manoeuvres, including tidal breathing, tidal breathing with inhalation flow restricted to 15 l/min, and inhalation of ≤ 80% of inspiratory capacity with a controlled flow rate of 15 l/min. The results showed that an inspiratory flow restriction aided total lung deposition (TLD), and that a TLD of > 50% required an inhalation volume of > 1 l and an aerosol residence time in the lung of > 5 s.

Subsequent research has shown the potential of a new mode of operation of the AAD system that will enable patients to achieve shorter treatment times [27]. A total of 20 patients diagnosed with COPD were included in an open-label clinical study designed to evaluate the acceptability of successively increasing the length of each inhalation through a prototype I-neb AAD system. The device limited the patients' maximal inspiratory flow rate to ~ 15 l/min to achieve a slow and deep inhalation – a 'target inhalation mode'. **Figure 11** shows a schematic representation of the target inhalation mode, in which the aerosol is pulsed during 6 s followed by a 2 s sedimentation time. The total inhalation time in this example is slightly > 8 s. The results showed that treatment times dropped by an average of 58% over the course of the treatments. The patients found the target inhalation mode to be easy to understand and learned the manoeuvre over the course of 3 – 6 treatments.

The target inhalation mode also has the potential to increase lung deposition, as it might enable larger particles to enter the airways. The lung deposition should be enhanced due to the 2 s long sedimentation time at the end of the aerosol pulse.

6.2 The 'patient logging system'

The AAD systems have been developed with the capability to incorporate a memory chip in the handpiece, which would support a 'patient logging system' (PLS) that could record the date and times of the treatments, and the delivered dose of drug. This means that the PLS could monitor adherence to treatments, compliance with device, and true adherence. This kind of data could be valuable in the follow-up of the individual patient started on a new drug delivered by an AAD system as lack of response may indicate the need for dose adjustment, but more often reflects poor adherence and compliance. The PLS has already been used in exploratory clinical studies.

6.3 E-health

The E-health capability of the AAD system has already been investigated in terms of data management and monitoring of patient adherence and compliance [28]. An e-health enabled AAD system was provided to 20 patients diagnosed with CF for 1 month. The system allowed automatic reordering and delivery of medication direct to the patient's home, as well as allowing remote collection of PLS data on patient adherence and compliance. Average adherence to regimen was 89% and compliance with device was 90%. Patients preferred the home delivery of medication over pharmacy collection of medication. Future e-health capable AAD systems may include FEV_1 monitoring capability, direct mobile communication to a central call centre, and internet support for healthcare professionals to access disease state indicators. This could allow physicians to access up-to-date information on adherence and compliance, which may be of use when considering the reasons for non-response to therapy by excluding lack of adherence or compliance as causes. It could also allow healthcare professionals to keep track of the progress of their patients and

could flag patients whose pulmonary function is in decline, possibly allowing preventative intervention before an exacerbation. Finally, it could also be used by expert patients who are able to manage their disease themselves, by allowing them to easily track their disease status and help them to determine when to take additional treatments.

6.4 Summary of expert opinion

The new, small and portable I-neb AAD system will be available shortly. Features such as accurate dosing, enhanced lung deposition through the target inhalation mode, patient monitoring via PLS and the e-health capability could create a platform for the delivery of potent drugs not presently delivered through inhalation. Due to its regulatory approval, the I-neb AAD system could offer a rapid route to market for drugs requiring doses in excess of 10 mg, which could not easily be delivered by conventional multi-dose systems, but which could be a suitable delivery system for drugs with a narrow therapeutic window or for drugs associated with severe systemic adverse effects. Lung transplantation is an example of one such application in which it is desirable to confine the action of immunosuppressive drugs to the locality of the lung, to reduce the risk of rejection while reducing the systemic effects. Other diseases of the lung that would require an accurate, well controlled intrapulmonary administration of drug include chronic lung infections, COPD, hereditary emphysema, lung cancer, pulmonary hypertension and idiopathic pulmonary fibrosis. Systemic diseases in which efficient drug delivery through the lungs can enhance patient adherence to treatment and produce a rapid onset of action include diabetes, breakthrough pain and thromboembolic diseases.

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