The Adaptive Aerosol Delivery (AAD) Technology: Past, Present, and Future

John Denyer, B.Sc. and Tony Dyche, B.Sc.

Abstract

Conventional aerosol delivery systems and the availability of new technologies have led to the development of “intelligent” nebulizers such as the I-neb Adaptive Aerosol Delivery (AAD) System. Based on the AAD technology, the I-neb AAD System has been designed to continuously adapt to changes in the patient’s breathing pattern, and to pulse aerosol only during the inspiratory part of the breathing cycle. This eliminates waste of aerosol during exhalation, and creates a foundation for precise aerosol (dose) delivery. To facilitate the delivery of precise metered doses of aerosol to the patient, a unique metering chamber design has been developed. Through the vibrating mesh technology, the metering chamber design, and the AAD Disc function, the aerosol output rate and metered (delivered) dose can be tailored to the demands of the specific drug to be delivered. In the I-neb AAD System, aerosol delivery is guided through two algorithms, one for the Tidal Breathing Mode (TBM), and one for slow and deep inhalations, the Target Inhalation Mode (TIM). The aim of TIM is to reduce the treatment time by increasing the total inhalation time per minute, and to increase lung deposition by reducing impaction in the upper airways through slow and deep inhalations. A key feature of the AAD technology is the patient feedback mechanisms that are provided to guide the patient on delivery performance. These feedback signals, which include visual, audible, and tactile forms, are configured in a feedback cascade that leads to a high level of compliance with the use of the I-neb AAD System. The I-neb Insight and the Patient Logging System facilitate a further degree of sophistication to the feedback mechanisms, by providing information on long term adherence and compliance data. These can be assessed by patients and clinicians via a Web-based delivery of information in the form of customized graphical analyses.

Key words: Adaptive Aerosol Delivery technology, Adaptive Aerosol Delivery System, AAD, I-neb AAD System, I-neb Insight, patient logging system

Introduction

THE CONVENTIONAL JET NEBULIZER powered by a compressor has been used for almost a century for delivery of inhaled drugs for the treatment of various respiratory disorders.⁽¹⁾ The nebulizer has become a well-established alternative to pressurized metered dose inhalers (pMDIs) and dry powder inhalers (DPIs), as it is ideal for delivery of high doses of drug, of drug mixtures, and of new drugs not formulated for pMDIs or DPIs.⁽²⁾ The drawback with conventional jet nebulizers has been the waste of drug mainly during exhalation, the large variability in the delivered dose depending on the patient’s breathing patterns, and the large residual with only 10 to 20% of the nebulizer fill volume delivered as aerosol to the patient. Recognition of the possibilities to improve

nebulized drug delivery by addressing some of these shortcomings led to the development of “intelligent” jet nebulizers based on Adaptive Aerosol Delivery (AAD) technology.⁽³⁾ The introduction of nebulizers based on the Vibrating Mesh Technology (VMT) has improved the efficiency of the aerosol delivery due to a smaller residual. These nebulizers do, however, still waste drug during exhalation due to continuous drug delivery without any adaptation to the patient’s breathing patterns.⁽⁴⁾ The latest iteration of the AAD technology, the I-neb AAD System, combines the mesh technology with the AAD technology.⁽⁵⁾

The AAD technology was first embodied in the HaloLite AAD System, which was codeveloped with Astra, Lund, Sweden, and made commercially available in 1997.⁽³⁾ The basic nebulizer technology in the HaloLite AAD System was

based on the Ventstream active venturi jet nebulizer technology. The AAD algorithm predicted the length of the patient's next inhalation based on the duration of the three previous inhalations, and delivered a pulse of aerosol into the first 50% of that inhalation. The HaloLite AAD System consisted of a battery-powered handpiece, including a mouthpiece, a medication chamber, an electronic control unit, and a compressor operated from mains electricity. The HaloLite AAD System was preset to deliver only 0.25 mL per preset dosage, and therefore, depending on the volume of drug in the vial used, a significant amount of drug remained as residual.

The Prodose AAD System was the second-generation AAD System, and was developed in conjunction with Schering AG (Bayer Schering Pharma AG, Berlin, Germany) for delivery of iloprost for treatment of pulmonary arterial hypertension, and launched in 2002.⁽³⁾ Although based on the same aerosol generation technology, it offered significant improvements in convenience and flexibility over the HaloLite AAD System. The Prodose AAD System consisted of a compressor connected to a self-powered handpiece fitted with a liquid crystal display. Improved versions of the AAD algorithms designed for the HaloLite AAD System were used, which allowed the pulse of aerosol to be extended beyond 50% in cases when the patient's inhalation exceeded 2 sec. The main difference between the HaloLite and the Prodose AAD Systems was that instead of using a factory-programmed preset dose handset, the Prodose AAD System was designed with the AAD Disc to control drug delivery and the AAD Disc could be supplied with the drug.

The I-neb AAD System is the third-generation AAD System, and is substantially smaller and lighter than the previous AAD System nebulizers (Table 1).⁽⁵⁾ The main parts of the I-neb AAD System (Fig. 1) are the body, the medication chamber assembly including the metering chamber, the mesh, and the mouthpiece. Due to the mesh design the I-neb AAD System is virtually silent.⁽⁵⁾ Built into the body are the microprocessor that runs the AAD algorithm, the electronic aerosol generation circuit, the piezo element connected to the horn, the pressure sensor, the LCD screen, the radio frequency antenna for the AAD Disc, the patient logging system (PLS), the infrared transmitter/receiver for I-neb Insight, the battery, buzzer, and the vibration device for the tactile feedback. The I-neb AAD System is approved as a general purpose nebulizer in the European Union, and for the delivery of drugs that are approved for use with the I-neb AAD System in the United States.⁽⁵⁾ For the purpose of this review of the AAD technology, the focus will be on the I-neb AAD System.

The AAD Algorithms

The I-neb AAD System can be operated in two breathing modes, the Tidal Breathing Mode (TBM; Fig. 2) and the

Target Inhalation Mode (TIM; Fig. 2).⁽⁵⁾ The breathing mode is selected by using a specific mouthpiece, which can be detected by the electronics in the I-neb AAD System (Fig. 1). In TBM, the patient breathes tidally through the mouthpiece, and this mode of inhalation is suitable for all patients who can use a mouthpiece. The results of a clinical study in which 52 patients with CF (age range 2–17 years) were transferred from jet nebulizers to the I-neb AAD System, indicate that patients as young as 2 years of age can use the mouthpiece.⁽⁶⁾ In TIM, the patient is guided through feedback to make a slow and deep inhalation, which is suitable for patients who can use a mouthpiece and comply with the demands of that breathing maneuver.

TBM

The aim of the AAD algorithm in TBM is to continuously predict the length of the patient's next inhalation. Based on this information a pulse of aerosol can be delivered at the beginning of the next inhalation and end after 50% of the predicted inhalation time has expired. The average length of the past three inhalations is used by the AAD algorithm for the prediction of the length of the next inhalation. This means that the I-neb AAD System will only deliver aerosol starting on the fourth breath of each new treatment. Thereafter, the average inhalation time is updated after each subsequent inhalation. The pulse time is continuously monitored and adjusted by the algorithm depending on variations in the patient's breathing pattern. In cases when the patient's inhalation exceeds 2 sec, the pulse time is extended beyond 50% of the predicted inhalation time and up to ~1 sec before the start of the predicted exhalation.

A combination of a pressure sensor and a flexible valve in the I-neb AAD System is used to monitor the patient's inspiratory flow pattern (Fig. 1). The valve has a known pressure to flow characteristic, which allows the pressure measurement to be transferred, via an analogue-to-digital converter, to the processor running the AAD software and interpreted as a flow measurement. A waveform analysis program is used to ensure that the I-neb AAD System can operate effectively with breathing patterns typical for children from ~2 years of age to adults.⁽⁷⁾ This ensures that the AAD algorithm remains sensitive for children without generating false triggers in adults. The waveform is monitored every 30 msec through the AAD software, which determines the slope of the curve over three consecutive 30 msec measurements (Fig. 2). A "positive" flow curve—two consecutive increases of at least 0.65 L/min—indicates that an inhalation is about to start. When the inspiratory flow rate is greater than 1.5 L/min the pulse of aerosol is triggered. Once an inhalation has started, the waveform is continuously monitored by the AAD software, to detect a "negative" slope—

TABLE 1. A TABLE COMPARING THE DIFFERENT FEATURES OF THE HALOLITE, PRODOSE, AND I-NEB AAD SYSTEMS

	Year of launch	Size (cm; h×w×d)	Weight (g)	Power (W)	Voltage (V)	AAD TBM	PLS	AAD Disc	AAD TIM
HaloLite	1997	14×29×18	2700	200	240 AC	✓	✓		
Prodose	2002	18×14×29	3190	200	240 AC	✓	✓	✓	
I-neb	2004	15×6.5×4.5	210	6	3.8 DC	✓	✓	✓	✓

AAD, Adaptive Aerosol Delivery; PLS, patient logging system; TBM, Tidal Breathing Mode; TIM, Target Inhalation Mode.

FIG. 1. The I-neb Adaptive Aerosol Delivery (AAD) System. The main components of the device are the mouthpiece, the medication chamber assembly, and the body. The I-neb AAD System has been designed to deliver aerosol with two different breathing pattern algorithms, the Tidal Breathing Mode (TBM) and the Target Inhalation Mode (TIM). In TIM the inspiratory flow through the valve in the mouthpiece is limited to ~20 L/min.

two consecutive decreases of at least 0.65 L/min—which would indicate the start of an exhalation. Once the flow reaches zero, the AAD software identifies this point as the end of inhalation. The analysis performed by the AAD software facilitates both an accurate triggering of the aerosol pulse, and the measurement of the inhalation time, which is

used in a calculation of the moving average over three breaths to predict the next aerosol pulse time.

TIM

The main aim of the long and slow inhalation is to reduce nebulization time in comparison with the TBM breathing pattern as a result of the increase in the total inhalation time per minute of treatment.⁽⁵⁾ An improvement in lung deposition by reducing impaction in the upper airways is also achieved.⁽⁸⁾ The aim of the AAD algorithm in TIM is to provide the patient with an optimal target time for each slow and deep inhalation. The AAD algorithm is used in conjunction with a mouthpiece designed with a special inhalation valve to restrict the inspiratory flow to ~20 L/min (Fig. 1). The initial target inhalation time for the slow and deep inhalation is set at 3 sec, which is equivalent to an inhaled volume of ~0.75 L. When the target inhalation time is reached, a vibrator informs the patient to end the inhalation. For the duration of the initial 3 sec of inhalation, aerosol is delivered during the first 2 sec followed by inhalation of room air without aerosol during the remaining 1 sec. This is to ensure that the aerosol is inhaled deep into the lung and remains there long enough to be deposited and not exhaled.⁽⁸⁾ The AAD algorithm monitors the time “ ΔT ” between the vibrator signal and the moment when the patient stops inhaling (Fig. 2). During breathing, the inspiratory and

TABLE 2. A SUMMARY TABLE OF THE LEVEL OF COMPLIANCE WITH THE CORRECT USE OF AAD SYSTEM NEBULIZERS DOCUMENTED IN CLINICAL STUDIES

AAD System	Number of patients	Age range (years)	Compliance level (%)	Reference
AAD System prototype	125	<1–6	90%	14
HaloLite	121	<1–65	98%	15
AAD System	47	<1–3	81%	16
HaloLite ped	50	7–53	84%	17
AAD System	19	11–45	90%	18
Prodose	96	^a	96%	19
I-neb AAD System	70	53–80	95%	12
I-neb AAD System	42	12–57	97%	11

^aInformation not available.

FIG. 2. Graphical presentation of the two breathing patterns used with the I-neb Adaptive Aerosol Delivery (AAD) System. The first part of the graph shows the patient's tidal breathing when using the I-neb AAD System in Tidal Breathing Mode (TBM). The second, third, and last parts of the graph show the process to extend the patient's slow and deep inhalations from a 3-sec inhalation (1-sec aerosol pulse) to an 8-sec inhalation (7-sec aerosol pulse) when using the I-neb AAD System in Target Inhalation Mode (TIM). The magnified area above to the left shows how the waveform is monitored every 30 msec through the AAD software, which determines the slope of the curve over three consecutive 30-msec measurements. Two consecutive increases of at least 0.65 L/min indicate that an inhalation is about to start, and when the inspiratory flow rate >1.5 L/min the pulse of aerosol is triggered. The magnified area above to the right shows the end of the inhalation during TIM. The ΔT time provides a measurement of when the patient has reached his or her instantaneous residual lung capacity, and allows the AAD algorithm to increase or decrease the length of the target inhalation time.

expiratory maneuvers are driven by different muscle groups. The inspiratory muscles are working against the flow restriction of the mouthpiece and if the lung is only partially inflated, it takes longer for the muscles to relax so that exhalation can start than it would if the lung was initially fully inflated.⁽⁹⁾ Thus, the change from inhalation to exhalation is slower for a partially inflated lung than for a fully inflated lung. The ΔT time provides a measurement of when the

patient has reached the instantaneous residual lung capacity, and allows the AAD algorithm to increase or decrease the length of the target inhalation time. The aim is to optimize the length of the target inhalation time to approximately 80% of the patient's forced vital capacity (FVC). Once the optimal target inhalation time has been set, the algorithm will adjust it to meet the patient's effort on each inhalation. At the end of the treatment, the achieved length of the target inhalation

time is filed in the memory for subsequent treatments. However, as the initial target inhalation time of 3 sec requires an inhaled volume of ~ 0.75 L, the patient should have an FVC ≥ 1.75 L to manage the slow and deep inhalation maneuver.⁽¹⁰⁾ These requirements might make the use of the I-neb AAD System in TIM challenging for children, and for patients with poor lung capacity as these will not generate a significant ΔT .

Clinical experience with TBM and TIM

The I-neb AAD System is presently used in the treatment of patients with cystic fibrosis (CF), and pulmonary arterial hypertension.⁽⁵⁾ A number of clinical studies have been performed to evaluate the I-neb AAD System in terms of patient acceptability and lung deposition.

The acceptability of the TIM breathing maneuver has been evaluated in 20 patients with CF during up to eight simulated nebulizer treatments with 10 min pauses between the treatments.⁽¹⁰⁾ The study design involved lengthening of the patient's inhalation time over successive breaths with guidance from auditory and tactile (vibratory) feedback from the prototype I-neb AAD System. At the end of the first treatment, most patients felt that the instructions were easy to understand (90%) and that the vibratory feedback was pleasant (65%). Half of the patients found the procedure to be comfortable. At the end of the final treatment, most patients felt that the breathing maneuver was easy to understand (90%) and use (80%), but that the duration of the breath was too long (100%). Logged data revealed that 90% of patients were able to comply with the breathing maneuver. The two patients unable to comply had a forced vital capacity of <1.75 L. The average treatment time decreased from 288.4 to 141.6 sec during the first and final treatments, respectively. This study provided preliminary evidence of the acceptability of the TIM breathing maneuver in patients with CF and their ability to perform repeated TIM maneuvers during simulated nebulizer therapy with the I-neb AAD System.

A 3-month patient handling study of the I-neb AAD System in 42 patients with CF aged 12–57 years has been performed with the aim to evaluate compliance with the correct use of the I-neb AAD System, and treatment times.⁽¹¹⁾ The secondary variables included ease of use with the I-neb AAD System based on a questionnaire at the end of the study. The I-neb AAD System was supplied in both TBM and in TIM, and the patients were trained to use the TIM maneuver for the delivery of all their inhaled medications. If they were not comfortable with the TIM maneuver they could change to the TBM maneuver. There were a total of 10,240 complete treatments and of these 88% were in TIM. Compliance with the correct use of the I-neb AAD System was 97.6%. The mean treatment time for complete treatments in TIM was 4.20 min, compared with 6.83 min when using the I-neb AAD System in TBM. The responses to the questionnaires indicated that over 77% of the patients found the I-neb AAD System in TIM to be either: very easy, easy, or acceptable to use.

The I-neb AAD System in TBM has been compared with the patients' previous nebulizers in a multicenter study with 98 patients with chronic obstructive pulmonary disease aged 53 to 80 years.⁽¹²⁾ The primary variables were ease of use and

satisfaction assessed after 3 months of use of the I-neb AAD System (assessed at visit 2) and after 3 months of use of the patient's previous nebulizer system (assessed at visit 1) using matched questions from pre- and poststudy questionnaires. Quality of life was also assessed at visits 1 and 2 using a validated Chronic Respiratory Questionnaire (CRQ), which consists of dyspnea, emotional function, fatigue, and mastery domains. Patient responses on the ease of use and satisfaction questions significantly ($p \leq 0.001$) favored the I-neb AAD System compared with the patient's previous nebulizer system. In addition, significant ($p \leq 0.015$) improvements in the CRQ dimensions of dyspnea and fatigue were reported with the I-neb AAD System compared with the patients' previous nebulizer systems.

The lung deposition of a radiolabeled aerosol from the I-neb AAD System with TBM and TIM breathing patterns was evaluated in a randomized, open-label, crossover study of 12 healthy subjects.⁽⁸⁾ The results showed that the mean lung deposition was significantly higher when using the I-neb AAD System in TIM (73.3%) than in TBM (62.8%). The mean exhaled fractions were low ($<1\%$) for both breathing patterns. The nebulization time was significantly shorter in TIM (3.0 min) than in TBM (4.7 min). With the combination of a high lung deposition, almost no loss of aerosol during exhalation, and a short nebulization time the I-neb AAD System with the TIM breathing pattern should be of special value to patients who require multiple daily dosing of aerosolized medication, are using drugs that should not be wasted into the room air, or would benefit from a more efficient delivery system.

Aerosol Generation and the VMT

The I-neb AAD System has been designed with a specific VMT to generate an aerosol. The VMT consists of an ultrasonic horn driven by a piezo element and a platinum mesh with ~ 7000 holes with an average diameter of $2\ \mu\text{m}$ (Fig. 3). The liquid (solution or suspension) fills the gap between the horn and the mesh by gravity, and is pumped through the mesh by the vibrations of the horn (178 kHz; Fig. 1). When the liquid in the medication chamber has been delivered, an electronic control circuit detects the change in power required by the horn, signaling the end of nebulization. The piezo element connected to the horn has a variable power range for the optimization of the aerosol output rate, which allows the performance of the aerosol generator to be tailored to the specific drug formulation.

The mass median aerodynamic diameter (MMAD) of the aerosol pumped through the mesh has been determined using an albuterol solution and the Next Generation Impactor (NGI; MSP Corporation, St. Paul, MN, USA). The I-neb AAD System was configured with a 0.25 mL metering chamber and programmed to operate in a continuous mode to facilitate continuous aerosol production at power level 10. The MMAD of the albuterol solution was $3.9\ \mu\text{m}$, the geometric standard deviation 1.7, and the fine particle fraction 67%.⁽¹³⁾

The piezo element used in conventional ultrasonic nebulizers has made these nebulizers less suitable for use with drug suspensions and drugs that are heat sensitive. The piezo element driving the ultrasonic horn in the I-neb AAD System operates at $\sim 10\%$ of the power of the piezo element

FIG. 3. The vibrating mesh of the I-neb Adaptive Aerosol Delivery (AAD) System in two different magnifications.

in the conventional ultrasonic nebulizers. Despite the lower power consumption, drug suspensions can be delivered with the I-neb AAD System.⁽¹³⁾

Medication Chambers

In the I-neb AAD System the aerosol is only generated in pulses during inhalation minimizing any losses. As a result of these design features a much smaller volume of drug is required to deliver the same volume to the lung compared with a pneumatic nebulizer.⁽¹³⁾

Metering and nonmetering chambers

To deliver precise, metered doses of aerosol to the patient with the I-neb AAD System, a metering chamber design has been developed (Fig. 4). As drug vials with volumes ranging from 2 to 5 mL designed for pneumatic nebulizers may be used with the I-neb AAD System, a range of metering chambers are available for metering of the correct volume. The metering chamber has a central section around the horn,

and it is the volume of this section which determines the dose (Fig. 4). The patient pours the medication into the central section and when full, any additional solution overflows into an outer chamber. When the lid is closed, the solution in the central section is sealed from the overflow and only that volume of drug in the central section is delivered as aerosol to the patient.

The I-neb AAD System can also be supplied with a non-metering chamber that has been designed for use with volumes from 0.25 to 1.7 mL. These are filled by using a pipette for the correct dosage.

The I-neb AAD System can be supplied with a range of different metering chambers, from 0.25 to 0.75 mL for different drug applications, which are color coded for ease of identification by the patient. Due to the flexibility of the metering chamber design, different doses can be delivered while using a single vial of drug. An example is inhaled iloprost (Ventavis; Actelion Pharmaceuticals US, Inc., South San Francisco, CA, USA) for treatment of pulmonary arterial hypertension. Iloprost is available in a 1 mL vial, whereas

FIG. 4. The medication chambers designed for the I-neb Adaptive Aerosol Delivery (AAD) System are shown, including the metering chamber (left) and the nonmetering chamber (right).

the I-neb AAD System for delivery of iloprost is supplied with two metering chambers, one for delivery of a 2.5 μg dose (0.25 mL metering chamber), and the other for delivery of a 5 μg dose (0.5 mL metering chamber).⁽¹²⁾ This gives the clinician the flexibility to titrate the dose of iloprost to the patient, while the drug supplier manufactures and distributes one vial size.

Residual and reproducibility

The gravimetric residual mass of liquid drug formulation remaining in the I-neb AAD System postnebulization has been evaluated during a standard (breathing simulation) output to filter analysis. Twenty-five nonmetering chambers were tested in triplicate using a single I-neb AAD System body. The I-neb AAD System including the mouthpiece was weighed, then filled with 0.4 mL of albuterol solution, weighed again, and weighed again postnebulization. The gravimetric residual mass remaining in the I-neb AAD System was determined as the weight postnebulization minus the filled nebulizer weight. The mean residual amount of albuterol was 84 mg (range 57–142 mg) corresponding to a mean volume of 84 μL .⁽¹³⁾

The reproducibility of the delivered dose of albuterol solution has been assessed *in vitro* through a breathing simulation test using fifty 0.3 mL metering chambers with a single I-neb AAD System in TBM, a power level 10 AAD Disc, and filters. The 0.3 mL metering chamber was designed to deliver 300 μL of albuterol (600 μg albuterol) ex-mouthpiece, that is, the fill volume has been designed to compensate for any residual in the metering chamber and mouthpiece to deliver the required metered dose. The mean metered dose of albuterol was 575.4 μg [95% confidence interval (CI) 563.3–587.5 μg], which equated to 288 μL albuterol solution (95% CI 282–294 μL) in metered volume.⁽¹³⁾

The Design of the Mouthpiece

In the I-neb AAD System, the aerosol is released through the VMT at a low velocity, and the patient's inspiratory flow is required to carry the aerosol through the mouthpiece. This ensures that there is minimal loss of aerosol in the patient's

upper airways due to impaction. It is important, however, to rapidly mix the dense aerosol plume generated at the surface of the mesh with the patient's airflow to prevent the aerosol droplets from coalescing. The mixing must be effective, but simultaneously avoid excessive turbulence, which would increase deposition on the internal surfaces of the mouthpiece and reduce the efficiency of the system. The design of the mouthpiece was optimized with the aid of computational fluid dynamics. The original design had the base of the mouthpiece parallel to the mesh, this caused uneven airflow from the single inhalation valve and this resulted in additional aerosol disposition on the mouthpiece wall. The resulting design used an 8 degrees slant to the base of the mouthpiece to ensure that the air flow from the inhalation valve is fed in evenly around the edge of the mesh, and mixes rapidly with the aerosol plume, which is retained in the center of the air flow to minimize losses on the internal surfaces of the mouthpiece (Fig. 5). In the study of lung deposition in healthy subjects following use of the I-neb AAD System in TBM *versus* TIM, the mean deposition of $^{99\text{m}}\text{Tc}$ -DTPA in the mouthpieces in percentage of the loaded doses was 5.1% for the TBM breathing pattern, and 5.0% for the TIM breathing pattern.⁽⁸⁾

Generation of excessive saliva during nebulization can be a problem for some patients. The mouthpiece has therefore been designed to ensure that saliva cannot run through the mouthpiece onto the mesh by channeling saliva into the outer mouthpiece chamber.

Patient Feedback and Compliance

The role of feedback signals to the patient during nebulization with the I-neb AAD System is fundamental to a successful drug delivery. Feedback mechanisms—both negative and positive—regulate a large number of human physiological processes. The human body is therefore naturally programmed to look for and understand feedback. This makes feedback signals a very powerful tool when designing the interfaces between the device and the patient. As the feedback function is important, the selection of the feedback signals must be made carefully and inadvertent feedback signals must be avoided for the desired result to be achieved.

FIG. 5. The mouthpiece of the I-neb Adaptive Aerosol Delivery (AAD) System. The design with an 8 degrees slant to the base of the mouthpiece has been made to ensure that the air flow from the inhalation valve is fed in evenly around the edge of the mesh, and mixes rapidly with the aerosol plume, which is retained in the center of the air flow to minimize losses on the internal surfaces of the mouthpiece.

For example, when using a pMDI, there is no feedback mechanism to inform the patient that they have inhaled the aerosol. The package insert will inform the patients that provided the pMDI was used correctly, they will receive the drug. The patient will most probably be looking for feedback signals indicating drug release such as the sound of the firing of the dose, or the taste of the drug on their tongue. Neither of these will indicate that they have inhaled the drug, only that they have fired the dose, which, for example, may not have been synchronized with inspiration, or which may have been deposited on the tongue.

In the I-neb AAD System the aim has been to give the patient very clear positive feedback signals at the completion of the aerosol delivery. The primary feedback signal is given at the end of nebulization, when no liquid remains in the metering chamber. The patient is then provided with a feedback cascade consisting of a signal with a smiling face on the LCD screen, an audio signal (buzzer), and a tactile vibrator signal. Feedback on the compliance with the correct use of the AAD System nebulizers have been recorded in several clinical studies (Table 2).^(11,12,14-19) In these studies, over 80% of the patients have completed each nebulization started, or in other words used the AAD System until the feedback cascade informed them that they had reached the end of nebulization.

In the I-neb AAD System a secondary positive feedback signal is provided on each inhalation. In TBM, the vibrator operates at the start of each breath to confirm that aerosol delivery has started as the VMT aerosol generation process is silent. In TIM, the vibrator operates at the end of each inhalation when the patient has reached the inhalation target time.

Customized Drug Delivery through the AAD Disc

Following activation, data programmed onto the AAD Disc is accessed by the I-neb AAD System. The AAD Disc, which is inserted into a slot on the front panel (Fig. 1), contains a microchip and an antenna, which communicates with the I-neb AAD System using a radio frequency protocol. The microchip in the AAD Disc is programmed with operational parameters such as power level, drug lot number, drug code, number of doses to be delivered, and expiration date. One of the key parameters that can be set is the power level of the drive circuit for the ultrasonic horn, and changes in the power level will adjust the rate of drug delivery. Changes in power level may be required for optimization of the duration of nebulization required for a specific drug, or for adjustment to the physicochemical characteristics of a drug such as viscosity and surface tension. The AAD Disc is programmed for each drug formulation, and can be packaged with the drug as part of the pharmaceutical packaging process. For example, if the drug pack contains 30 doses, the AAD Disc is programmed with 30 treatments. As each treatment is delivered, the number of treatments left on the AAD Disc is decremented by one, until all the treatments have been delivered. A new AAD Disc will be supplied with the next drug pack.⁽¹⁸⁾

I-neb Insight and the PLS

A PLS has been incorporated in the I-neb AAD System. This function consists of a memory chip designed to record data on up to 4000 treatments, and an infrared interface to

transmit the data to a computer. Each nebulization is recorded as an individual line of data, and the data recorded includes: the date and time of the nebulization, the dose delivered, the drug, TBM or TIM mode, and the duration of the nebulization. To ensure the data is accurately recorded and retrieved, every line of data is accompanied by a checksum and the number of data lines recorded is logged. On recovery, every data line can be checked against its individual checksum, and the total number of data lines compared to the logged number. This method ensures a high level of data integrity for use for example in clinical trials. The PLS function also records any errors recorded by the operating system of the I-neb AAD System while in use, which can be used to aid diagnosis when a patient reports a system fault.

The PLS data is accessed via the I-neb Insight function, which is a PC-based software program with an infrared interface. The software program can be used as a feedback tool to train patients to perform the slow and deep inhalations in TIM (Fig. 6). The feedback is given via an interactive screen display, which allows the patient to monitor the inspiratory maneuver and to visualize when the inspiration is optimal in terms of flow rate. It can also be used to extract the PLS data, which can be displayed on the PC screen or saved to a file. The PLS data is actively used by clinicians to monitor their patients.^(20,21) Through the PLS function, the clinician can identify patients who are not adhering to their treatment regimen, or not complying with the correct use of the I-neb AAD System (Fig. 7).

Regulatory Considerations

In the United States, different regulatory pathways are used by the Food and Drug Administration (FDA) to approve new inhaled drugs and medical devices. New medical devices are processed by the Center for Devices and Radiological Health (CDRH). New drug applications (NDA) are processed by the Center for Drug Evaluation and Research (CDER), or the Center for Biologics Evaluation and Research (CBER). The process is governed by the FDA, which nominates one center to take the lead for the review of an application, with other centers providing support. A review of a combination product, in which the drug is integral to the inhaler (pMDI or DPI) would most probably be lead by CDER in coordination with CDRH. A company submitting an application for a new drug for delivery with a generic nebulizer should probably approach CDER, whereas an application for a generic nebulizer for delivery of a range of drugs should be submitted to CDRH.

The FDA approval of the iloprost inhalation solution (Ventavis; Actelion) with the I-neb AAD System in 2005 was achieved using a route different from any of the three outlined above. The existing NDA drug process and the 510(k) device process were run in parallel, and the 510(k) was only issued after the approval of the NDA. The I-neb AAD System was specifically approved for administration of drugs, which are approved for use with the I-neb device. This meant that the I-neb AAD System and any improvements not related to drug delivery were controlled under the 510(k) process. The use of the 510(k) route was possible as many of the technical features of the I-neb AAD System could be found in predicate devices, whereas information on drug-specific performance was only included in the NDA, not in the 510(k). This

FIG. 6. The software program in the I-neb Insight can be used as a feedback tool to train patients to perform the slow and deep inhalations in TIM.

meant that the I-neb AAD System was not classified as a generic nebulizer, and that for each new drug application a new reimbursement code could be processed. As iloprost has been approved with the I-neb AAD System, the 510(k) may be referenced in future new drug developments. This could potentially reduce the regulatory burden on both the regulator and companies seeking future approvals.

In Europe, the I-neb AAD System has been approved as a medical device and has been classified as a small volume nebulizer for administration of medicines in spontaneously breathing patients. It is, however, only available in specific applications where it has been included on the drug license. In Europe, the device is regulated alone under the Medical Device Directive. The manufacturer will be audited by a

Notified Body to determine if the device meets the technical requirements of the directive. Once the audit is complete, the manufacturer can apply the CE mark. Where the device is part of a combination product, the drug will be approved with the CE marked device by one of the national agencies, and approved as a combination product to be delivered by that medical device. Once approved in one member state, approval in the remaining member states is achieved through the centralized Mutual Recognition Process (MRP), which allows for the harmonization of product authorization between member states.

The recent approval in Europe of the iloprost inhalation solution (Ventavis; Bayer Schering Pharma AG, Berlin, Germany) with the I-neb AAD System was achieved using the normal approval process. The manufacturer obtained the CE mark for the I-neb AAD System from the Notified Body. The CE marked I-neb AAD System was then used in the drug studies required for submission to the German Federal Institute for Drugs and Medical Devices for the approval of the combined product. Once approval was obtained, an MRP was used to obtain approval in the other member states.

The features of the I-neb AAD System results in the regulatory approval of both the I-neb AAD System and the drug being interlinked, this means that the device and the drug are then promoted and priced as a system.

FIG. 7. Through the Patient Logging System function in the I-neb Adaptive Aerosol Delivery (AAD) System, the clinician can identify patients who are not adhering to their treatment regimen, or not complying with the correct use of the I-neb AAD System. The graph shows number of treatments per day, and the legends are (•) complete treatment, (x) incomplete treatment, and (○) no treatment.

Future Directions

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, the healthcare payers, and the investors. This means that new pulmonary drug delivery systems—such as the I-neb AAD System—must provide a sustainable competitive advantage by creating a technical solution that meets the patient's

demands, is cost effective to meet the payer's demands and generates a new market or extends the commercial life of the drug to meet the investor's demands. To meet these market requirements, the capabilities of the I-neb AAD System are continuously expanded. The novel TIM breathing mode reduces treatment times and enhances lung deposition, and has been widely adopted in the treatment of patients with cystic fibrosis. I-neb Insight provides detailed information on patient adherence and compliance, and a remote monitoring service is being developed using the internet to enable patients to upload their data from home. This data is then processed on a central server into a graphical format, in which it can be accessed by the patient and clinician via a password-protected Internet portal to monitor and enhance patient adherence and compliance. The AAD technology can be used to ensure that the patient's inhalation is coordinated with aerosol delivery, and that patients complete their treatments. Continued development of the patient-device interface could be an effective route to reduce deposition of aerosol in the upper airways.

Acknowledgments

The authors acknowledge Nicholas Smith (PS Writing Ltd, Portsmouth, UK) for his assistance with graphics, and Kurt Nikander (Philips Respironics, Respiratory Drug Delivery, Parsippany, NJ) for guidance and input on the manuscript.

Author Disclosure Statement

John Denyer and Tony Dyche are employees of Philips Respironics.

References

1. Anderson PJ: History of aerosol therapy: liquid nebulization to MDIs and DPIs. *Respir Care*. 2005;50:1139–1149.
2. Geller D: The science of aerosol delivery in cystic fibrosis. *Pediatr Pulmonol*. 2008;43:S5–S17.
3. Denyer J, Nikander K, and Smith NJ: Adaptive Aerosol Delivery (AAD) technology. *Expert Opin Drug Deliv*. 2004;1:165–176.
4. Hess, D: Aerosol delivery devices in the treatment of asthma. *Respir Care*. 2008;53:699–723.
5. Nikander K, and Denyer J: Adaptive Aerosol Delivery (AAD) Technology. In: Rathbone MJ (ed). *Modified Release Drug Delivery Technology*, 2nd ed. Informa Healthcare USA, Inc., New York, NY; pp. 603–612, 2008.
6. McCormack P, McDonald A, and Southern KW: Establishing paediatric patients on an Adaptive Aerosol Delivery (AAD) device. *J Cyst Fibros*. 2006;5(Suppl 1):S76.
7. Potter R, Prince I, Dyche T, Hatley RHM, Smith N: Consistent drug delivery into eight breathing patterns using a prototype I-neb adaptive aerosol delivery (AAD) device—an in vitro study. *J Aerosol Med*. 2005;18:112–113.
8. Nikander K, Prince I, Coughlin S, Warren S, and Taylor G: Mode of breathing—tidal or slow and deep—through the I-neb Adaptive Aerosol Delivery (AAD) System affects lung deposition of ^{99m}Tc-DTPA. *J Aerosol Med Pulm Drug Del*. 2010;23(Suppl 1):S37–S44.
9. Sanders CE, and Milsom WK: The effects of tonic lung inflation on ventilation in the American bullfrog *Rana Catesbeiana* Shaw. *J Exp Biol*. 2001;204:2647–2656.
10. Denyer J, Prince I, Dixon E, Agent P, Pryor J, Hodson M: Evaluation of the Target Inhalation Mode (TIM) breathing maneuver in simulated nebulizer therapy in patients with cystic fibrosis. *J Aerosol Med Pulm Drug Del*. 2010;23(Suppl 1):S29–S36.
11. Denyer J, Black A, Nikander K, Dyche T, and Prince I: Domiciliary experience of the Target Inhalation Mode (TIM) breathing maneuver in patients with cystic fibrosis. *J Aerosol Med Pulm Drug Del*. 2010;23(Suppl 1):S45–S54.
12. Goodman N, Morgan M, Nikander K, Hinch S, and Coughlin S: Evaluation of patient-reported outcomes and quality of life with the I-neb AAD System in patients with chronic obstructive pulmonary disease. *J Aerosol Med Pulm Drug Del*. 2010;23(Suppl 1):S61–S70.
13. Hardaker LEA, and Hatley RHM: In vitro characterization of the I-neb Adaptive Aerosol Delivery (AAD) System. *J Aerosol Med Pulm Drug Del*. 2010;23(Suppl 1):S11–S20.
14. Nikander K, Arheden L, Denyer J, and Cobos N: Parents' adherence with nebulizer treatment of their children when using an Adaptive Aerosol Delivery (AAD) System. *J Aerosol Med*. 2003;16:273–281.
15. Denyer J, and Dyche T: Patient compliance with inhaled treatment using a novel aerosol delivery system. *Eur Respir J*. 1998;12(S28):P0647.
16. Everard ML, Ritson S, Denyer J: Aerosol delivery systems acceptable to young children improve drug delivery. *Drug Deliv Lungs IV*;1998:P120.
17. Conway S, Dodd M, Marsden R, Paul E, and Weller P: Comparison of compliance in cystic fibrosis patients using either a Halolite Adaptive Aerosol Delivery (AAD) system or a conventional high output nebuliser system. *J Cyst Fibros*. 2002;1(Suppl 1):S67.
18. Nikander K, Denyer J, Dodd M, Dyche T, Webb K, Weller P, and Stableforth D: The Adaptive Aerosol Delivery System in a telehealth setting: patient acceptance, performance, and feasibility. *J Aerosol Med Pulm Drug Del*. 2010;23(Suppl 1):S21–S28.
19. Dyche T, Prince IR, and Nikander K: Use of I-neb AAD patient logging system data to identify aerosol treatment issues in patients with cystic fibrosis. *Am J Respir Crit Care Med*. 2007;175:A782.
20. Latchford G, Duff A, Quinn J, Conway S, and Conner M: Adherence to nebulised antibiotics in cystic fibrosis. *Patient Ed Counsel*. 2009;75:141–144.
21. McNamara P, McCormack P, McDonald AJ, Heaf L, and Southern KW: Open adherence monitoring using routine data download from an adaptive aerosol delivery nebuliser in children with cystic fibrosis. *J Cystic Fibros*. 2009;8:258–263.

Received on September 9, 2009
in final form, December 6, 2009

Reviewed by:
James Fink

Address correspondence to:
John Denyer, B.Sc.
Philips Respironics
Respiratory Drug Delivery (UK) Ltd
Chichester Business Park
City Fields Way, Tangmere
Chichester, West Sussex
UK, PO22 2FT

E-mail: john.denyar@philips.com