

The I-neb Adaptive Aerosol Delivery (AAD) System

John Denyer Respironics Respiratory Drug Delivery (UK) Ltd, Chichester, West Sussex, UK.

Kurt Nikander Philips Respironics, Respironics New Jersey, Inc., Parsippany, NJ, USA.

► **Inhalation of aerosolized drugs is the primary route of administration in the treatment of most respiratory disorders.**

Inhalation of aerosolized drugs is the primary route of administration in the treatment of most respiratory disorders. By delivering the inhaled drug to the lungs the onset of action is fast, and the systemic side-effects less than with other treatment modalities. Today three different inhalation systems are commonly used: nebulizers, pressurized metered dose inhalers (pMDIs) with or without valved holding chambers and dry powder inhalers (DPIs). Nebulizers may be used to administer large doses of drugs, drug mixtures and most importantly drugs not currently available for use in pMDIs or DPIs. For these reasons conventional constant output nebulizers are often used for the delivery of solutions or suspensions of antibiotics, anticholinergics, bronchodilators, corticosteroids, mucolytics and other drugs.

Conventional nebulizers

When using conventional constant output nebulizers as aerosol systems, the inhaled amount of drug is primarily a function of the patient's breathing pattern, and in particular the duty cycle, i.e., inspiratory time / sum of inspiratory and expiratory times. The duty cycle of a single breath is usually given as $TI/TTOT$ (TI = inspiratory time; $TTOT$ = sum of inspiratory and expiratory times). The $TI/TTOT$ ratio has been shown to be highly variable and range from 0.25 to 0.55 [1]. For example, with a $TI = 1$ s and a $TTOT = 3$ s, the respiratory frequency would be 20 breaths/minute and the total inspiratory time per minute would be 20 s. The patient would in this case inhale aerosol during 20 s per each minute of nebulization (~33%) and the rest of the nebulizer's drug output (~67%) would be lost to the environment. Many new drugs have a narrow therapeutic window, are rather expensive and are not available as pMDIs or DPIs. The delivery of these drugs requires an inhalation device which delivers a precise amount of aerosol with minimal waste and caregiver exposure. The conventional constant output nebulizer can obviously not meet these demands.

► **AAD System nebulizers deliver precise and reproducible doses of aerosol.**

The AAD technology

The Adaptive Aerosol Delivery (AAD) technology was developed in the nineties as a basis for the development of nebulizers designed to minimize the variability of the inhaled amount of aerosol, and the waste of aerosol to the environment [2-3]. The aim was to create a dosimetric nebulizer with precise dose delivery that adapted to the patient's variable breathing patterns. The AAD System nebulizers were therefore designed to analyze the breathing patterns of the individual patient and to time the pulse of aerosol into 50% of each inspiration based on this analysis. The analysis of the breathing patterns continues throughout the treatment, and the AAD System nebulizer continually adapts the pulse of aerosol to changes in the breathing pattern.

The first AAD System nebulizer designed based on the AAD technology was the HaloLite AAD System developed in cooperation with Astra (AstraZeneca, Lund, Sweden) and launched in 1997 [4]. The second was the Prodose AAD System developed in cooperation with Schering AG (Bayer Schering Pharma AG, Berlin, Germany) and launched in 2002 [4]. The basic atomization technology in these AAD Systems was based on jet nebulizer technology. Results of both *in-vitro* and clinical studies suggested that the HaloLite and Prodose AAD System nebulizers could deliver precise and reproducible doses of aerosol, and that the AAD System nebulizers were superior to conventional jet nebulizers in terms of lung deposition, elimination of waste of aerosol to the environment and patient adherence to treatment [4].

The I-neb AAD System

The 3rd generation AAD System nebulizer – the I-neb AAD System (Figure 1) – is a portable, small (150 x 65 x 45 mm, h x w x d), lightweight (210 g), and virtually silent mesh nebulizer [5]. The main parts are the body (battery charger not shown), the medication chamber assembly with the mesh and the drug guide, and the

mouthpiece. Built into the body are the electronics, the LCD screen, the piezo element connected to the horn, the pressure sensor, the radio frequency antenna for the AAD Disc (contains information on power level, drug lot number, drug code and expiration data), the infrared transmitter/receiver for I-neb Insight, the battery, buzzer, the vibration device for tactile feedback, and the Patient Logging System (PLS).

The I-neb AAD System algorithms

Algorithms for two different breathing modes have been built into the I-neb AAD System, these are the Tidal Breathing Mode (TBM, Figure 2) and the Target Inhalation Mode algorithms (TIM, Figure 2). The breathing mode is selected by choosing one of two mouthpieces, and the specific mouthpiece is recognized by the electronics of the I-neb AAD System [6]. The TBM mouthpiece is selected for patients breathing tidally during the treatment, which is suitable for most patients from 2 years to adults. The TIM mouthpiece is selected to guide the patient - through feedback - to make a slow and deep inhalation through the mouthpiece, which is suitable for patients from 8 years to adults with moderate to good lung function.

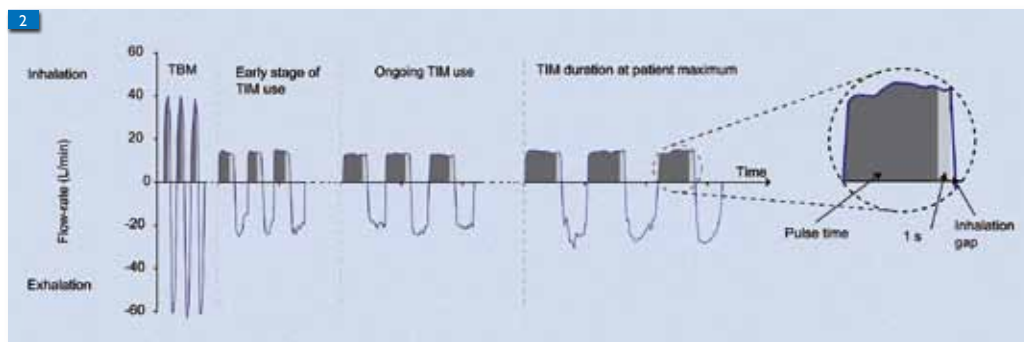
The TBM algorithm continuously records the patient's breathing pattern, and continuously predicts the length of the patient's next inhalation. Aerosol is pulsed at the beginning of the next inhalation and ends after 50% of the predicted inhalation time has expired. For the prediction of the length of the next inspiration, the average length of the past three inspirations is used by the AAD algorithm. The I-neb AAD System will therefore only deliver aerosol on the fourth breath of a new treatment, after which the average inspiration time is updated after each



▲ Figure 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.

subsequent breath. A pressure sensor and a flexible valve are used to monitor the patient's inspiratory flow pattern. Depending on variations in the patient's breathing pattern the pulse time is continuously monitored and adjusted by the AAD algorithm.

The aim of the AAD TIM algorithm is to provide the patient with an optimal target time for each slow and deep inhalation and thereby reduce the nebulization time. The TIM mouthpiece has been designed with an inhalation valve to restrict the inspiratory flow to a slow and deep inspiration at ~15 L/min [6]. The initial inhalation target time is set at 3 s - equivalent to an inhaled volume of ~0.75 L - and when that inhalation target time has been reached, a vibrator signals the end of



▲ Figure 2. Graphical presentation of the two breathing patterns used with the I-neb AAD System. The first part of the graph shows the patient's tidal breathing when using the I-neb AAD System in Target Inhalation 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 s inhalation (1 s aerosol pulse) to an 8 s inhalation (7 s aerosol pulse) when using the I-neb AAD System in Target Inhalation Mode (TIM).

the inspiration. Aerosol is delivered during the first 2 s of the 3 s inhalation target time and is followed by inspiration without aerosol during the remaining 1 s to ensure that the aerosol is inhaled deep into the lung and not exhaled. The goal is to guide the patient to extend the length of the inhalation target time to ~80% of the forced vital capacity (FVC). When the patient has set the optimal inhalation target time, the algorithm will adjust it to meet the patient's efforts on each inspiration. The achieved length of the inhalation target time is filed in the memory for subsequent treatments at the end of the treatment.

Aerosol generation and the mesh

The aerosol generation used on the I-neb AAD System is based on a vibrating mesh technology including (Figure 3) an ultrasonic horn driven by a piezo element and a platinum mesh with ~7000 holes with an average diameter of 2 µm [6]. The drug formulation fills the gap between the horn and the mesh by gravity, and is pumped through the mesh by the vibrations of the horn. The droplet size of the aerosol delivered through the mesh has been determined using a solution of salbutamol (albuterol) and an impactor, showing a mass median aerodynamic diameter of 3.9 µm and a fine particle fraction of 67% [7]. This means that the aerosol is well within the respirable range. The piezo element has been designed with a variable power range (1-15) to adapt the output rate to the demands of the drug formulation (viscosity, surface tension, volume to be delivered) and the patients being treated (treatment times).

The medication chamber assembly

The I-neb AAD System has been designed to deliver precise, preset metered doses of aerosol. The preset dose is determined by the metering chamber with a central section around the horn. Due to the design of the metering chamber, the pulsing of aerosol per part of each inspiration and a low residual, the losses of aerosol prevalent with conventional constant output nebulizers are avoided. This means that much smaller volumes of drug are required to deliver the same inhaled amount of drug, and these volumes tend to be 2.5-5 times lower than when using constant output nebulizers [7]. The metering chambers available cover volumes of 0.25-0.75 mL for different drug formulations and are color coded for ease of use (Figure 4). The I-neb AAD System can also be supplied with a non-metering chamber which has been designed for use with volumes from 0.25-1.7 mL. These are filled by using a pipette for the correct dosage.

I-neb Insight and the PLS

The Patient Logging System built into the body of the I-neb AAD System consists of a memory chip (records up to 4000 treatments) and an infrared interface to transmit the recorded data to a PC [7]. Every nebulization is recorded as an individual line of data including date and time, dose delivered, drug, TBM or TIM mode, and duration. The PLS data can be accessed via I-neb Insight, a PC-based software program with an infrared interface. I-neb Insight can also be used as a feedback tool - via an interactive screen display - for the patient to show how the slow and deep inhalations in TIM should be performed (Figure 5). It shows the patient the inspiratory maneuver and the optimal inspiration in terms of flow rate. I-neb Insight can be used to extract the PLS data to be displayed on the PC screen or saved to a file. This function has been actively used by clinicians to monitor their patients in terms of adherence to treatment and compliance with the correct use of the I-neb AAD System. Home monitoring is provided by the Insight Online internet portal which allows patients to upload their data remotely using their personal computer, and provides feedback to both the patient and clinician regarding different aspects of the treatment. This makes it easy to see changes in the treatment such as adherence, treatment time, inhalation maneuver and device performance, and allows the clinical team to optimize the therapy [8].

Clinical experience

In the European Union the I-neb AAD System is approved as a general purpose nebulizer, and in the USA for the delivery of drugs that are approved for use with the I-neb AAD System. The I-neb AAD System is presently used in Europe for the treatment of patients with cystic fibrosis (CF) to deliver colistimethate sodium (Promixin; Profile Pharma Ltd, UK), an antibiotic for treatment of *Pseudomonas aeruginosa*, and in Europe and the USA for the treatment of pulmonary arterial hypertension to deliver iloprost (Ventavis; Bayer AG/Actelion Pharmaceuticals Ltd), a pulmonary vasodilator [4, 9]. The I-neb AAD System has also been used by pharmaceutical companies in a number of clinical studies of new drugs. Apart from these a number of clinical studies have been run to evaluate the I-neb AAD System in terms of patient acceptability, lung deposition, ease of use and satisfaction.

An evaluation of the acceptability of the TIM breathing maneuver was performed in 20 patients with CF during up to eight simulated nebulizer treatments with 10 min pauses between the

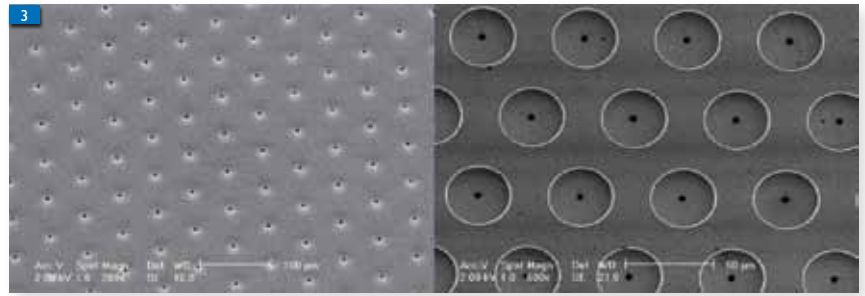
► Home monitoring is provided by the Insight Online internet portal.

► The I-neb AAD System has been designed to deliver precise, preset metered doses of aerosol.

nebulizations [10]. In the study the patients' inspiratory times were increased over successive breaths using auditory and tactile (vibratory) feedback built into a prototype I-neb AAD System. Ninety percent felt that the instructions were easy to understand, 65% that the vibratory feedback was pleasant at the end of the first treatment, and 50% found the procedure to be comfortable. Most patients felt that the breathing maneuver was easy to understand (90%) and use (80%), but that the duration of the inspiration was too long (100%) at the end of the final treatment. Ninety percent were able to comply with the breathing maneuver, whereas two patients with FVC values of <1.75 L could not. The mean nebulization time decreased from 288.4 s to 141.6 s during the first and final treatments, respectively. This was the first clinical study of the TIM breathing maneuver and provided early evidence of the acceptability of the maneuver.

A handling study of the I-neb AAD System was performed (42 patients with CF, 12-57 years) to evaluate compliance with the correct use of the I-neb AAD System, and nebulization times [11]. Based on a questionnaire at the end of the study, ease of use with the I-neb AAD System was evaluated as a secondary outcome. For this 3-month study the I-neb AAD System nebulizers were supplied in both TBM and in TIM, with the patients trained to use the TIM maneuver for delivery of all their inhaled drugs. The patients could change to the TBM maneuver if they felt uncomfortable with the TIM maneuver. A total of 10,240 complete treatments were recorded during the study and of these 88% were in TIM. Compliance with the correct use of the I-neb AAD System was 97.6%, whereas the mean treatment time for complete treatments in TIM was 4.20 min, and in TBM 6.83 min. The questionnaires showed that >77% of the patients scored the I-neb AAD System in TIM as either very easy, easy or acceptable to use.

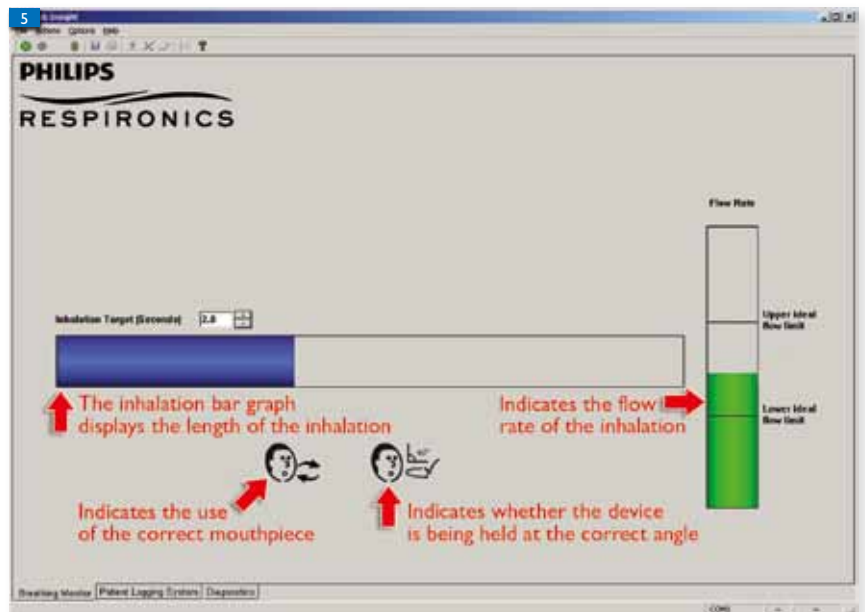
In a randomized, open-label, crossover study, lung deposition following administration of a radiolabelled aerosol from the I-neb AAD System with the TBM and TIM breathing patterns in 12 healthy subjects was evaluated [12]. The mean lung deposition was significantly higher in TIM (73.3%) than in TBM (62.8%) expressed as percent of the ex-mouthpiece dose, and 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). The combination of a high lung deposition, minimal loss of aerosol during exhalation, and short nebulization times makes the I-neb AAD System especially valuable to



▲ Figure 3. The vibrating mesh of the I-neb AAD System in two different magnifications.



▲ Figure 4. The medication chambers designed for the I-neb Adaptive Aerosol Delivery (AAD) System.



▲ Figure 5. 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. The horizontal bar to the left displays the length of each inspiration, and the vertical bar to the right displays the flow rate of the inspiration.

patients that are on multiple daily nebulization treatments, are using drugs that should not be wasted into the room air, or would benefit from a more efficient delivery system.

We have also compared the I-neb AAD System in TBM with the patients' previous conventional nebulizers in a multicenter study design including 98 patients with chronic obstructive pulmonary disease (COPD, aged 53–80 years) [13]. The primary outcome variables included 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). The evaluation of the ease of use and satisfaction was based on matched questions from pre- and post study questionnaires. Quality of life was assessed at visits 1 and 2 using a validated Chronic Respiratory Questionnaire (CRQ) with dyspnea, emotional function, fatigue, and mastery domains. The patients' responses favored ($P \leq 0.001$) the I-neb AAD System compared with their previous nebulizer system on the ease of use and satisfaction questions. Significant ($P \leq 0.015$) improvements in the CRQ dimensions of dyspnea and fatigue were also reported with the I-neb AAD System compared with the patients' previous nebulizer systems.

Conclusions

The main customers for pulmonary drug delivery are the patients, the clinicians, the healthcare system payers and the investors.

New inhalation devices – such as the I-neb AAD System - must therefore provide a sustainable competitive advantage by providing a treatment modality that meets the patients' and the clinicians' demands, is cost effective to meet the demands of the payers and extends the commercial life of an existing drug or creates a new marketing opportunity to meet the investors' demands. The design and the capabilities of the I-neb AAD System have to be continuously expanded to meet these requirements, such as the development of the TIM AAD algorithm to reduce patient treatment times, and the Insight Online home monitoring system which enables the patients to upload data from home via the internet allowing the clinical team to optimize the therapy. The advantages of effective drug delivery and patient monitoring from the I-neb AAD System are now being recognized as the way forward for controlled delivery of inhaled pharmaceuticals and adopted as good practice in clinical guidelines [14] ■

► **The advantages of effective drug delivery and patient monitoring are now recognized as the way forward.**

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