

Soft Mist Inhalers: A Review of Current Technology

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Introduction

Metered dose inhalers (MDI) and dry powder inhalers (DPI) have been the mainstay of portable inhalation therapy for over 30 years. The disadvantages of these currently used inhalation drug delivery devices have been well understood for a number of years. These systems often offer poor dose delivery efficiency, with only about 5-20% of the label claim dose being delivered to the lungs, the remainder being deposited in the oropharynx and ultimately being swallowed. In addition, there is often high *in vivo* dosing variability, both intra- and inter-subject, due to either difficulty in using the MDI or the patient inspiratory effort-dependent nature of the DPI. However, despite these problems, they are highly successful when employed with potent drugs with wide therapeutic windows that are traditionally used to treat respiratory disorders (e.g. albuterol).

The impetus to improve the quality of pharmaceutical aerosols, in part, came from the desire to use the lungs as a route of systemic administration. In particular, pharmaceutical companies such as **Nektar** and **Aradigm** have pioneered the development of inhalation devices and formulations for the delivery of insulin via the lungs. Such treatment required a new generation of inhalers capable of accurate and reproducible *in vivo* dosing. Development of the next generation of inhalers has taken many routes and numerous pharmaceutical companies have active research programmes in this area.

Soft Mist Aerosols

Research has focused on a new method of pharmaceutical aerosol generation that involves passing a solution formulation through a nozzle or series of nozzles to generate a 'soft mist' aerosol as a bolus dose. Aerosol generation is achieved by mechanical, thermo-mechanical or electro-mechanical processes depending upon the particular technology employed. It is worth noting that these devices are bolus dose delivery inhalers, rather than the new generation of continuous generation nebulisers, which generate aerosols by vibrating porous membranes at ultrasonic frequencies. Such devices include the eFlow (**Pari**), Aerodose (**Aerogen**) and the Omron nebuliser.

Four major development efforts are currently ongoing in the area of soft mist inhalers. In this review, the common characteristics of these aerosol inhalers will be described, together with a review of the published data for the Respimat® Inhaler (**Boehringer Ingelheim GmbH**), the AERx® inhaler (Aradigm Corp.), the Mystic™ inhaler (**Ventaira Pharmaceuticals, Inc.**, formerly Battelle Pharma) and the Aria™ inhaler (**Chrysalis Technologies Incorporated**). While the precise mechanism of soft mist aerosol generation may differ between inhalers, a number of common characteristics can be observed. They are propellant-free and produce slow moving aerosols over an extended duration with high *in vitro* fine particle fractions compared with MDIs and DPIs. The aerosols are often generated from simple solution formulations containing pharmaceutically acceptable excipients. Water and ethanol are the most commonly employed vehicles for soft mist aerosols. Perhaps the most simple and advantageous vehicle is water. There is often a well known and established stability profile for many pharmaceuticals in aqueous solutions, accelerating the route to the clinic in any development programme. Drug solubility can be manipulated by choice of water, ethanol or mixtures of the two, to increase formulation options and dose. In the case of multi-dose reservoir type devices, a preservative would be required to prevent microbial contamination. This is in addition to the current federal regulations that now require all aqueous based drug products for oral inhalation to be manufactured to be sterile.

Respimat®

The Respimat inhaler was recently launched in Germany as a combination product of fenoterol and ipratropium hydrobromide (Berodual) and this was licensed for the treatment of chronic obstructive airway disease. A large body of literature now exists documenting the aerosol characteristics and clinical performance of the Respimat inhaler with a number of different drugs. Aerosolised formulations include the steroids, budesonide and flunisolide, in addition to the beta-agonist, fenoterol, as well as the commercially available combination product of fenoterol and ipratropium bromide.

The Respimat device is a multi-dose reservoir system that is primed by twisting the device base. This compresses a spring and transfers a metered volume of formulation from the drug cartridge to the dosing chamber. The metered volume is between 11-15 μl , depending upon the drug formulation. When the device is actuated (in co-ordination with the patient's inspiration), the spring is released. This forces a micro-piston into the dosing chamber and pushes the solution through the uniblock. The uniblock is the heart of the aerosol generation system and consists of a filter structure with two, fine outlet nozzle channels. The uniblock produces two fine jets of liquid that converge at a precisely set angle and then collide. This collision aerosolises the liquid to form an aerosol.

Aerosols generated from the Respimat inhaler have been characterised as having a prolonged aerosol cloud duration compared with MDIs, and have a slower cloud velocity as measured using video camera imaging. Hochrainer and Holz (2001) measured the cloud duration of the Respimat aerosol to be 0.2–1.6 seconds compared with less than 0.2 seconds for HFA and CFC MDIs. Aerosol velocities have been reported as less than 1 ms^{-1} for the Respimat, compared with 6-8 ms^{-1} for CFC-MDI inhalers. While a degree of patient co-ordination is required to actuate the Respimat and to inhale, the longer duration of aerosol cloud generation makes this manoeuvre less critical than with MDIs.

Aqueous and ethanolic formulations have been employed with the Respimat and the *in vitro* aerosol performance determined. Zierenberg (1999) reported fine particle fractions of 66% for an aqueous fenoterol formulation and 81% for an ethanolic flunisolide formulation. The respective mass medium aerodynamic diameters (MMAD) were $2.0 \pm 0.4 \mu\text{m}$ for the aqueous formulation and $1.0 \pm 0.3 \mu\text{m}$ for the ethanolic formulation.

Gamma scintigraphy studies compared lung deposition of a radiolabelled aqueous fenoterol formulation delivered via the Respimat inhaler and a MDI. The Respimat delivered significantly more fenoterol to the lungs (39.2% of the metered dose) compared with the MDI (11.0%). Oropharyngeal deposition was significantly lower (37.1%) for the Respimat compared with the MDI (71.7%). For an ethanolic formulation of flunisolide, a similar increase in lung deposition with the Respimat formulation was observed compared with the MDI (Newman *et al.*, 1998).

Perhaps the most striking evidence of the efficacy and improved clinical performance with the Respimat inhaler comes from the numerous large scale clinical studies that have been performed in support of product licensing. Using the combination product of fenoterol and ipratropium bromide in a population of asthmatic patients, studies revealed that delivery via the Respimat enabled a 2- to 4-fold reduction of the daily dose without loss of therapeutic efficacy compared with the MDI (Vincken *et al.*, 2001). Similar conclusions were observed for populations of asthmatic children (2- to 4-fold dose reduction) and COPD patients (2-fold dose reduction) (van Berg *et al.*, 2000; Kilfeather *et al.*, 2004). The incidence of paradoxical

bronchoconstriction was reported as very low and similar to the incidence observed in the population treated with MDI (Vincken *et al.*, 2001). The fenoterol/ipratropium bromide formulation is formulated with benzalkonium chloride and ethylenediametetraacetic acid (EDTA) as a preservative. Two Phase II studies have indicated that patient use of the Respimat[®] did not produce microbial contamination of the formulation in the drug cartridge (Schmelzer and Bugel, 2001).

To date, studies using the Respimat have been restricted to the low dose drugs traditionally employed to treat respiratory disorders. The applicability of Respimat to deliver the milligram quantity doses required for some systemic delivery or proteins remains unknown.

AERx[®]

The AERx system was developed for the systemic delivery of insulin. Unit dose aqueous solution formulations were produced in a blister strip design. The first-generation AERx device is a battery operated device that guides the patient through the inhalation technique required to successfully deliver a dose. It can also monitor dose times and frequency, together with the facility to download dosing data in the clinic. A number of macromolecules (insulin, rhDNase, interferon-alpha, interferon-gamma, plasmid-DNA and IL-4 receptor) and traditional small molecules (morphine, fentanyl and testosterone) have been investigated using the AERx technology.

Aerosol generation using the AERx system is achieved by mechanically forcing a dose of the liquid formulation through a nozzle array in its disposable unit dose blisters. The electronic version of the AERx inhaler guides the patient to inhale at the required flow rate. A cam-operated piston mechanism is actuated to compress the blister and extrude the dose as an aerosol through the nozzle array into warmed flowing air. The nozzle array consists of a number of laser drilled holes. Nozzle design characteristics can be altered depending upon the formulation characteristics and the desired droplet particle size. The single use nature of the blister avoids potential problems such as microbial contamination from a dosing solution reservoir and nozzle clogging issues. In addition to the electronic microprocessor-controlled device, Aradigm is also developing an all-mechanical device, the AERx Essence without the air temperature control system. This would offer a lower cost, disposable alternative while maintaining the performance benefits of the soft mist aerosol for compounds with wider therapeutic windows.

A number of prototype versions of the AERx system have been investigated. In general, the *in vitro* aerosol characteristics revealed that about 50-60% of the loaded dose was emitted from the device, of which over 90% was respirable. MMADs ranged from 1–3 μm depending upon the formulation and nozzle array (Farr *et al.*, 2000). In a scintigraphic study, lung deposition following inhalation from the AERx was 53.3% (expressed as a percentage of the radioactivity in the AERx blister) compared with 21.7% for an MDI.

In vitro studies using the AERx system and an aqueous formulation of INS 365 (a novel agonist for the P2Y2 receptor) revealed that aerosolisation performance was dependent upon formulation viscosity, surface tension and solids concentration (Cipolla *et al.*, 2000). These studies demonstrated the feasibility of delivering milligram quantities of drug with good aerosol characteristics. *In vitro* experiments revealed that using a 45 µl dose, the AERx generated a 3.5 µm aerosol with 49.9% of the 11.25 mg dose being emitted as aerosol. Gamma scintigraphy from this high dose study revealed a lung deposition of 36.7% (expressed as percentage of the initial radioactivity), compared with 12.4% and 16.8% for the Pari LC Plus and Pari LC Star nebulisers, respectively (Cipolla *et al.*, 2000).

A number of clinical studies delivering insulin to diabetic patients using the AERx system are currently ongoing. Hermansen *et al.* (2004) concluded that in type 2 diabetics, preprandial inhaled insulin via the AERx was as effective as preprandial subcutaneous insulin in achieving glycaemic control. Clinical studies with morphine revealed comparable analgesic efficacy for a matched dose of inhaled and intravenous morphine in a postsurgical pain model (Thippahawong *et al.*, 2004). In addition, the AERx inhaler has been employed for the topical delivery of rhDNase to cystic fibrosis patients. A mean relative increase in FEV₁ of 7.8 was observed after 15 days' treatment compared with control (Geller *et al.*, 2003).

Mystic™

The Mystic inhaler offers a soft mist aerosol generated from solution or suspension formulations. Unlike the previously described soft mist inhalers, which use purely mechanical forces to generate the aerosol, the Mystic inhaler applies an electric field to the formulation within the spray nozzle. An electric charge builds on the fluid surface and, as the droplets exit the nozzle, the repelling force of the surface charge overcomes the surface tension of the droplets to form a soft mist droplet aerosol. This process is known as electrohydrodynamic aerosolisation or electrospray. The particle size characteristics of the aerosol can be controlled by adjusting the physical and chemical characteristics of the formulation, together with the formulation flow rate and electrical field properties. The inhaler consists of a number of components, a drug containment system, metering system, aerosol nozzle, power supply and microprocessor, all enclosed in a housing. To date, Ventaira reports that the inhaler has been successfully employed to generate aerosols from small molecule formulations (albuterol, triamcinolone, cromolyn, budesonide and terbutaline), and macromolecules, including insulin.

In vitro characterisation of an unnamed formulation revealed that aerosols generated from the Mystic inhaler produced mean emitted doses of 93.7% of the label claim. The MMAD was 2.85 µm with a fine particle fraction of 90% of the emitted dose. A Phase I study in healthy volunteers using a prototype device compared deposition by gamma scintigraphy for an EHD device with a DPI using

an unnamed drug. The mean whole lung depositions were 78%, 65% and 58% (expressed as a percentage of emitted dose, for 400 µg, 150 µg and 250 µg doses, respectively) (Zimlich *et al.*, 2000).

To date, clinical data for the Mystic is limited. Placke and Zimlich (2002) briefly reported similar therapeutic outcomes (percentage change FEV₁) in asthmatics administered 20 and 40 µg of albuterol via the Mystic compared with 200 µg from an MDI.

Aria™

The *Aria* technology platform is based on a proprietary capillary aerosol generation system. In the *Aria* system, the aerosol is formed by pumping the drug formulation through a small, electrically heated capillary. Upon exiting the capillary, the formulation is rapidly cooled by ambient air to produce an aerosol. The generated aerosol characteristics are dependent upon the formulation employed. Using propylene glycol as a condensing vehicle, drug containing condensation aerosols are generated. *In vitro* studies have been performed to demonstrate the pharmaceutical characteristics of these aerosols. Aerosol MMADs ranged from 0.5-2.0 µm with high fine particle fractions, and it was possible to control particle size by altering capillary configuration, aerosolisation conditions and formulation (Gupta *et al.*, 2003; Shen *et al.*, 2004).

When using water, ethanol or combinations of both, as non condensing excipients, a stream of solid particles are delivered as a soft mist aerosol. *In vitro* studies using budesonide, cromolyn sodium, buprenorphine, albuterol and insulin have been performed to demonstrate various applications of the *Aria* technology. These studies are characterised by high emitted doses and high fine particle fractions. Using non-condensing excipients it is possible to produce aerosols with vastly different size characteristics, depending upon the required application. Brown *et al.* (2003) reported the generation of a budesonide nanoparticle aerosol from an ethanolic formulation. The MMAD of this aerosol was 40 nm with a geometric standard deviation of 1.8. Hindle *et al.* (2004), described the aerosolisation of insulin using the *Aria* technology, using a formulation of 1% insulin in ethanol/water (85%/15%). The mean fine particle fraction of this aerosol was 85.6% of the emitted dose. An *in vivo* activity study, together with LC-MS indicated that insulin remained biologically active and chemically intact following aerosolisation.

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