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International Journal of Pharmaceutics 283 (2004) 1–9
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

A review of the development of Respimat® Soft Mist™ Inhaler

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Received 3 January 2004; received in revised form 6 June 2004; accepted 7 June 2004
Available online 20 August 2004

Abstract

Respimat® Soft Mist™ Inhaler (SMI) is a new generation inhaler from Boehringer Ingelheim developed for use with respiratory drugs. The device functions by forcing a metered dose of drug solution through a unique and precisely engineered nozzle (the uniblock), producing two fine jets of liquid that converge at a pre-set angle. The collision of these two jets generates the soft mist. The soft mist contains a high fine particle fraction of approximately 65 to 80%. This is higher than aerosol clouds from conventional portable inhaler devices, such as pressurised metered dose inhalers (pMDIs) and dry powder inhalers (DPIs). In addition, the relatively long generation time of the aerosol cloud (approximately 1.5 s) facilitates co-ordination of inhalation and actuation – a major problem with pMDIs. These features, together with the slow velocity of the soft mist, result in larger amounts of the drug reaching the lungs and less being deposited in the oropharynx compared with either pMDIs or DPIs. Generation of the soft mist from Respimat® SMI is purely mechanical, so propellants are not necessary. The innovative design of Respimat® SMI, using water-based drug formulations, ensures patients receive consistent and reliable doses of the drug with each actuation. The device was initially tested in scintigraphic lung deposition studies and produced encouraging results when compared with the chlorofluorocarbon-based pMDI (CFC-MDI). Subsequent clinical studies have confirmed that Respimat® SMI is effective and safe in delivering bronchodilators to patients with asthma or chronic obstructive pulmonary disease.

Keywords: Respimat® Soft Mist™; Inhaler (SMI); Lung deposition; Fine particle fraction; Aerosol; Obstructive lung disease; Inhaler device

1. Introduction

Inhalation therapy has led to considerable improvements in the treatment of obstructive airways diseases, such as asthma and chronic obstructive pulmonary disease (COPD). As the drug is delivered directly to its site of action, a low dose can be used to produce a therapeutic response and, consequently, side effects

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0378-5173/$ – see front matter © 2004 Published by Elsevier B.V.
doi:10.1016/j.ijpharm.2004.06.018

are minimised. Additionally, inhaled drug delivery circumvents the limitations imposed by first-pass hepatic metabolism and fast absorption results in an onset of action that is more rapid than that achieved by oral administration.

The efficacy of an inhaled drug is largely dependent on the amount of the drug deposited in the lungs and its topographical anatomical distribution; this is influenced by various interacting factors, including the characteristics of the aerosol, the type of delivery device used, the mode of inhalation and the architecture of the airways (Ganderton, 1997; Pavia, 1997). The characteristics of the aerosol will affect the amount of drug reaching the lung. The method by which fine particles are produced for pulmonary delivery and the size distribution of these particles significantly affects drug deposition within the airways (Newman, 1984; Pavia, 1997). It may be possible to deliver drugs more precisely by using aerosols with a defined particle size distribution; for example, particles with a diameter of 2–5 μm are generally deposited in the smaller bronchioles and peripheral airways (Ariyananda et al., 1996). Larger particles tend to be deposited in the upper airways, whereas those smaller than 2 μm are, to a large extent, breathed in and out of the alveoli with minimal actual deposition (Pavia, 1997; Ariyananda et al., 1996; Matthys, 1990); small particles that do manage to deposit in the alveoli may be rapidly absorbed and exert no pharmacodynamic effect (Pritchard, 2001). A study by Zanen et al. found that the optimal particle size for β_2 agonist and anticholinergic aerosols in patients with severe airflow obstruction was approximately 3 μm (Zanen et al., 1996). More recently, the effects of bronchodilator particle size on airway drug deposition in asthmatic patients was studied (Usmani et al., 2003). Monodisperse salbutamol aerosols of 1.5, 3 and 6 μm in size were inhaled and lung function changes were determined; the 3 and 6 μm aerosols were significantly more effective bronchodilators than the 1.5 μm aerosol.

Several types of portable devices are currently available for the delivery of drugs by inhalation; these include the chlorofluorocarbon (CFC) and hydrofluoroalkane (HFA) pressurised metered dose inhalers (pMDIs), and the dry powder inhalers (DPIs). The CFC-MDI has been the cornerstone of asthma and COPD maintenance therapy for many years. However, many patients experience problems in using CFC-MDIs and do not obtain optimal therapeutic benefit from their medication (Giraud and Roche, 2002). The limitations of the pMDI, and the move to eliminate CFC propellants for environmental reasons, have accelerated the development of alternative inhaler devices. Inherent in the development of these new devices has been a determination to improve on known device deficiencies (Steed et al., 1997).

Respimat® Soft Mist™ Inhaler (SMI) is a new generation inhaler that uses mechanical power from a spring rather than liquid-gas propellant to generate an aerosol cloud suitable for inhalation. This article reviews the development of Respimat® SMI and describes how the latest advances in aerosol technology have been used in order to improve upon existing inhaler performance.

2. Respimat® SMI

Respimat® SMI is a new generation, propellant-free, multi-dose inhaler developed by Boehringer Ingelheim. The term ‘soft mist’ is used to describe both the mechanism of aerosol generation and the qualities of the aerosol cloud. Respimat® SMI does not belong to any of the existing categories of inhaler device and represents an innovative approach to patient-oriented inhalation therapy.

2.1. Rationale for the development of Respimat® SMI

Respimat® SMI was developed in order to overcome the limitations of traditional inhaler devices and to meet the need for a convenient propellant-free inhaler that could effectively deliver aerosols from solutions. Currently, the most common inhaler devices used for bronchodilator and anti-inflammatory drug administration are pMDIs and DPIs; both have inherent disadvantages relating to lung deposition and ease of use.

The pMDI produces particles that travel very fast, generating a high-velocity cloud over a short period of time. Two consequences of this are deposition of the drug on the back of the throat (the oropharynx) and difficulties in synchronising the generation of the dose with inspiration. Only about 10–20% of the dose released from CFC-MDIs is deposited in the lungs; the remainder of the dose is lost through impaction in

the oropharynx (Newman et al., 1981). HFA-MDIs are similarly inefficient; only one HFA-MDI formulation has shown lung deposition >50% (Leach et al., 1998). Many patients, particularly children and the elderly, are unable to co-ordinate actuation of pMDIs with inhalation, which is crucial for proper lung deposition; thus the amount of drug reaching the lungs is both small and variable. Numerous other inhaler technique errors have been observed with pMDIs, including stopping inhalation when the aerosol hits the back of the throat (Pavia, 1997). The soft mist generated by Respimat® SMI travels much slower and lasts much longer than aerosol clouds from other devices. The relatively long period over which the dose from Respimat® SMI is released facilitates co-ordination of actuation and inhalation compared with pMDIs. This should help the patient to achieve the correct inhaler technique, which is important for successful long-term treatment. Furthermore, Respimat® SMI is easy and convenient to use; it retains the 'user-friendliness' of pMDIs, but does not require cumbersome spacer devices to slow the aerosol cloud and reduce oropharyngeal deposition (Denyer et al., 2000).

DPIs are breath-actuated and therefore require no co-ordination between device actuation and inhalation. However, both the aerosolisation and delivery of the drug to the lung are dependent on an adequate inspiratory effort from the patient. Airflow achieved early in the inspiratory profile deaggregates the drug from its carrier powder (usually lactose) and determines the particle size distribution of the aerosol. Because of the great variability in inspiratory flow, both between patients and within an individual patient, the proportion of the metered dose that is inhaled varies considerably, but is typically quite low (Meakin et al., 1998). A large fraction of the drug often remains bound to the carrier and deposits in the oropharynx (Ganderton, 1997,1999). For some DPIs, lung deposition is lower than that seen with pMDIs (Newman, 1999; Zainudin et al., 1990). Importantly, some powder formulations are extremely moisture-sensitive; adsorption of moisture can significantly increase powder cohesiveness, leading to decreased generation of fine particles during inhalation.

Energy to generate the soft mist delivered by Respimat® SMI comes from a compressed spring inside the inhaler; consequently, the particle size produced from the device is not dependent on the patient's inspiratory effort. Moreover, Respimat® SMI generates an aerosol cloud from a solution rather than a powder, avoiding moisture adsorption and powder agglomeration problems. These characteristics ensure that the dose delivered with each actuation from Respimat® SMI remains uniform.

Respimat® SMI is designed to be environmentally friendly and to increase lung deposition and reduce oropharyngeal deposition of the drug compared with pMDIs and DPIs, without the use of spacer devices. One design goal was to realise clinical improvements and minimise side effects by lowering the nominal inhaled dose compared with conventional delivery systems.

2.2. The concept of a soft mist inhaler

The generation of an inhalable aerosol from a drug solution requires the metered dose of liquid to be converted into appropriately sized droplets without the use of propellants. One technique involves the use of electrical energy to produce vibrations (which is common in ultrasonic and piezo-electric devices). A second approach is to use mechanical energy to force drug solution through a nozzle. Respimat® SMI derives mechanical energy from a spring that can be easily compressed by the patient (Zierenberg et al., 1996). The spring mechanism ensures that the aerosol is generated by a reliable and reproducible energy source and, consequently, dose and particle size distribution of the aerosol are independent of the variable inspiratory flow of the patient.

The soft mist concept was initially demonstrated in a prototype model, which consisted of a metal pump body and a syringe serving as a solution reservoir. A lever arm was used to simultaneously compress the spring and withdraw a metered volume of drug solution from the reservoir. The liquid was forced through a two-channel nozzle upon release of the spring, resulting in aerosol generation. The droplet size distribution in the aerosol was demonstrated to be in the range suitable for inhalation (Zierenberg, 1999; Zierenberg and Eicher, 2002).

Following further development of this early prototype, including the introduction of the uniblock nozzle (see below), the device was successfully used in lung deposition studies in healthy volunteers

Fig. 1. The marketed version of Respimat® Soft Mist™ Inhaler.

(Steed et al., 1995a,b). Additional refinement of the device occurred after patient focus groups evaluated four different design prototypes. The preferred version of the device was used for phase II and phase III clinical trials. Several additional aesthetic modifications have been made to the device in advance of its launch onto the market. These include a hinged cap, colour-coded to identify specific drug classes contained in the device, and a transparent base to allow easy identification of the drug product (Fig. 1). A schematic illustration of the device is shown in Fig. 2.

The marketed device delivers 120 metered actuations and has a dose indicator to remind patients when a new prescription is needed. A locking mechanism automatically prevents the use of the device after all 120 actuations have been delivered. This ensures that there is no detectable 'tail-off', commonly seen with pMDIs, during which reduced doses are delivered close to container exhaustion. Spray content uniformity of doses delivered via Respimat® SMI was established gravimetrically, using 10 devices from three batches (Spallek et al., 2002). The delivered volume was con-

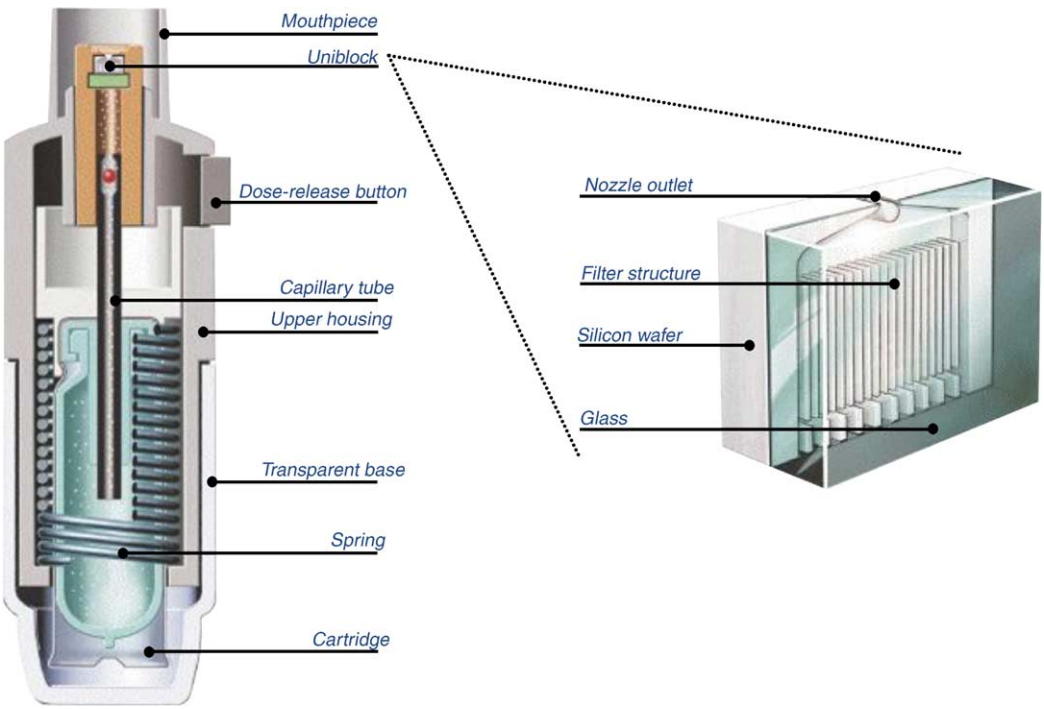

Fig. 2. Schematic illustration of Respimat® Soft Mist™ Inhaler, showing the key components of the device and details of the uniblock (Spallek et al., 2002).

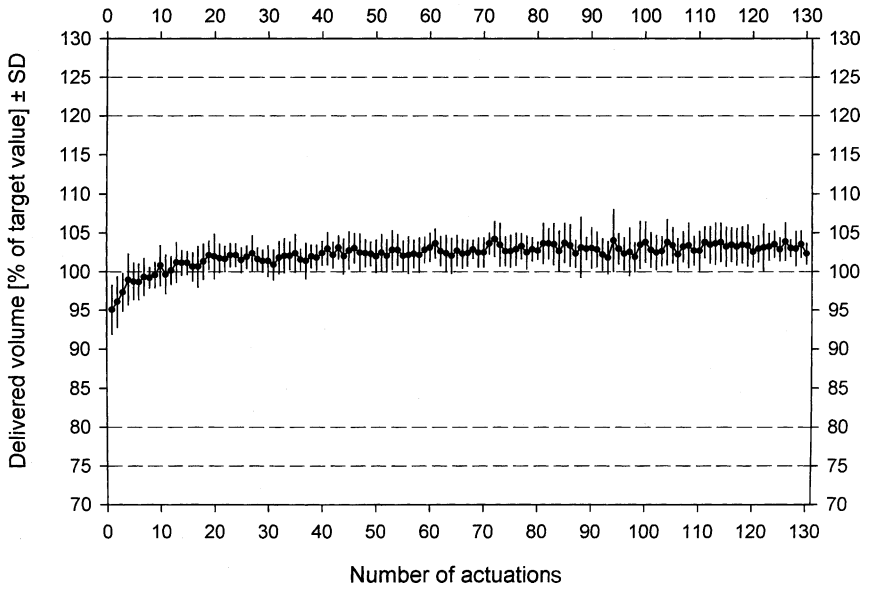

Fig. 3. Spray content uniformity data (of an aqueous solution) over 120 actuations delivered via Respimat® Soft Mist™ Inhaler (with 10 devices from 3 batches) (delivered volume ± S.D.) (Spallek et al., 2002).

sistent throughout 120 actuations of the device and no 'tail-off' effect was observed (Fig. 3).

Respimat® SMI is similar in size to pMDIs and DPIs (such as the Turbohaler®).

2.3. Mode of action of Respimat® SMI

Medication to be delivered by Respimat® SMI is stored as a solution in the drug cartridge. The cartridge consists of an aluminium cylinder containing a double-walled, plastic, collapsible bag, which contracts as the solution is withdrawn.

The initially sterile solution may be formulated with either ethanol, which acts both as a solvent and preservative, or water, with added preservatives (e.g. benzalkonium chloride). Either strategy maintains the microbial stability of the solution following initial puncture of the cartridge prior to first use of the device by the patient. Tests on used cartridges have shown that patient use of Respimat® SMI does not result in microbiological contamination of the inhalation solution (Schmelzer and Bagel, 2001).

The energy from a 180° twist of the device base compresses the spring. This transfers a pre-defined metered volume of the inhalation solution from the drug cartridge, through a capillary tube (via a non-return valve), to the pump cylinder. When the patient depresses the dose-release button, the energy of the spring forces the metered volume of drug solution into the uniblock.

The uniblock is the key element of Respimat® SMI, consisting of a nozzle fed by multiple extremely fine filter channels. In the initial prototype of Respimat® SMI, the nozzle openings were tiny holes pierced into a stainless steel disk; however, this design was not suitable for mass production (Spallek et al., 2002). The problem was overcome by the development of a miniature 'sandwich' concept, the uniblock, composed of a structured silicon wafer bonded to a small (2 mm × 2.5 mm) borosilicate glass plate (Fig. 2). Inlet, outlet and filter channels (which prevent the nozzle from becoming blocked) are etched into the silicon wafer using a technique derived from microchip production technology (Zierenberg et al., 1996; Zierenberg, 1999; Zierenberg and Eicher, 2002; Spallek et al., 2002). This allows the units to be produced on a large scale with high precision and accuracy. The configuration of the inlet and outlet channels is engineered to produce a high fine particle fraction (droplets <5.8 μm in diameter). The robustness of the uniblock (and the device as a whole) has been confirmed by rigorous mechanical testing (Spallek et al., 2002).

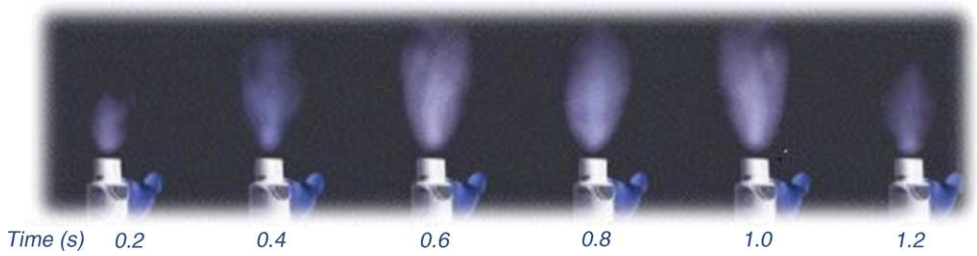

Fig. 4. Photographs, taken at intervals of 0.2 s, showing the generation of the Soft Mist™ from Respimat® Soft Mist™ Inhaler (Hochrainer and Hölz, 2001).

The metered drug solution is forced through the channels in the uniblock, producing two fine jets of liquid at the outlet; these converge at a precisely set angle (Zierenberg, 1999; Zierenberg and Eicher, 2002), generating a slow-moving cloud of inhalable particles – the soft mist (Hochrainer and Hölz, 2001). The soft mist emerges from the nozzle with a velocity approximately one-tenth of the speed of release of an aerosol cloud from a pMDI (Newman et al., 1996). Hochrainer and Hölz compared the velocity of the aerosol cloud and the aerosol generation time (spray duration) from Respimat® SMI with those delivered from various CFC– and HFA-MDIs (Hochrainer and Hölz, 2001). They found that aerosol clouds generated from Respimat® SMI were considerably slower-moving and had a longer spray duration time compared with either CFC- or HFA-MDIs (Fig. 4).

A high proportion of the droplets in the aerosol cloud from Respimat® SMI fall into the fine particle fraction (droplets of <5.8 μm in diameter) (Wachtel and Ziegler, 2002; Spallek et al., 2002); these droplets are likely to be deposited in the lungs after inhalation. Studies on an aqueous solution of fenoterol and an ethanolic solution of flunisolide delivered from Respimat® SMI have shown that fine particle fractions are approximately 66% for the aqueous formulation and 81% for the ethanolic formulations (Zierenberg, 1999; Zierenberg and Eicher, 2002). Fig. 5 shows a typical example of the particle size distribution of an aqueous solution measured in an Andersen Cascade Impactor (Spallek et al., 2002). For comparison, the fine particle fractions of the aerosols delivered by pMDIs and DPIs are typically less than 40% (van Noord et al., 2000; Steed et al., 1997; Newman et al., 1998; Hill and Slater, 1998; Kamin et al., 2002).

Because Respimat® SMI generates a slow-moving aerosol cloud with a high fine particle fraction, radiolabelled aerosols imaged by gamma scintigraphy have been able to demonstrate that less of the dose from Respimat® SMI is deposited in the oropharynx and more reaches the lungs than with pMDIs and DPIs (Newman et al., 1996, 1998; Steed et al., 1997; Wilding et al., 2002). Newman et al. investigated lung and oropharyngeal deposition of flunisolide administered to 12 healthy subjects via Respimat® SMI, pMDI or pMDI plus Inhacort® spacer (Newman et al., 1996). Mean whole lung deposition of flunisolide from Respimat® SMI (39.7%) was significantly higher than from pMDI (15.3%) or pMDI plus spacer (28.0%). Typical scans of the distribution of radiolabelled aerosol from each device are shown in Fig. 6. In a more recent study, in 12 healthy volunteers,

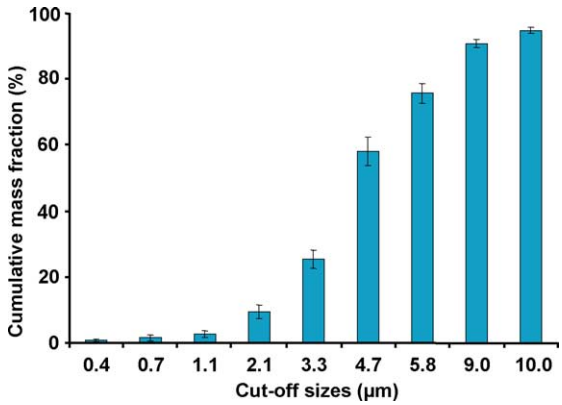

Fig. 5. Typical aerodynamic particle size distribution for the aerosol generated by Respimat® Soft Mist™ Inhaler, using an aqueous drug solution and an Andersen cascade impactor (relative humidity >90%) (cumulative mass fraction; % ± S.D.) (Spallek et al., 2002).

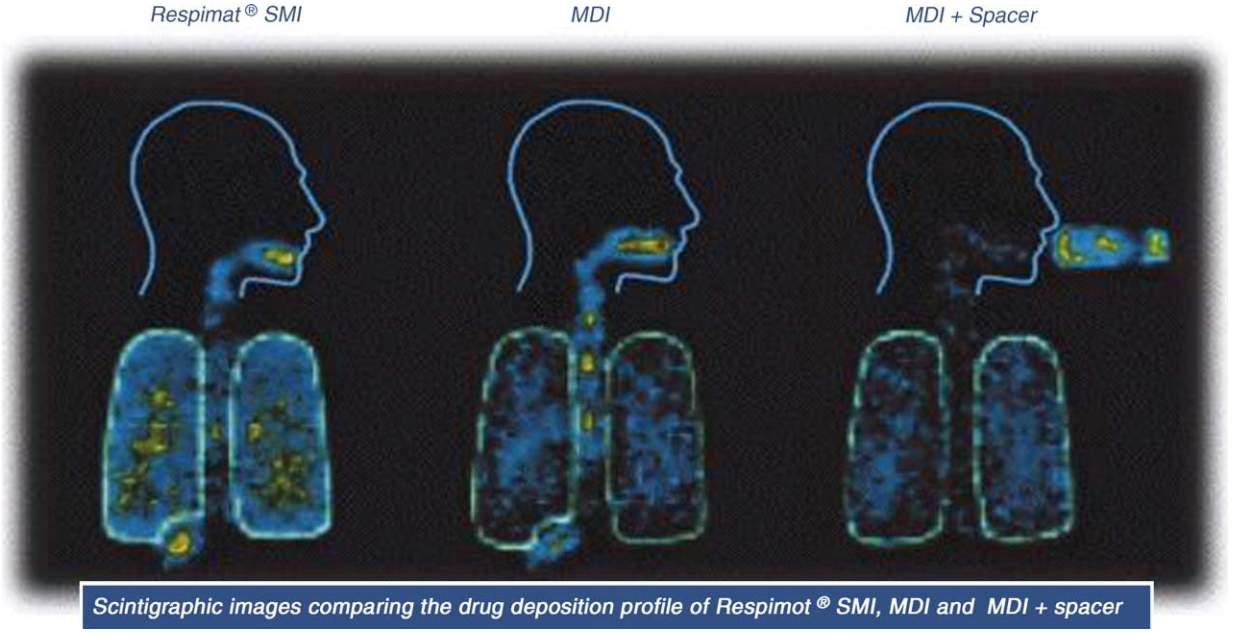

Fig. 6. Scintigraphic scans from one individual showing the deposition of radiolabelled aerosol in the lungs immediately after administration of a single dose of 250 μg flunisolide delivered via Respimat® Soft Mist™ Inhaler, pressurised metered dose inhaler (pMDI) or pMDI plus spacer, on each of three study days (Newman et al., 1996).

Table 1
The distribution of a metered dose of fenoterol in the lungs and oropharynx of 12 healthy subjects using Respimat® Soft Mist™ Inhaler (SMI), a pressurised metered dose inhaler (pMDI) or a pMDI plus spacer as the delivery device

	Amount of fenoterol (as % metered dose)		
	Respimat® SMI	pMDI	pMDI plus spacer
Whole lung	39.2 (12.7)	11.0 (4.9)	9.9 (3.4)
Central lung zone	11.0 (3.7)	3.1 (1.1)	2.5 (0.9)
Intermediate lung zone	14.1 (4.9)	3.7 (1.8)	3.6 (1.2)
Peripheral lung zone	14.1 (4.8)	4.2 (2.1)	3.8 (1.5)
Oropharynx	37.1 (10.4)	71.7 (7.4)	3.6 (2.4)
Delivery device	21.9 (6.1)	16.7 (5.4)	86.2 (5.2)
Exhaled air	1.9 (1.7)	0.6 (0.4)	0.4 (0.3)

The proportions of fenoterol deposited in the delivery device and detected in the exhaled air are also shown. Fenoterol distribution was detected by gamma scintigraphy. Data are given as mean and S.D. (Newman et al., 1998).

whole lung deposition of the bronchodilator fenoterol was greater when delivered by Respimat® SMI compared with pMDI or pMDI plus spacer (Table 1) (Newman et al., 1998). Additionally, Respimat® SMI deposited more of the fenoterol dose in the central, intermediate, and peripheral lung regions than either the pMDI or the pMDI plus spacer. The mean oropharyngeal deposition of fenoterol was significantly lower via Respimat® SMI than via the pMDI (37.1% versus 71.7% of metered dose, respectively).

2.4. Clinical performance of Respimat® SMI

Because Respimat® SMI increases the amount of drug deposited in the lungs, Boehringer Ingelheim expected that inhaled drugs would maintain their efficacy even when smaller nominal doses than would normally be delivered by a pMDI were administered. This concept has been tested in a number of clinical studies.

Respimat® SMI is being developed for use with a range of drugs for the treatment of asthma or COPD. Some of these studies have been conducted using a fixed combination of ipratropium bromide (IB) and fenoterol hydrobromide (FEN) (Berodual®); IB/FEN is indicated for the symptomatic treatment of airway narrowing in patients with asthma or COPD. Five clin-

ical studies of IB/FEN delivered via Respimat® SMI have already been completed.

In phase II, a dose-ranging and a cumulative dose-response study were conducted in adult asthmatics (Goldberg et al., 2001; Kunkel et al., 2000); the first of these demonstrated a dose-response relationship for IB/FEN delivered via Respimat® SMI, producing safe and efficacious bronchodilation in asthmatic patients (Goldberg et al., 2001). The cumulative dose study showed that Respimat® SMI improves the delivery of IB/FEN compared with pMDIs, providing an equipotent bronchodilatory effect at only one-half of the cumulative dose needed with a pMDI (Kunkel et al., 2000).

Three phase III trials have been completed; two of these were in asthma patients–one in adults (Vincken et al., 2004) and one in children (von Berg et al., 2004) and the third was in COPD patients (Kilfeather et al., 2004). The results showed that Respimat® SMI enables a 50% reduction of the nominal daily dose of IB/FEN in patients with asthma or COPD while offering similar therapeutic efficacy and safety to the corresponding CFC-MDI (which was used with a spacer in the paediatric study) (Vincken et al., 2004; von Berg et al., 2004; Kilfeather et al., 2004).

3. Conclusions

The performance of the inhaler device is critical for optimal drug delivery, lung deposition and subsequent clinical effects. Respimat® SMI represents an innovative approach to inhalation therapy; this propellant-free, multi-dose inhaler generates an inhalable aerosol cloud (the soft mist) with superior properties to those produced by existing devices, such as pMDIs and DPIs.

The soft mist generated by Respimat® SMI is produced by the collision of two jets of liquid forced through a specially designed nozzle. The aerosol cloud is much slower moving than those produced by pMDIs and DPIs and contains a much higher fine particle fraction than most of these devices. In addition, the aerosol generation time (cloud duration) is longer compared with pMDIs and DPIs. The combination of these features improves the efficiency of drug delivery via inhalation by increasing the proportion of the inhaled dose that is deposited in the lung. This benefit has been validated in clinical studies, in which Respimat® SMI has been shown to allow a reduction in the dose of a combination bronchodilator compared with delivery via CFC-MDI, while offering the same level of therapeutic efficacy and safety. Therefore, the development of Respimat® SMI represents a significant step forward in pulmonary drug delivery.

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