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International Journal of Pharmaceutics 198 (2000) 63–70

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Comparison of in vitro and in vivo efficiencies of a novel unit-dose liquid aerosol generator and a pressurized metered dose inhaler

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Received 2 August 1999; received in revised form 9 November 1999; accepted 29 November 1999

Abstract

Gamma scintigraphic imaging was employed in 10 healthy volunteers to compare the total and regional lung deposition of aerosols generated by two delivery platforms that permitted microprocessor-controlled actuation at an optimal point during inhalation. An aqueous solution containing ^{99m}Tc-DTPA was used to assess the deposition of aerosols delivered by inhalation from two successive unit-dosage forms (44 μl volume) using a prototype of a novel liquid aerosol system (AERx™ Pulmonary Delivery System). This was compared with aerosol deposition after inhalation of two 50 μl puffs of a ^{99m}Tc-HMPAO-labeled solution formulation from a pressurized metered dose inhaler (MDI). The in vitro size characteristics of the radiolabeled aerosols were determined by cascade impaction. For the AERx system, the predicted lung delivery efficiency based on the product of emitted dose (60.8%, coefficient of variation (CV) = 12%) and fine particle fraction (% by mass of aerosol particles < 5.7 μm in diameter) was 53.3% (CV = 13%). For the solution MDI, the emitted dose was 62.9% (CV = 13%) and the predicted lung dose was 44.9% (CV = 15%). The AERx system demonstrated efficient and reproducible dosing characteristics in vivo. Of the dose loaded into the device, the mean percent reaching the lungs was 53.3% (CV = 10%), with only 6.9% located in the oropharynx/stomach. In contrast, the lung deposition from the solution MDI was significantly less (21.7%) and more variable (CV = 31%), with 42.0% of the radiolabel detected in the oropharynx/stomach. Analysis of the regional deposition of the radioaerosol indicated a homogeneous pattern of deposition after delivery from the AERx system. A predominantly central pattern of distribution occurred after MDI delivery, where the pattern of deposition was biased towards a central zone depicting the conducting airways. The AERx system, in contrast to MDIs, seems highly suited to the delivery of systemically active agents via pulmonary administration.

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0378-5173/00/$ - see front matter
PII: S0378-5173(99)00452-4

Keywords: Aerosol deposition; Metered dose inhaler; Liquid aerosol generator; Microprocessor-controlled device; Gamma scintigraphy

1. Introduction

The pulmonary route of drug administration has been shown to offer favorable conditions for the effective absorption of systemically active agents (Byron and Patton, 1994). Optimized aerosol delivery to the peripheral lung is a requisite for promoting good efficiency of solute transfer to blood (Colthorpe et al., 1992, 1995). Equally important is the fact that inter- and intra-subject variability in the extent of lung deposition of the aerosolized drug should be within accepted levels obtained with more conventional methods of dosing; for example, oral administration. It has been suggested (Byron and Patton, 1994), based on published experimental data, that an inter-subject coefficient of variation (CV) of around 10% for lung dosing is possible. This level of control may be especially important for inhaled drugs with a narrow therapeutic index.

The need for a new generation of aerosol systems for systemic drug delivery can be rationalized with reference to the extensive literature describing the scintigraphic assessment of aerosol deposition from conventional metered-dose inhalation devices (Newman, 1993). CFC-based pressurized metered dose inhalers (MDIs), for example, result in only a small fraction of each emitted dose penetrating beyond the oropharynx, and the dose reaching the lung exhibits a predominantly central deposition. Even in well-controlled studies, where subjects are given extensive training in the use of MDIs, the reported values for the inter-subject coefficient of variation in lung delivery are frequently in excess of 30%. In studies simulating more realistic conditions of use of MDIs, this value and the corresponding value for within-subject variability can be significantly higher (Borgström et al., 1998). Recently, a microprocessor-controlled accessory (SmartMist™) was shown to lead to optimization of the extent of pulmonary deposition of aerosols from a commercially available MDI (Farr et al., 1995). Using this device, the moment of aerosol actuation was varied with respect to inhalation flow rate and cumulative inspired volume. There was an approximate threefold difference in aerosol deposition between the best and worst combinations of inspiratory flow and volume at actuation, the maximum deposition being 18.6% (inter-subject coefficient of variation = 26%) of the dose metered by the MDI.

In this paper, a gamma scintigraphic study in a group of healthy subjects is described which compares the extent and pattern of pulmonary deposition of ^{99m}Tc-labeled aerosols emitted from a prototype AERx device (Schuster et al., 1997) and a solution formulation of a MDI. Upon in vitro testing, the solution MDI showed the potential to improve the percentage of metered dose delivered to the lungs over commercially available suspension-based systems. This MDI system was designed to deliver fentanyl to the lung for the purpose of achieving rapid analgesia following systemic absorption (Mather et al., 1998).

2. Methods

2.1. Preparation and in vitro evaluation of radioaerosol systems

Placebo formulations were utilized in both the AERx and MDI systems. Radiolabeling of the solution-phase MDI was performed using an established method (Harnor et al., 1993). A vial of Ceretec™ (HMPAO; Amersham Healthcare, UK) was reconstituted with 5 ml sterile 0.9% w/v solution containing approximately 1 GBq ^{99m}Tc as pertechnetate. The resultant ^{99m}Tc-HMPAO complex was extracted into Analar grade ether. An aliquot, equivalent to 800 MBq ^{99m}Tc, was added to an empty anodized aluminum canister (20 ml capacity) and the solvent evaporated to dryness under a stream of nitrogen. A cooled (-60°C) blend of 28:72% w/w trichlorofluoromethane:

dichlorodifluoromethane propellants (ICI Chemicals, UK) containing 0.05% w/w sorbitan trioleate (Span™ 85; ICI Chemicals) was added to the canister. A 50 μl metering valve (BK356; Bespak, UK) was immediately crimped into position on the canister and the contents briefly shaken to ensure complete dissolution of the lipophilic ^{99m}Tc-HMPAO complex.

For the AERx system, ^{99m}Tc-DTPA (Amersham Healthcare) in 0.9% w/v saline was diluted with the same solvent to provide a radioactive solution containing 160 MBq/ml ^{99m}Tc-DTPA. Aliquots (44 μl) of this solution were individually sealed into unit-dosage forms for use in the AERx device.

Aerosol output or emitted dose (expressed as percentage of loaded or metered dose) from the two devices was characterized using an Andersen sampler fitted with a glass induction port specified under USP〈601〉 Aerosols, Apparatus 2 (US Pharmacopeia, 1995). For the AERx system, the cascade impactor was configured to run at a flow rate of 70 l/min (Schuster et al., 1997), i.e within the preset flow firing point of the device. Stage 7 was removed and a pre-separator was fixed on top of the impactor. The effective cut-off diameters (ECD) of the remaining stages (including the pre-separator) were calculated from Stokes' Law using the manufacturer's ECD's at the standard operating flow rate of 28.3 l/min The standard flow condition and impactor configuration was used for analysis of aerosols emitted from the MDI. In both instances, the distribution of the radiolabel marker following actuation into the Andersen impactor was assessed by quantitatively washing the nonvolatile components of the aerosol from the actuator, throat and the impactor collection plates. Radioactivity was quantified by gamma counting (LKB Wallac, 1282 Compugamma CS). The mass balance of recovered radioaerosol ranged from 94.8 to 107.1%. The mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were calculated from a plot of the probit of cumulative percent undersize for the various collection stages of the Andersen sampler versus the log of the corresponding ECD. The fine particle fraction (FPF, %) was determined from the amount of radioactivity deposited on the stages of the Andersen impactor representing droplets of aerodynamic diameter < 5.7 μm (Stage 0 to filter for 'AERx configuration') or < 5.8 μm (Stage 1 to filter for 'MDI configuration') as a percentage of the recovered emitted dose. The predicted lung delivery efficiency was calculated from the product of emitted dose and fine particle fraction.

2.2. Study protocol

Ten healthy male volunteers between the ages of 20 and 32, with normal lung function for age, weight and height, completed the study. All subjects gave written informed consent and the study was approved by the Department of Health, UK and the South Glamorgan Health Authority Joint Ethics Committee, UK. Before taking part, each volunteer was required to complete a practice session using the SmartMist™ system loaded with a non-radioactive, placebo MDI and the AERx system loaded with dosage-forms containing 0.9% saline.

Each volunteer inhaled two puffs of ^{99m}Tc-labeled aerosol either from a solution MDI fitted within a SmartMist system or from the AERx device in a randomized cross-over fashion on two study days, separated by at least 48 h. The SmartMist was programmed to fire the MDI at the optimum flow/volume setting (flow rate range, 68–112 l/min; cumulative inhaled volume range, 180–420 ml) as defined in a previous study (Farr et al., 1995). The corresponding parameters for the AERx system were: inspiratory flow rate, 65–80 l/min; cumulative inhaled volume, 250–500 ml. A 10 s breath-holding maneuver after each puff was adopted and the exhaled dose was retrieved on a low-resistance air-filter (Whatman GF/A). Immediately following dosing, the volunteers were provided with a slice of bread and a drink of water to encourage removal of radioactivity originally deposited in the oropharyngeal region into the stomach. Posterior and anterior views of the lung and stomach, and a lateral head and neck view were recorded using a gamma camera (GEC MaxiCamera II fitted with a parallel-hole, low-energy collimator). All images were of a maximum 200 s duration and were captured

on a dedicated SUN SPARC station IPX computer operating with commercial software (MAPS 10,000; Link Medical Systems, Bourne End, UK). A complete record of each subject's inspiratory flow before, during, and after dosing was downloaded in real time from the SmartMist or AERx device to a personal computer running software developed for this purpose.

After dosing each volunteer with the AERx system, the device was disassembled and all components that had been in contact with the radiolabeled solution or aerosol were carefully washed. The washings were quantitatively transferred to volumetric flasks to enable, by gamma counting, an accurate determination of the delivered (emitted) dose. It was not possible to dismantle the MDI/SmartMist combination between subjects, hence the emitted dose during the in vivo studies was assumed to be the same as that derived in the in vitro experiments.

On a single occasion prior to the randomized study, each volunteer received a ventilation scan (anterior and posterior images) by tidal breathing ^{81m}Kr gas from a generator (Regional Radioisotope Centre, Dudley Road Hospital, Birmingham, UK) via a mouthpiece until views containing 200 000 counts were accumulated (approximately 100–200 s) by the gamma camera fitted with a medium energy collimator. A region of interest was drawn around the 20% contour of the geometric mean ventilation image to delineate the lung margin of each volunteer. This was superimposed on the anterior and reflected posterior deposition images, and other regions of interest drawn around areas equivalent to the central and peripheral lung. The ratio between aerosol counts in the central and peripheral zones (C/P) was calculated to determine the regional distribution of aerosols deposited in the lung after the various methods of administration relative to an ^{81m}Kr ventilation scan. Regions of interest were also drawn to encompass radioactivity located in the stomach and mediastinum, with a further area selected to quantify background radiation. After background correction, the geometric mean counts in those areas of interest were calculated from the appropriate pair of anterior and posterior counts. Background corrected mouth and pharyngeal counts were determined from the lateral views. The relative distribution of radioactivity in each of the areas of interest was calculated after further correction of counts in the anatomical regions for attenuation using a previously published method (Farr et al., 1995).

The scintigraphic data were evaluated for statistically significance differences by pairwise comparison using paired t-testing ($\alpha = 0.05$).

3. Results

The results from the in vitro characterization studies of aerosols emitted from the two inhalation systems are shown in Table 1. The solution MDI produced a mean emitted dose of 63.2%. A higher level of actuator deposition (35.9%) was

Table 1
In vitro characterization of output from the solution MDI and AERx system

	Solution MDI ($n = 4$)		AERx system ($n = 4$)	
	Mean	S.D.	Mean	S.D.
Emitted dose (%)[a]	63.2	8.2	60.8	7.1
FPF (%)[b]	71.0	5.6	90.6	1.6
Predicted lung delivery (%)[c]	44.9	6.7	55.3	7.1
MMAD (μm)	1.2	0.1	2.6	0.1
GSD	1.8	<0.1	1.5	0.3

[a] Percentage of radioactivity contained in the AERx dosage form or dispensed from the valve of the MDI.
[b] FPF = amount of aerosolized radioactivity in droplets <5.7 μm.
[c] Predicted lung delivery efficiency (% of loaded (AERx) or ex-valve (MDI) dose) = emitted dose × FPF.

Table 2
AERx and SmartMist solution MDI firing points (inspired flow rate/cumulative inhaled volume) and inspiratory parameters obtained with the devices operating at these firing points in ten volunteers

	AERx system	SmartMist solution MDI
Firing flow (l/min) (set range)	65–80	68–112
Firing volume (ml) (set range)	250–500	180–420
Actual firing flow (l/min) ($\pm$S.D.)	67 ± 4.7	84 ± 11
Actual firing volume (ml) ($\pm$S.D.)	305 ± 77	227 ± 23
Mean flow post-dose (l/min) ($\pm$S.D.)	65 ± 5.7	84 ± 12
Overall mean flow (l/min) ($\pm$S.D.)	63 ± 4.1	81 ± 11
Maximum flow (l/min) ($\pm$S.D.)	80 ± 2.9	118 ± 14
Total inspired volume (l) ($\pm$S.D.)	4.29 ± 0.67	3.84 ± 0.79
Inhalation time (s) ($\pm$S.D.)	4.0 ± 0.67	2.9 ± 0.64

obtained than is evident normally with conventional suspension MDI systems. This was due to the use of an actuator with a narrow nozzle orifice (internal diameter, 0.25 mm), which was shown in a preceding formulation optimization study (unpublished observations) to result in the most effective disruption of the solution formulation into small droplets upon leaving the valve assembly. An actuator with a small diameter orifice has been shown to create a wider aerosol plume than conventional suspension MDI actuators (Evans et al., 1991), leading to higher deposition within the confines of the mouthpiece. Of the radioaerosol emitted from the MDI, 71.0% of the aerosol mass was contained in droplets < 5.8 μm, the remainder, depositing occurred within the throat inlet or on the upper stages of the cascade impactor. The mean predicted lung delivery efficiency was 44.9% of the radioactivity metered by each actuation of the MDI.

The AERx system provided a similar emitted dose and aerosol size distribution to that reported recently with morphine sulfate (Schuster et al., 1997). The vast majority of the emitted aerosol was contained in the fine particle fraction determined by cascade impaction such that the mean predicted lung delivery efficiency was 55.3% of the ^{99m}Tc-DTPA loaded into the system.

A summary of the parameters obtained for the complete inspiratory maneuvers adopted by the subjects using the solution MDI (in the SmartMist) and the AERx system is shown in Table 2. The mean firing values for inhalation flow and cumulative inspired volume were within the programmed ranges for both the SmartMist and AERx delivery systems. The benefit of the visual guidance system for the subject during the inspiratory maneuver is demonstrated by the fact that the mean flow post-actuation of either device was consistent with the overall mean flow; this in turn was very similar with the actual firing flow.

Typical scintiscans for each device are shown in Fig. 1. Mean $\pm$ S.D. oropharyngeal/stomach deposition was $42.0 \pm 6.7\%$ of the metered radioactivity for the solution MDI, compared with just $6.9 \pm 3.3\%$ of the loaded radioactivity obtained for the AERx system ($P < 0.0001$). Consequently, whole lung deposition (comprising left and right sides of the lung) for the AERx system was greatest at $53.3 \pm 5.8\%$ of the loaded radioactivity compared with $21.7 \pm 6.7\%$ of the metered activity for the solution MDI (Table 3; $P < 0.0001$). Regional aerosol deposition, characterized by sC/P, favored peripheral deposition with the AERx system (1.15 ± 0.34) compared with the solution MDI (1.66 ± 0.47) ($P < 0.01$ following comparison of inter-subject differences in individual values of sC/P for AERx and MDI delivery).

For the AERx system, the majority of dose not accounted for by deposition in the oropharynx/stomach and lung was retained in the device. The exhaled dose was $< 0.1\%$ of the total radioactivity, a value which is probably the result of the 10 s breath hold maneuver adopted by the subjects after inhalation of each dose. Mean $\pm$ S.D. dose emitted from the AERx system was $60.2 \pm 6.3\%$, a value very similar to that determined in the in vitro studies. Neither radioactivity retained in the actuator nor exhaled following administration was measured during the MDI phase of the study. However, it is unlikely that the dose retained in

the actuator during subject use would be different to that obtained in the in vitro study. In this case, the exhaled dose would have been as small as determined for the AERx system.

4. Discussion

This is the second gamma scintigraphic study to demonstrate the utility of a device incorporating microprocessor technology to automatically actuate aerosol delivery at a pre-programmed point, defined by both flow rate and cumulative inspiratory volume, during inhalation. In the first study (Farr et al., 1995), using the SmartMist device, it was shown that altering the point of aerosol actuation had a significant effect on the extent of drug depositing in the lung from a commercially available suspension-type MDI (Ventolin, Glaxo Wellcome). Using the firing point shown to be optimal in that study, this present investigation showed that the efficiency of lung deposition did not

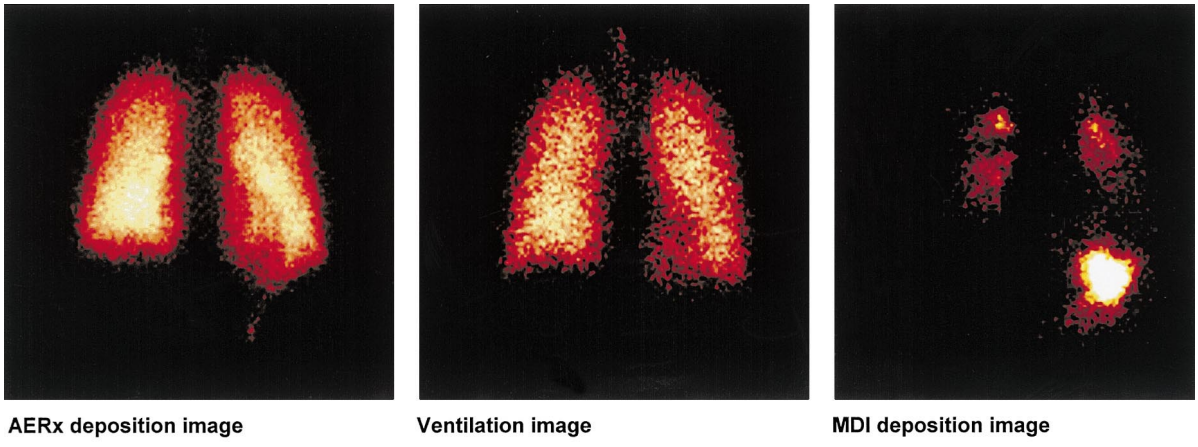

Fig. 1. Comparison of scintiscans for aerosol deposition after AERx and MDI aerosol delivery with a ^{81m}Kr ventialtion image (subject number 1).

Table 3
Radioaerosol deposition in the various anatomical regions following AERx and MDI dosing

Subject number	Deposition (% of loaded or ex-valve radioactivity[a])					
	Oropharynx/stomach		Lung		Regional deposition (sC/P)	
	AERx delivery	MDI delivery	AERx delivery	MDI delivery	AERx delivery	MDI delivery
1	7.1	51.6	51.7	12.1	0.99	2.42
2	6.6	33.5	52.7	30.2	1.52	1.73
3	13.5	44.6	60.0	19.1	1.03	1.26
4	6.5	40.4	59.1	23.3	0.77	1.14
5	4.6	33.7	51.7	30.0	1.77	2.43
6	3.5	34.1	61.0	29.6	0.74	1.36
7	3.0	50.3	50.5	13.4	0.91	1.77
8	4.5	45.7	56.6	18.0	1.52	1.63
9	8.8	45.7	45.9	18.0	1.15	1.72
10	10.4	40.3	43.9	23.4	1.12	1.16
Mean	6.9	42.0	53.3	21.7	1.15	1.66
S.D.	3.3	6.7	5.8	6.7	0.34	0.47

[a] Percentage of radioactivity contained in the AERx dosage form or dispensed from the valve of the MDI.

increase appreciably with the use of a solution MDI system. Leach (1996) (also using breath control) reported lung deposition values of 56 ± 9% of the emitted dose for a novel solution formulation of beclomethasone in an HFA-based MDI. By way of comparison, the lung deposition for the MDI in this study would be approximately 34% of the emitted dose.

This study has shown that the AERx system is capable of delivering efficiently and reproducibly to the lungs of human subjects. In a recent abstract, Smaldone et al. (1999), using a later AERx prototype, showed an even higher level of efficiency, where total lung deposition in mild to moderate asthmatics was 80 ± 2% of the originally loaded dose. Results from both these studies were due to the fact that a small-droplet aerosol cloud is generated by the device early in the breath and during slow inhalation, without the ballistic component associated with MDIs. Deposition in the oropharyngeal region is therefore largely avoided. The presence of light-emitting diodes on the device guides the subject to maintain the appropriate flow rate at the initiation, during and after aerosol actuation. This is shown by the inhalation parameters listed in Table 2.

In addition to efficiency, reproducibility of the dose of drug delivered to the lung will be a key requirement in the acceptance of the pulmonary route as a means of giving drugs for systemic therapy. Even with systems capable of generating aerosols of a constant size distribution, changes in inspiratory flow rate upon administration can lead to variation in the ratio of oropharynx:lung deposition. This has been demonstrated for MDIs (Farr et al., 1995) and most recently for a dry powder inhaler device (Dolovich and Rhem, 1997). The fact that appreciable variation exists in oropharyngeal anatomy between individuals will further contribute to inter-patient differences in lung dosimetry (Yu et al., 1981). Avoidance of the oropharynx through selection of the appropriate particle size distribution together with control of inhalation flow rate at the point of firing and throughout the remainder of the inspiratory maneuver should help minimize variations in lung dosimetry. This was demonstrated with the AERx system in this study (and that of Smaldone et al. (1999)), in which the level of inter-subject variability for lung dosimetry was very low, similar to values of variability obtained for the in vitro derived aerosol parameters (i.e. around 11–12%). In contrast, the level of inter-subject variability for lung dosimetry for the solution MDI was around 35%, a value typically reported for a number of conventional aerosol delivery systems evaluated in a well-controlled experimental setting. Under more realistic conditions of use, these values of variability will substantially increase (Borgström et al., 1998). The prototype AERx device was shown in vivo to possess the necessary dosing attributes for the delivery of potent systemically active drugs. This has been substantiated in studies involving inhaled morphine given via the AERx system, where levels of inter- and intra-subject variability in the main pharmacokinetic parameters were similar to intravenous injection (Ward et al., 1997; Gonda et al., 1999).

Another noteworthy finding of this study was that the actual lung dose obtained with the AERx system dose (as determined by gamma scintigraphy) was comparable with that predicted from in vitro methods. While in vitro methods, such as cascade impaction, are routinely used in the characterization of the pharmaceutical inhalation dosage-forms, usually there is relatively poor absolute agreement between the dose contained within fine 'respirable' particles determined in vitro and the actual lung dose measured in vivo (Newman, 1998). In this work, it has been shown that the data obtained by cascade impaction was highly predictive of lung deposition of aerosols emitted by the AERx system. This provides confidence in employing such methods as meaningful laboratory tests in the development of this novel pulmonary delivery system.

Acknowledgements

A.M.R. gratefully acknowledges the support of a research assistantship awarded by Aradigm Corporation.

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