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A comparison of the lung deposition of salbutamol inhaled from a new dry powder inhaler, at two inhaled flow rates

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Summary

A method of radiolabelling micronised salbutamol with ^{99m}Tc and blending it with lactose, for use in a multidose dry powder inhaler (Pulvinal, Chiesi) was developed. In vitro experiments with a multistage liquid impinger demonstrated that the labelling process did not affect the particle size distribution of the drug, and that the radiolabel was a marker for the drug substance across a range of particle sizes. Gamma scintigraphy was used to measure the in vivo deposition of salbutamol in 10 healthy volunteers, at a fast peak inhaled flow rate (mean 46.0 l/min) and at a slow peak inhaled flow rate (27.8 l/min). A significantly higher percentage of the dose ($p = 0.05$) was deposited in the lungs at the fast flow rate (14.1 ± 3.2%) compared to the slow flow rate (11.7 ± 2.3%). Deposition patterns within the lung regions were similar at the two flow rates. The major site of deposition was the oropharynx, and approx. 1% of the dose was exhaled. The deposition patterns from the Pulvinal inhaler were similar to those observed previously both for other powder inhalers and for pressurised metered dose inhalers.

Introduction

Respiratory diseases such as asthma are treated with a range of drugs which may be delivered either systemically or by inhalation. Direct administration of bronchodilators to the lungs by inhalation provides swift relief for the patient and allows the therapeutic dose to be reduced when compared to that of an oral formulation. Consequently, any side effects attributed to systemic administration of the drug are reduced (Clark et al., 1992). The conventional method of delivering drug to the lungs is via a pressurised metered dose inhaler (MDI). However, MDIs require that actuation of the device is coordinated with inhalation, a problem for many patients particularly the very young and the elderly (Crompton, 1982). An alternative inhalation device, the dry powder inhaler (DPI) avoids this problem by being breath actuated, thus removing the need for coordination since the patient's inspired flow of air delivers drug to the lungs (Bell et al., 1971; Wetterlin, 1988; Ganderton and Kassem, 1992). In addition, DPIs do not contain chlorofluorocarbon propellants which have proved environmently harmful (Newman, 1990) and which have been linked with

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adverse effects such as bronchoconstriction and heart palpitations (Lancet, 1975).

The majority of dosage forms for DPIs consist of micronised drug particles blended with a carrier substance, normally lactose (Ganderton and Kassem, 1992). The larger carrier particles provide a surface to which the cohesive drug particles adhere, allowing a reproducible dose to be metered and delivered to the patient. The energy necessary to separate the drug-excipient complex is provided by the patient's inspiratory flow rate. The efficiency of the separation has been shown to be dependent upon flow rate, with higher flow rates producing more particles in the respirable fraction of a blend (Jaegfeldt et al., 1987; Kassem et al., 1989; Zanen et al., 1992).

The use of radiotracer techniques to determine lung deposition is well established. An inherent problem, however, with these techniques is that the labelling process can adversely affect the aerodynamic properties of the formulation, thus reducing deposition of labelled drug compared to unlabelled drug (Newman et al., 1989b). An objective of the present study was to develop a method of directly labelling salbutamol powder with the radionuclide ^{99m}Tc, whilst not affecting the formulation. This method would then be used to assess aerosol deposition of salbutamol from a multidose powder inhaler (Pulvinal, Chiesi, Fig. 1), used at low and maximal flow rates, in a group of healthy volunteers.

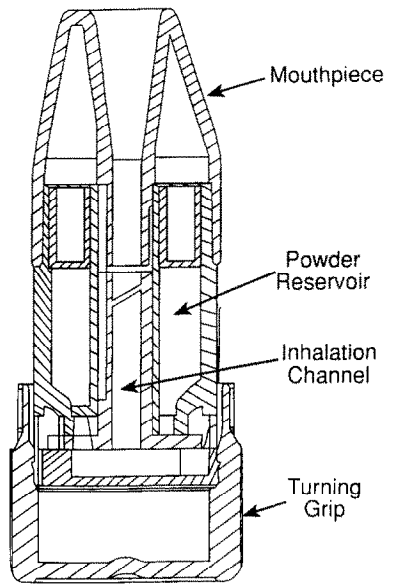

Fig. 1. The Pulvinal inhaler (Chiesi Farmaceutici S.p.A), delivering 80 metered doses of 200 μg salbutamol with 24 mg lactose carrier.

Materials and Methods

Radiolabelling method

Micronised salbutamol powder (Chiesi) was radiolabelled with the gamma-emitting radionuclide ^{99m}Tc in the following manner. The radionuclide was extracted into methyl ethyl ketone from a solution of sodium pertechnetate in saline, and the solvent evaporated to dryness. The radionuclide was re-suspended in chlorofluorocarbon 11 and this solution was added to the salbutamol powder (100 mg). The chlorofluorocarbon 11 was evaporated and lactose (0.5 g, Meggle EP D50) added to the recovered drug. This mixture was ground thoroughly and then passed through a sieve (150 μm), followed by lactose (11.5 g, Chiesi). The powder blend was then mixed thoroughly in a Turbula mixer (5 min at 42 rpm) and 2.5 g of labelled blend was loaded into a Pulvinal inhaler according to the manufacturers' instructions.

Assessment of radiolabelling method

In order to assess the effect of the labelling process on the formulation, the particle size distributions of the labelled drug formulation and of the radiolabel were determined in a multistage liquid impinger (MLI), as previously described (Jaegfeldt et al., 1987). These measurements were compared with the size distribution of salbutamol from a formulation that had not been radiolabelled. The distributions were fractionated into the mass of drug, or amount of radiolabel, on the mouthpiece, 'throat' (a 90° bend), four impaction stages and the final filter. The MLI was operated at 60 l/min, and was subsequently washed out with methanol. The particle size cut off points for the throat and each stage were as follows: throat, 25 μm; stage 1, 10 μm; stage 2, 5.5 μm; stage 3,

3.3 μm; stage 4, 0.8 μm. The respirable fraction of a formulation was defined as the quantity of drug or radiolabel recovered on stage 3, stage 4 and the final filter (particles with a diameter < 5.5 μm).

Volunteers

10 healthy volunteers (five male and five female), aged 21–44 years (mean 24 years) were included in the study. The subjects' lung function was within normal limits (forced expiratory volume in 1 s, FEV_1, 96–121% predicted (Quanjer, 1983)). All were non-smokers of at least 1 year's duration and were declared healthy by a physician, provided that they were free from clinically significant pathology and that they had passed a physical examination. The physical examination was repeated within 14 days of completing the studies. All subjects provided informed consent in writing. The objectives and methods used in the study were approved by the Quorn Research Review Committee, U.K. and were conducted in accordance with the Declaration of Helsinki. The administration of radioactivity to the subjects was approved by the Department of Health, U.K.

Clinical procedures

The study was performed in a randomised cross-over fashion. Each subject was studied twice, at least 48 h apart, and on both occasions inhaled two doses from a Pulvinal inhaler (a total of 400 μg of salbutamol, containing 10 MBq ^{99m}Tc, on each study day). The inhalation device was connected in series with a Vitalograph MDI-compact spirometer which allowed the peak inhaled flow rate, inhaled volume and breath holding time to be recorded during the inhalation procedure. An empty Pulvinal inhaler was used to train the subjects to inhale deeply at the targeted flow rates, followed by a breath holding pause of approx. 10 s. Subjects were instructed to inhale as fast as possible ('fast' flow rate) on one study day, and at 30 l/min ('slow' flow rate) on the other day. Following a 10 s breath-holding pause, exhalation was made into a filter (Pall Ultipor, U.K.) to capture inhaled drug that was not deposited in the lungs.

Lung function tests (forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and peak expiratory flow rate (PEFR)) were measured immediately before inhalation of the radiolabelled drug. These tests were repeated 15 min after dosing to ensure that lung function had not been adversely affected by the procedure.

Scintigraphy

A gamma camera (General Electric Maxicamera) connected on-line to a Nodecrest computer system was used to scan the subjects. Posterior

TABLE 1

Deposition pattern of radiolabelled powder formulation at fast peak inhaled flow rate

Subject	Fractionation of dose				Regional lung deposition			
	% lung	% oropharynx	% mouthpiece	% exhaled	% central	% intermediate	% peripheral	P/C ratio
1	18.8	75.8	5.1	0.3	6.5	5.2	7.1	1.1
2	14.3	77.8	7.8	0.2	4.4	5.2	4.7	1.1
3	15.4	79.8	4.4	0.4	6.1	4.5	4.8	0.8
4	14.8	77.3	4.1	3.9	5.0	4.1	5.6	1.1
5	12.9	82.0	3.7	0.4	4.5	3.9	4.4	1.0
6	10.6	84.3	5.0	0.2	3.9	3.2	3.5	0.9
7	7.6	85.6	5.6	1.2	2.1	2.3	3.1	1.5
8	15.3	81.7	2.4	0.5	5.6	4.7	5.1	0.9
9	13.7	81.4	4.6	0.3	4.7	4.2	4.7	1.0
10	17.7	77.1	4.7	0.5	6.1	5.8	5.8	1.0
Mean	14.1	80.3	4.8	0.8	4.9	4.3	4.9	1.0
SD	3.2	3.3	1.4	1.1	1.3	1.0	1.1	0.2

Results are expressed as percentages of the nominal dose of 400 μg salbutamol.

and anterior views of the lungs and a lateral view of oropharynx were taken immediately after inhalation. Additional scans of the device mouthpiece and the exhalation filter were also taken. A lung ventilation scan was obtained by inhalation of the inert gas ^{81m}Kr for each subject, on one of the study days. All images were stored on magnetic tape for subsequent data analysis.

The lung images were divided into central, intermediate and peripheral areas as previously described (Newman et al., 1989a). Computer-generated regions of interest were drawn around these areas and around the oropharynx, stomach, exhalation filter and mouthpiece. The number of counts in each region of interest were calculated and corrected for background and for radioactive decay. The counts from the anterior and posterior views of the lungs, from the oropharynx and from the stomach were combined by taking the geometric mean values. The counts were further corrected by applying factors to allow for tissue attenuation of gamma rays (Fleming, 1979). Counts from the stomach were assumed to arise from particles initially deposited in the oropharynx and subsequently swallowed. Counts found on the mouthpiece of the exhalation filter were also added to the oropharyngeal counts as they were not considered to be due to exhaled material. The nominal dose was fractionated into percentages deposited in the lungs and oropharynx, retained on the mouthpiece or recovered from the exhaled air. The effective dose equivalent to each volunteer from participation in the study was estimated to be 0.2 mSv.

Statistical test

The Wilcoxon matched-pairs signed-ranks test was used to determine whether differences between the two study days were significant. A p value of ≤ 0.05 was considered significant.

Results

In vitro validation of radiolabelling method

The particle size distributions of unlabelled drug, labelled drug and radiolabel, as determined in the MLI, are shown in Fig. 2. The mean ($\pm$SD) respirable fractions of unlabelled drug, labelled drug and radiolabel were 16.3% ($\pm$3.2%), 16.7% ($\pm$2.5%) and 15.0% ($\pm$1.5%), respectively. The labelling method used gave a ratio of the respirable fractions for unlabelled drug/radiolabel as 1.09. The results showed firstly that the particle size distribution of salbutamol was not adversely affected by the labelling procedure, and secondly that the radiolabel was a valid marker for the drug substance.

TABLE 2

Deposition pattern of radiolabelled powder formulation at slow peak inhaled flow rate

Subject	Fractionation of dose				Regional lung deposition			
	% lung	% oropharynx	% mouthpiece	% exhaled	% central	% intermediate	% peripheral	P/C ratio
1	15.9	79.3	4.2	0.6	5.1	5.0	5.9	1.2
2	10.9	78.4	4.8	5.9	3.8	3.8	3.3	0.9
3	11.0	82.5	4.7	1.7	3.4	3.5	4.1	1.2
4	11.9	83.5	4.1	0.4	3.4	3.5	5.0	1.4
5	9.8	77.6	12.2	0.4	3.1	3.2	3.4	1.1
6	14.5	78.8	6.4	0.2	4.3	5.2	5.0	1.2
7	8.7	79.6	10.8	0.8	2.2	2.6	3.9	1.8
8	13.5	69.9	15.7	0.9	4.4	4.2	4.9	1.1
9	9.4	77.9	12.4	0.2	3.3	2.7	3.3	1.0
10	11.5	79.1	9.3	0.1	4.7	3.2	3.6	0.8
Mean	11.7	78.7	8.5	1.1	3.8	3.7	4.2	1.2
SD	2.3	3.6	4.2	1.7	0.9	0.8	0.9	0.3

Results are expressed as percentages of the nominal dose of 400 μg salbutamol.

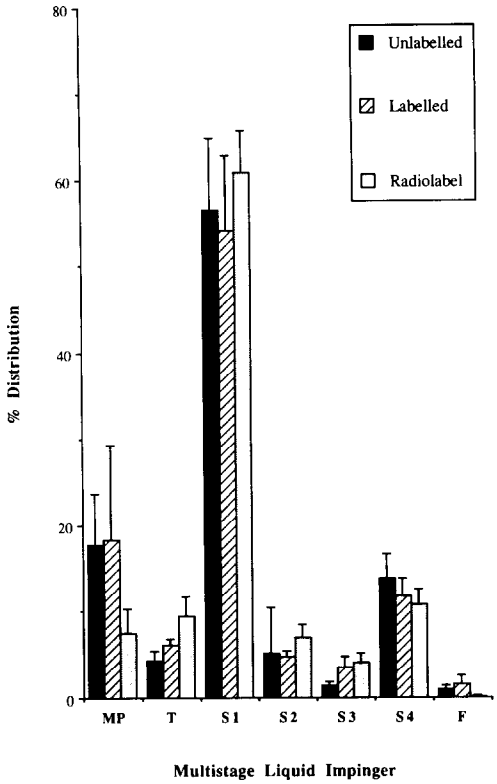

Fig. 2. Validation of radiolabelling technique, showing percentage distributions of 'unlabelled' drug ($n = 10$), 'labelled' drug ($n = 3$) and radiolabel ($n = 3$) in a multistage liquid impinger, for salbutamol/lactose blends delivered from a Pulvinal inhaler. MP, mouthpiece; T, throat; S1–4, impinger stages 1–4; and F, final filter. The respirable fractions, calculated as the sum of S3, S4 and F, were 16.3, 16.7 and 15.0% for unlabelled drug, labelled drug and radiolabel, respectively.

In vivo study

The deposition patterns of labelled salbutamol at fast and slow peak inhaled flow rates are shown on Tables 1 and 2, respectively. The percentage of the dose ($\pm$SD) deposited in the lungs at the fast peak inhaled flow rate ($14.1 \pm 3.2\%$) was significantly greater ($p = 0.05$) than the dose deposited at the slower peak inhaled flow rate ($11.7 \pm 2.3\%$). Deposition in the central, intermediate and peripheral regions of the lung averaged higher at the fast flow rate than at the slow flow rate, but only the difference in central lung deposition was significant ($p = 0.01$). The ratio between peripheral and central deposition (P/C) was similar for the fast and slow flow rates. The majority of the dose was deposited in the oropharynx (means 80.3 and 78.7% at fast and slow flow rates, respectively) and only about 1% of the dose was exhaled. Typical deposition patterns in one subject are shown in Fig. 3.

Inhalation details for the fast and slow peak inhaled flow rates are shown on Table 3. The mean ($\pm$SD) peak inhaled flow rates were 46.0 (± 4.4) l/min at the fast flow rate and 27.8 (± 2.5) l/min for the slow flow rate. All subjects took deep inhalations (1.9–4.1 l) and maintained the required breath-holding pause (9–13 s). On both study days the lung function tests for each subject were within normal limits both before and after administration of the labelled drug.

Discussion

Various radiotracer techniques have been used to determine the deposition of drug from DPIs. In a comparative study between inhalation devices, radiolabelled Teflon particles were used to label an MDI and a DPI (Zainudin et al., 1990). Similar lung deposition values were recorded from both devices, although the Teflon particles did not match exactly the size and shape of the micronised drug particles. Vidgren et al. (1988) radiolabelled spray-dried sodium cromoglycate particles with ^{99m}Tc, although again these particles differed in size, shape and flow properties compared to micronised particles (Vidgren et al., 1987). In the present study we have developed a radiolabelling method for a salbutamol/lactose blend formulation which achieves an almost perfect match between the particle size distributions of labelled drug, radiolabel and unlabelled drug. This technique allows the lung deposition of salbutamol to be accurately determined from the distribution of radiolabel within the body. The technique was based partly on an earlier method used to radiolabel a pure drug formulation of terbutaline sulphate for delivery from a multidose powder inhaler, Turbuhaler (Newman et al., 1989b; Borgström et al., 1993).

The lung deposition results for the Pulvinal inhaler are comparable with those obtained for other powder inhalers. Vidgren et al. (1988) in-

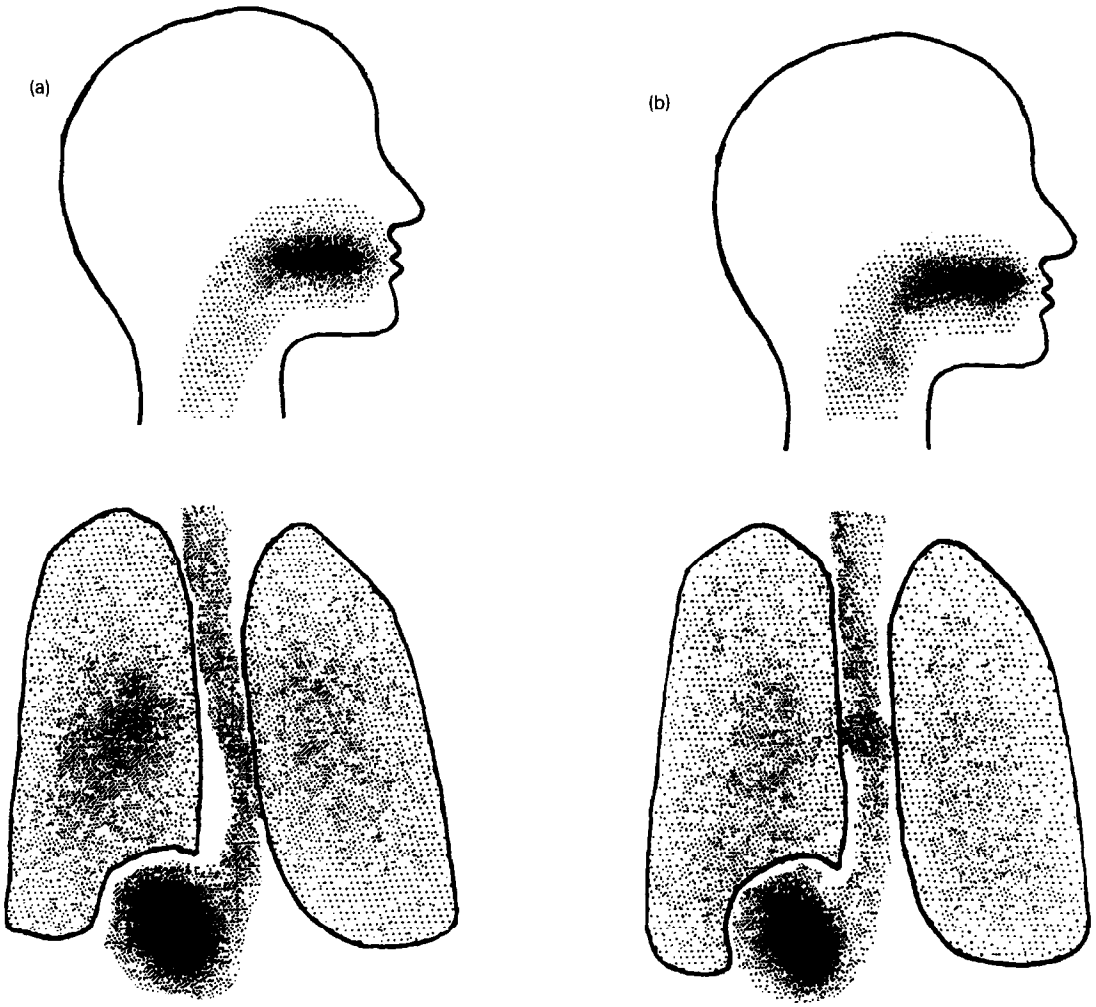

Fig. 3. (a,b) Typical deposition patterns in the respiratory tract of one subject, after inhalation from a Pulvinal inhaler at a 'fast' (a) and 'slow' (b) peak inhaled flow rate.

vestigated four single dose powder inhalers, used at an inhaled flow rate of 60 l/min and reported mean lung depositions ranging from 6.2% of the dose for the Rotahaler to 16.5% of the dose for the Inhalator device. However, caution must be exercised in comparing lung deposition results between powder inhalers tested at a single flow rate, as different flow rates will be obtained through different devices, for a given inspiratory effort. Similar deposition data to those obtained in the present study have been shown for the Turbuhaler device when compared at peak inhaled flow rates of 60 and 30 l/min (Newman et al., 1991), and also for other powder devices (Vidgren et al., 1990a,b; Melchor et al., 1991). The fractionation of the dose for the Pulvinal device at a fast flow rate, showing 14% of the dose in the lung, 80% of the dose in the oropharynx, and 1% of the dose exhaled is also virtually identical to that reported previously for the pressurised MDI used with optimal inhalation technique (Newman et al., 1989a, 1982). It is important to note, however, that deposition patterns from both MDI and DPI will vary according to

TABLE 3

Inhalation details for inhalations at fast and slow peak inhaled flow rates

Subject	Fast flow rate			Slow flow rate		
	Flow rate (l/min)	Inhaled volume (l)	Breath-hold (s)	Flow rate (l/min)	Inhaled volume (l)	Breath-hold (s)
1	43.0	2.00	NR[a]	29.0	1.93	9.9
2	49.5	4.47	10.7	29.5	3.32	10.2
3	50.5	2.99	10.1	25.0	4.32	9.3
4	46.5	2.91	10.7	30.5	2.57	10.2
5	41.5	3.15	10.7	26.0	3.70	10.6
6	40.5	2.99	11.7	30.5	3.28	11.3
7	40.5	2.58	13.2	27.0	2.69	11.5
8	53.0	3.61	10.3	23.0	4.10	9.5
9	48.0	3.55	12.2	28.0	3.67	10.3
10	46.5	2.82	11.6	30.0	2.76	11.1
Mean	46.0	3.11	11.2	27.8	3.23	10.4
SD	4.4	0.67	1.0	2.5	0.74	0.7

Data are means of two doses at each flow rate.
[a] NR, not registered.

the inhalation mode, the nature of the formulation, and airways of the subject who inhales the drug aerosol.

Significantly more drug was deposited in the lungs at the fast inhaled flow rate. This observation is in agreement with results from previous deposition studies (Newman et al., 1991) and various clinical studies, which showed greater improvement in FEV1 values at higher flow rates (Groth and Dirksen, 1983; Pedersen, 1986; Pedersen and Steffersen, 1986; Pedersen et al., 1990). The similarity between the peripheral zone/central zone deposition ratios at the the fast and slow flow rates indicates that the Pulvinal inhaler provides a reasonably uniform distribution of drug within the lungs, irrespective of the flow rate. Owing to relatively high resistance of the Pulvinal device to air flow, it was not possible for volunteers to achieve a flow rate in excess of 50 l/min through the device, even though this could be attained in vitro via the MLI with a powerful suction pump.

It is important to note that this study was carried out in healthy volunteers. Consequently, the Pulvinal inhaler needs to be assessed in asthmatic patients, in order to ascertain the flow rates they are capable of generating through the device, the total and regional deposition patterns in such patients and the minimum flow rate at which a full bronchodilator response is achieved.

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