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A Widely Available Method for the Assessment of Aerosol Delivery in Cystic Fibrosis

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SUMMARY: Whilst nebulisers are commonly used in the treatment of cystic fibrosis (CF), nebulised aerosol lung deposition in individual patients is not routinely assessed in clinical practice. The present study was designed to evaluate whether a comparative measurement of aerosol lung deposition from nebulisers using a widely available scintigraphic method could be employed to assist the selection of the best system for individual patients. Lung deposition of the radiolabelled aerosol from the Pari LC Plus (Pari Medical Ltd) nebuliser and the HaloLite Adaptive Aerosol Delivery (AAD®) system (Profile Therapeutics Ltd) was measured using planar scintigraphy in 10 healthy volunteers and 6 CF patients. The HaloLite AAD® delivered on average 2.1 times ($P = 0.003$) as much aerosol to the lungs compared with Pari LC Plus. Only two subjects had higher lung deposition from Pari LC Plus than HaloLite AAD® system. There was marked inter-individual variation in the deposition pattern in CF patients. The aerosol deposition from HaloLite AAD® had higher central distribution than that obtained with the Pari LC Plus. The overall intersubject variability of the delivered dose was 56% with Pari LC Plus and 24% with HaloLite AAD® ($P < 0.05$). The measurement of aerosol deposition from nebulisers can be performed using a simple and widely available methodology, and may improve nebuliser selection in CF patients.

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INTRODUCTION

Nebulisers have been commonly used in the management of patients with lung disorders. Their main advantages include an easy mode of operation and the ability to deliver high doses of medications or drug combinations that are not available for other delivery systems.[1] Unfortunately, aerosol delivery with nebulisers has variable lung deposition and is associated with considerable aerosol wastage.[2,3] Furthermore, lung deposition is affected by particle size and the patient's breathing pattern.[1,4] Thus, in individual patients the aerosol drug delivery from nebulisers is difficult to predict. Despite these disadvantages, the use of nebulisers in patients with chronic lung disorders has been increasing in recent years.[5]

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Pari LC Plus (Pari Medical Ltd, GmbH, Starnberg, Germany) and HaloLite (Profile Therapeutics Ltd, Bognor Regis, UK) are examples of jet nebulisers that have similar operating characteristics but utilise different technological systems for the aerosol delivery (Table 1). Pari LC Plus is a breath assisted, open vent nebuliser with enhanced characteristics of aerosol output.[6] HaloLite is a nebuliser system that applies Adaptive Aerosol Delivery (AAD®) technology.[7,8] The AAD® system monitors patient's breathing parameters including flow, frequency, and inspiratory time, targeting aerosol delivery with the aerosol pulse timed for each patient.[9] The aerosol is delivered during the first half of each inspiratory cycle and the system adapts during the full duration of nebulisation ensuring that the pre-set dose is delivered to each patient.

The management of chronic lung disorders such as cystic fibrosis (CF) involves the regular

Table 1 The operational characteristics for the HaloLite AAD® system and the Pari LC Plus nebuliser with Pari TurboBoy compressor, data from the respective manufacturers product information.

Nebuliser	Respirable particles* (%)	Mass median diameter (μm)	Compressed air (kPa)	Flow rate (L/min)
HaloLite	80	3.0	175	1.5 (6[†])
Pari LC Plus	65	3.8	150	4.4

* = Particles < 5 μm aerodynamic diameter.
[†] = Pulse flow rate.

administration of an increasing number of nebulised medications.[10,11] These are expensive and their delivery can be time consuming for the patients. Therefore, it is important to establish that the most appropriate nebuliser system is being used for the individual patient. This assessment can be made indirectly using the measurements of plasma[12] or urine[13] drug levels or, as suggested in this study, through the imaging of aerosol lung deposition.

The present study was designed to evaluate whether a comparative measurement of aerosol lung deposition from nebulisers could be performed using a scintigraphic technique routinely employed in ventilation scanning. For this purpose, we compared radio-labelled aerosol deposition from the Pari LC Plus nebuliser with Pari TurboBoy compressor and the HaloLite AAD® system in healthy volunteers and in patients with stable CF in a district general hospital setting.

METHODS

Subjects

We tested 16 subjects: 10 (9 males) healthy non-smoking volunteers with mean (range) age of 29.7 (19–46) years and six non-smoking male patients with CF, aged 24.8 (19–42) years. The diagnosis of CF was confirmed by gene analysis. The CF patients were on regular nebulised therapy, which was continued during the study days, and their disease was stable with no pulmonary infective exacerbations for at least four weeks prior to the study. Their mean (±SD) FEV_1 was 2.8 (±1.0) L, 63.2 (±20.2)% of predicted, the median (range) Northern score for the chest radiograph was 4.5 (2–9), and the Shwachman score was 86.5 (61–90). All subjects gave written informed consent prior to entering the study, which was approved by the local research ethics committee and the Administration of Radioactive Substances Advisory Committee, Department of Health, London UK.

All subjects were instructed on the use of both nebulisers and their technique was proficient as judged by the investigators. In this randomised cross over study, each subject was tested on two occasions, 7 days apart. During each visit the subjects underwent clinical examination and spirometry, before and 30 min after the testing. The spirometry was performed according to American Thoracic Society criteria[14] using a Vitalograph compact spirometer (Vitalograph Ltd, Maids Moreton, Buckinghamshire, UK).

Imaging

The imaging system applied was the same as that used for ventilation perfusion lung scanning. Each nebuliser was loaded with 3 ml of normal saline containing approximately 150 MBq of Technetium-99m Diethylenetriaminepentaacetic Acid (Tc-99m DTPA) (CIS, UK). The exact activity was measured using a radionuclide calibrator to measure the activity in a syringe containing Tc-99m DTPA radiolabelled saline before and after transfer to the nebuliser. The body of the nebuliser was contained in a lead shield. The use of the Pari LC Plus nebuliser was modified slightly to allow the addition of an exhalation filter to minimise environmental contamination. All subjects inhaled the aerosol via the nebuliser's mouthpiece in a seated position using relaxed tidal breathing. No additional instructions on breathing methods were provided. Cotton wool nasal plugs were used to reduce nasal breathing and to improve the accuracy of the measurements of the exhaled activity. The duration of nebulization with the HaloLite AAD® system was as per the preprogrammed pulse time defined by the manufacturer. This gave an average total nebulisation time of 5 (range 4–6) min that delivered 0.25 ml of solution. The nebulisation time for Pari LC Plus was fixed at 5 min as per manufacturer's recommendations. At the end of nebulisation, each subject was asked to rinse their oropharynx thoroughly with water, which was then collected for scintigraphic measurements.

Immediately after nebulisation static images of the lungs and the gastrointestinal tract, (anterior and posterior), oropharynx (left and right lateral), nebuliser and exhalation filter port as well as nose plugs and mouthwash were acquired with a gamma camera (Sopha Medical Vision (SMV) Sophycamera DSX, Buc France) fitted with a low energy, general purpose collimator. All the images from the subjects were acquired into matrices of 128 × 128 for duration of 240 s. The images of the nebulisers post-nebulisation were acquired into matrices of 256 × 256 over 10 s.

The images of the mouthpieces and filters were acquired into matrices of 256×256 over 30 s.

Processing was performed using Sopha XT software (Sopha Medical Vision SMV, Buc, France). The images were displayed on the computer screen and regions of interest were defined around each lung, the stomach, and the oropharynx to allow quantification of detected counts in each region. The geometric mean of the detected counts was calculated using anterior and posterior images for the lungs and stomach, and left and right lateral images for the oropharynx. These values were multiplied by the previously measured sensitivity of the gamma camera system, giving an index of deposited activity. No attenuation correction was performed since for comparison within individuals the attenuation is constant. Similarly, regions of interest were drawn to allow the calculation of activity within the nebuliser, exhalation filter, mouthpiece, mouthwash and nose plugs. All the values were corrected for the radioactive background and for radioactive decay of Tc-99m. The deposition index for the lungs, oropharynx and gastrointestinal tract for each patient was expressed as a percentage of the total starting activity. The ratio of HaloLite deposition over Pari LC Plus deposition was calculated. The total delivered dose was calculated by subtraction of the radioactivity of the nebuliser post nebulisation together with the radioactivity of the mouthpiece and the baffle from the total starting activity.

Analysis of central to peripheral aerosol lung deposition

Regions of interest (ROIs) were defined around the 15% contour of each lung. For each subject the largest ROI from the two nebuliser studies was used for all further calculations on both studies. A central ROI was defined as a rectangle having a width of two-fifths the width of the whole lung ROI and a height half that of the whole lung ROI. This ROI was positioned centrally within the lung in the vertical direction and with the medial edge against the medial edge of the whole lung ROI. The medial edge of the central ROI was then modified so that it followed the edge of the whole lung ROI exactly. The peripheral ROI was defined as the remainder of the whole lung ROI.

The average number of counts (counts/pixel) were calculated for the central and peripheral ROIs and expressed as a ratio of central to peripheral. In addition, the coefficient of variation (CoV) of pixel values in the whole lung ROI was calculated for each lung.

Qualitative analysis of aerosol homogeneity within the lungs

The lung images were displayed, normalised to the 'hottest' pixel, reflecting detection of largest quantity of radioactivity within the lungs, and printed to thermal paper. Two experienced nuclear medicine radiologists ranked the 32 sets of images in order of homogeneity by consensus. A score of 1 represented the least homogeneous image and that of 32 the most homogeneous. The observers were blinded to the nebuliser that had been used to obtain the images and to whether the subject was a healthy volunteer or a CF patient.

Data and statistical analysis

Analysis was performed using the SPSS for Windows version 9 (SPSS Inc., Chicago, IL, USA). Measured values were quoted as median with 95% confidence interval (95% CI) unless stated otherwise. Comparisons in organ uptakes, the ranks given to images, and the ratios of central to peripheral lung deposition between the two nebulisers were tested using a Wilcoxon signed rank sum test or paired t-test, as appropriate. The variability in uptakes of the delivered dose was compared using the Siegel and Tukey modification of the Wilcoxon signed rank sum test. Comparisons of ratios of central to peripheral lung deposition, coefficient variation, and the ranks given to images between healthy volunteers and CF patients were performed using a Mann–Whitney test or unpaired t-test, as appropriate. The correlation was assessed using Spearman's method. A P value of <0.05 was regarded as statistically significant.

RESULTS

All subjects finished the study without adverse events. There was no significant change in measurements mean (range) of FEV_1 3.2 (1.2–4.5) L vs. 3.2 (1.2–4.7) L, and FVC 4.4 (2.6–5.9) L vs. 4.5 (2.5–6.0) L, prior and post administration of radiolabelled aerosol ($P = 0.5$). Similarly, the baseline FEV_1 measurements were similar on days of testing 3.2 (1.2–4.5) L vs. 3.2 (1.1–4.6) L ($P = 0.9$).

Dose delivered from HaloLite AAD® expressed as a percentage of the total starting dose was 13.4 (7.2–20.9)%, compared with that of 9.2 (4.3–25.8)% with Pari LC plus ($P = 0.11$). The lung deposition with HaloLite AAD® system was higher compared with Pari LC Plus (all subjects: 2.1 [0.7–3.6] times, $P = 0.003$, healthy volunteers 2.2 [0.8–3.6] times, $P = 0.007$, and in CF patients 1.5 [0.7–2.1] times, $P = 0.12$). The ratios of HaloLite AAD® to Pari LC Plus aerosol lung deposition in the individual subjects are shown in Table 2. The overall gastrointestinal and oropharyngeal deposition were significantly higher for HaloLite AAD® 13.7 (4.7–75.6) times, and 6.6 (2.2–98.6) times respectively ($P < 0.01$).

Table 2 Aerosol lung deposition and homogeneity scores in the individual subjects expressed as the ratio of HaloLite AAD® to Pari LC Plus. The ratios >1 represent higher deposition or homogeneity score with HaloLite system and the ratios <1 represent higher deposition or homogeneity score with Pari LC Plus nebuliser in the individual subjects.

Subject	Lung deposition expressed as HaloLite/Pari LC Plus ratio	Homogeneity score expressed as HaloLite/Pari LC Plus ratio
Healthy volunteers		
1	0.8	0.6
2	1.5	1.0
3	1.5	0.7
4	2.1	0.5
5	2.2	0.4
6	2.2	1.4
7	2.8	0.6
8	3.0	0.7
9	3.5	0.3
10	3.6	0.5
Cystic fibrosis		
11	0.7	1.9
12	1.0	0.5
13	1.3	0.5
14	1.7	0.9
15	2.1	0.6
16	2.1	0.4

Fig. 1 Static images of the lung deposition from the HaloLite AAD® system (a) and the Pari LC Plus nebuliser with Pari TurboBoy compressor (b) in healthy volunteers. POST LUNGS = Posterior lung images, ANT LUNGS = Anterior lung images.

Fig. 2 Static images of lung deposition from the HaloLite AAD® system (a) and the Pari LC Plus nebuliser with Pari TurboBoy compressor (b) in patient with CF. The posterior lung images are shown on the left and the anterior lung images on the right.

The coefficient of variation of the total delivered dose was lower for HaloLite AAD® compared with Pari LC Plus (all subjects: 24.0% vs. 56.0%, $P < 0.05$, healthy volunteers: 23% vs. 69%, $P > 0.05$, CF patients: 22% vs. 39% $P > 0.05$). Examples of the static aerosol deposition images from the two nebulisers are shown in Fig. 1 (healthy volunteers), and Fig. 2 (CF patients). Mean ± SD central to peripheral count ratios for the lung deposition were higher in images obtained with the HaloLite AAD® then with Pari LC Plus nebuliser (all subjects: 1.16 ± 0.28 vs. 0.97 ± 0.15, $P < 0.001$, healthy volunteers: 1.13 ± 0.16 vs. 0.96 ± 0.05, $P < 0.004$, and CF patients: 1.22 ± 0.42 vs. 0.98 ± 0.26, $P = 0.05$). The central to peripheral count ratios for the lung deposition for the individual subjects are shown in Table 3. There was no significant difference, for either nebuliser, in the central to peripheral count ratios between healthy volunteers and CF patients. Mean ± SD coefficient of variation of pixel counts were higher for images obtained with the HaloLite AAD® then the Pari LC Plus nebuliser (all subjects: 58 ± 14% vs. 51 ± 7%, $P < 0.001$, healthy volunteers: 53 ± 6% vs. 49 ± 2%, $P = 0.005$, CF patients: 65 ± 19% vs. 54 ± 12%, $P = 0.003$). The coefficient of variation of pixel counts was higher in images from CF patients than from healthy volunteers for HaloLite AAD® (65 ± 19% vs. 53 ± 6%, $P = 0.015$), and Pari LC Plus (54 ± 12% vs. 49 ± 2%, $P = 0.03$).

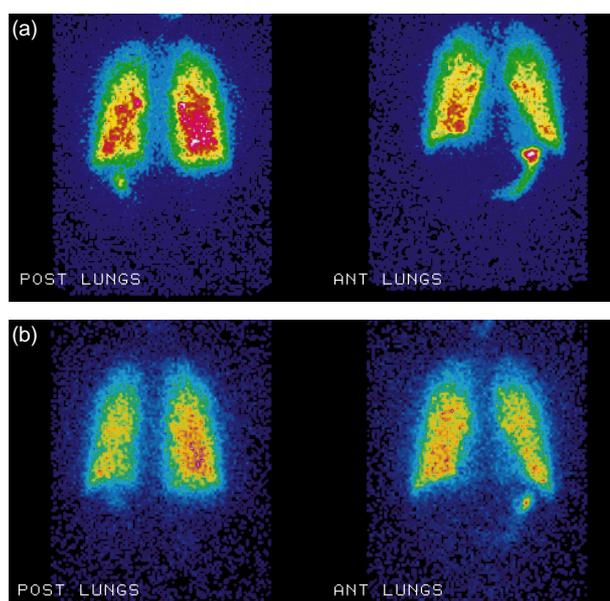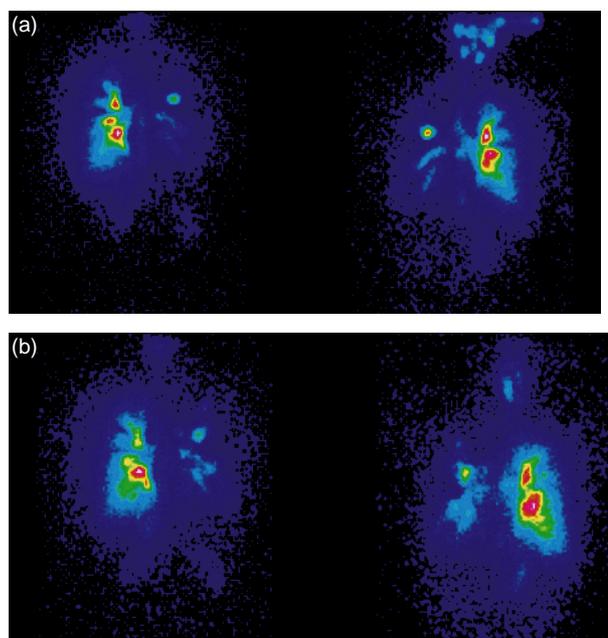When homogeneity of aerosol deposition was assessed, the sums of the ranks given to each nebuliser were 214 for HaloLite AAD®, and 314 for Pari LC Plus nebuliser ($P = 0.009$), indicating more homogeneous images with the Pari LC Plus nebuliser. The median (range) ranks given to images obtained from CF patients and healthy volunteers were 8 (2–21) and 21 (16–32), respectively ($P = 0.002$). The deposition from both nebulisers in CF patients was less homogeneous compared with healthy volunteers (Fig. 3).

Table 3 Ratios of central to peripheral lung deposition for the individual subjects. The ratios >1 represent higher central deposition, and the ratios <1 represent higher peripheral deposition.

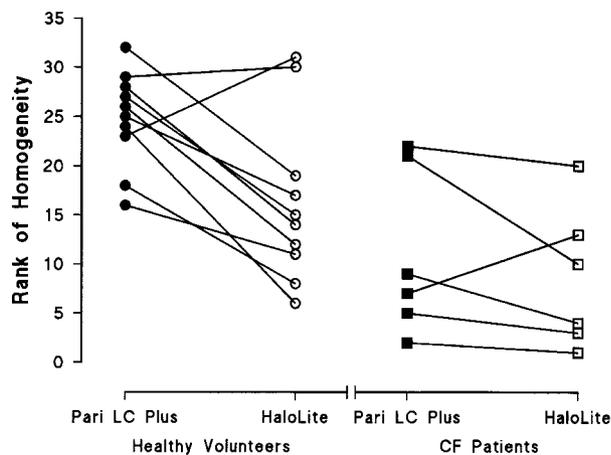| Subject	HaloLite AAD® nebuliser (ratio of central to peripheral lung deposition)		Pari LC Plus nebuliser (ratio of central to peripheral lung leposition)	
	Right	Left	Right	Left
Healthy volunteers				
1	1.1	1.0	0.9	1.0
2	0.8	1.0	0.8	1.0
3	1.0	0.8	0.9	1.1
4	1.1	1.2	0.9	1.0
5	1.0	1.5	0.9	1.0
6	0.9	1.0	0.9	1.0
7	0.9	1.2	0.8	1.0
8	1.0	1.4	1.0	1.2
9	1.3	1.6	0.8	1.1
10	0.9	1.3	0.9	1.1
Cystic fibrosis patients				
11	1.6	1.9	0.9	1.3
12	1.5	2.0	1.3	1.6
13	0.8	1.0	0.7	0.8
14	1.1	1.0	1.0	1.0
15	0.8	0.9	0.8	0.8
16	1.1	0.8	0.8	0.9

Fig. 3 Homogeneity rank scores for aerosol lung deposition from the HaloLite AAD® system and the Pari LC Plus nebuliser in healthy volunteers and CF patients.

There was no statistically significant correlation between lung deposition and height, FEV_1, FVC, Northern score or Schwachman score.

DISCUSSION

The domiciliary use of nebulisers is estimated to be 70 per 100 000 of population equating to approximately 40 000 compressors in the UK.[5] However, the increasing number of new nebulisers, compounds the problem of selecting the most appropriate system for the individual patient.[15] In CF, the lung deposition and clinical response to aerosolised antibiotics have been shown to be affected by the nebuliser used.[16–19] Whilst pharmacodynamic assessment of bronchodilators can be achieved with spirometry, the clinical effects of nebulised medications, such as antibiotics or mucolytics, may only become evident after a long period of therapy. The regulatory authorities therefore, suggest that the new drug formulations for nebulisation should only be approved for use with the delivery systems evaluated during clinical trials.[20,21] However, this advice is a gross oversimplification since it hides marked differences in drug deposition within the study population. In practice, medications are administered using a variety of nebulisers with no attempt being made to select the most appropriate system for the individual patient.

In this study, we assessed a simple and widely available methodology to measure aerosol lung deposition from nebulisers. The technology used is similar to that routinely employed during ventilation scanning, and therefore available in the nuclear medicine departments of most district general hospitals. In addition, this is the first report of a direct comparison of the aerosol deposition from two modern nebulisers Pari LC Plus and HaloLite AAD® system. We have chosen these particular systems due to their increasing usage amongst the patients with CF. Pari LC Plus has better aerosol output compared with other jet nebulisers,[6,22] and has been recommended as one of the systems for the administration of aerosolised tobramycin.[23] The HaloLite AAD® system, whilst using jet nebulisation, is claimed to reduce the variability of the delivered dose by adapting to a patient's breathing pattern.[8,24]

Our findings demonstrated that overall intersubject variability of the delivered dose with HaloLite AAD® system was lower compared to that of Pari LC Plus, and similar to that previously reported.[24,25] However, when the groups were analysed separately the differences were not significant. Overall, the HaloLite AAD® system had a significantly higher lung deposition compared with Pari LC Plus nebuliser. This difference was more obvious in healthy volunteers, and less pronounced in CF patients. However, aerosol lung deposition was more homogeneous with Pari LC Plus nebuliser. One possible explanation may be that the uniformity of aerosol penetration with HaloLite AAD® system was affected by the more central aerosol deposition. In CF patients, as expected, the aerosol deposition was less homogenous with both nebulisers. As the lung involvement in CF is heterogeneous with varying degree of mucus plugging, local infection, or inflammation, both nebulisers delivered to more intact normal airways rather than all the lung fields. We also measured an increased oropharyngeal and gastrointestinal aerosol deposition with HaloLite AAD®

system compared to the Pari LC Plus nebuliser. However, the clinical significance of this observation remains unclear. Similar disparity in gastrointestinal aerosol deposition were reported with other nebulisers including Ventstream and Optimist,[18] and could be related to the inertial impaction of the larger particles resulting in a difference of swallowed aerosol.

Although it could be argued that the different delivery times for each nebuliser might have influenced the results, the nebulisation times adopted for both systems were recommended by the manufacturers. It is unlikely that a longer nebulisation time would have affected lung deposition from Pari LC Plus, as over 80% of medication is delivered within 5 min and the lung deposition reaches plateau with longer nebulisation time.[26,27] We accept the limitations of our study in that we compared the deposition of aerosol from the nebulisers using an indirect radionuclide marker, and did not perform attenuation correction. However, the use of a substitute labelled with radiotracer has been suggested as a suitable alternative if a radio-labelled drug analogue is not available.[17,28,29] As we did not perform attenuation correction, we simplified our method, but consequently we were unable to calculate the absolute values of the lung deposition. We believe that calculation of the attenuation correction was not necessary and would not have affected the results, as the attenuation was identical for each nebuliser in the same subject. In addition, the main objective of our study was not to assess which delivery system was superior, but to select the more appropriate nebuliser for each individual subject. The data showed that two subjects had a lower lung deposition using the HaloLite AAD® system as compared with the Pari LC Plus, and our method allowed for their detection. A possible explanation for this reversal of the performance of the devices, in these two subjects, may be related to the particularly high central deposition, with sparing of the lung periphery, of the aerosol with HaloLite AAD®.

A limitation of the quantitative analysis of homogeneity of lung deposition is the difficulty in defining the whole lung ROI when there are large areas of the lung, which have little aerosol deposition. In these cases, it is likely that the degree of inhomogeneity has been underestimated, however the same ROI was used for both nebulisers therefore comparisons between nebulisers are still possible. In addition, the coefficient of variation of the pixel counts in the lungs will in part depend upon statistical noise within the images and therefore the degree of lung deposition. Since the overall lung deposition was higher with the HaloLite AAD® system, there will be less statistical noise in these images. Despite this, the overall coefficient of variation was higher in the HaloLite AAD® images, suggesting that the difference is truly due to differences in homogeneity.

In conclusion, we have described a method of comparing lung deposition from two different nebuliser systems that can be performed using a simple and widely available method. Scintigraphy provides two-dimensional images of lung deposition and allows for a comparison of aerosol lung deposition from different delivery systems in individual subjects. Owing to the wide availability of the equipment used, this method may be readily employed in the majority of district general hospitals.

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