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An investigation into the deposition of inhalation aerosol particles as a function of air flow rate in a modified 'Kirk Lung'†

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The effect of air flow rate on the deposition of inhalation aerosol particles in a modified 'Kirk Lung' has been studied. Two commerical products were used. The amount depositied in the mouthpiece and throat regions decreases with increasing flow rate. The amount in the collector rises to maximum of approximately 50%. This material represents the therapeutically available portion. Such an apparatus would be useful for routine quality control of the size distribution ratios for inhalation aerosol particles.

The use of inhalation aerosol devices for asthmatic and bronchial therapy has now become almost routine therapy. The wide usage of this method of medication was recognized by the B.P.C. and consequently standards were introduced in 1973. However, while these included a test for particle size, this is carried out under static air conditions. But the conditions in the respiratory tract are very different and will give rise to significantly different penetration characteristics. Therefore, although particle size is relevant, it is the dynamic size of the particles in the aeorosol cloud which is a dominant factor. The penetration of particles into the lung tissues is dependent not only on particle size but also on inspiratory flow rate, tidal volume and breathing rate (Hatch & Gross, 1964).

The air flow rates in the deep lung regions of patients suffering from respiratory tract constriction are not known with certainty although Landahl (1950) and Olson, Sudlow & others (1973) have calculated flow contours for various sites in the lung. In view of the uncertainty of the actual flow conditions it seems all the more important to restrict the size range of particle produced by the aerosol device. Particles greater than about 7 μm will not penentrate beyond the trachea while those of less than about 0·5 μm tend not to deposit but be exhaled (Mitchell, 1960). As with the penetration, the actual deposition is dependent on a variety of factors (Stuart, 1973) including, for example, the amount of mucoid material present in the tube spaces.

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A number of techniques have been used to examine the particle size and respirable portion of inhalation aerosols. Some of the more recent studies include the use of the Royco counter (Bell, 1967) and microscopy linked to such systems as the Quantimet analyser (Hallworth & Barnes, 1974). Bell, Brown & Glasby (1973) reported studies using a cascade impactor to measure the proportions of various sizes of particles. These techniques are expensive, complex in use and time consuming. Kirk (1972) recognized the need for a simple rapid quality control check for inhalation aerosols and devised an arbitary 'lung' unit (Fig. 1a). Correlation between *in vitro* deposition of particles on the filter and *in vivo* clinical response was good. The problem with the original apparatus is that the filter restricts the flow rate to 16 litres min^{-1} and the apparatus is required to be coated internally with a layer of agar gel. This total filter approach takes no account of the presence of fine particles which may be exhaled and which represent a measurable portion of the total dose. Breath-holding procedures have been proposed for reducing this loss by exhalation (Palmes, 1973) but they are not entirely satisfactory.

We have redesigned the unit and replaced the filter with the end unit of a cascade impinger of the type described by May (1966) which has enabled a range of flow rates up to 80 litres min^{-1} to be obtained (Fig. 1b). This flow rate represents the lowest peak inspiratory flow rates recorded by Coady, Davies & Barnes (1976). Investigations have been carried out to measure the amount of deposition in a modified 'Kirk Lung' at various air flow rates using two commercially available inhalation aerosols (Medihaler-iso and Ventolin).

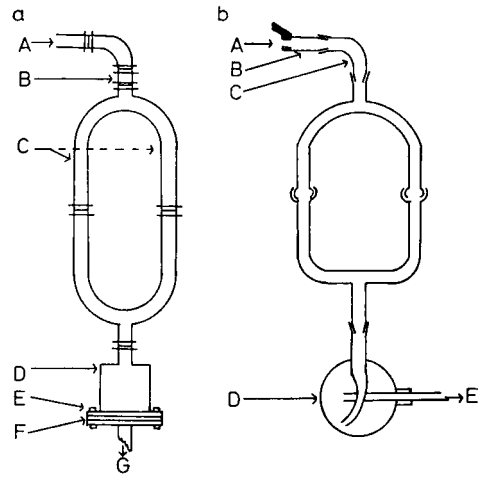

FIG. 1a. Original 'Kirk' lung. A—Inhaler, B—trachea, C—bronchi, D—adaptor, E—seitz-type filter holder, F—Millipore filter, G—to vacuum.
b Modified 'lung'. A—inhaler, B—mouthpiece, C—throat, D—collector, E—to vacuum. Tubing 1 inch bore with Quickfit ground glass or ball and socket joints. Collector 250 ml flask.

METHODS

Assay of aerosol delivery

The amount of medicament delivered by the aerosol was determined by actuating it five times into 0·1 N sulphuric or hydrochloric acid. The solution was made up to 25 ml and the absorbance measured spectrophotometrically in 4 cm cells, the isoprenaline at 280 nm and the salbutamol at 276 nm. The solutions obey the Beer-Lambert Law in the concentration ranges examined. This technique has the advantages over the B.P.C. method of simplicity and rapidity.

Simulated lung unit

Kirk's initial studies on the original 'lung' involved coating the inner surfaces with agar gel to give a mucosal-like suface. This procedure was not only slow but also gave irregular results. Alpin (1974) investigated the use of this and a wide range of other materials. The most satisfactory was found to be polyethylene glycol 400. However, we have found that the apparatus could be run 'dry' without any coating and this method has been used.

Two modified 'Kirk Lung' units were set up with a G.A P. flow meter (G. A. Platon Limited, Basingstoke, Hants). (Tube A10, stainless steel float) placed downstream of the exhaust tube of the collector. The control of air flow rate was carried out by adjustment of the suction downstream from the flowmeter. The mouthpiece was designed to ensure that the aerosol unit lined up along the long axis of this section of the apparatus.

The air flow was adjusted, the aerosol placed in the mouthpiece and actuated five times at intervals of approximately 20 s. Under these conditions there was no valve cooling due to the small volume of propellant delivered by a metering valve.

Initially it was found that the results were irregular due to deposition of airborne contaminants. This problem was overcome by performing a blank run immediately after a test run. The apparatus was dismantled into its various sections, each inner surface washed with acid and made up to 25 ml and the absorbance measured.

RESULTS AND DISCUSSION

The amount of drug deposited in the mouthpiece was very high at low air flow rates but fell as the flow rate was increased (Fig. 2). This effect is due to a reduction in the effective spray diameter at the high flow rates which prevents the particles coming near the surfaces of the mouthpiece. The presence of large particles in the spray is detected by the amount of deposition in the mouthpiece and throat regions arising as a result of the large inertial forces acting on the particles, especially as they pass through the right angle bend of the throat. This suggests that if the aerosol is actuated at low inhalation rates much of the product would be deposited into the mouth of the patient and little would penetrate into the lung space.

Little material is deposited in the central divided region and it seems that this could be eliminated from

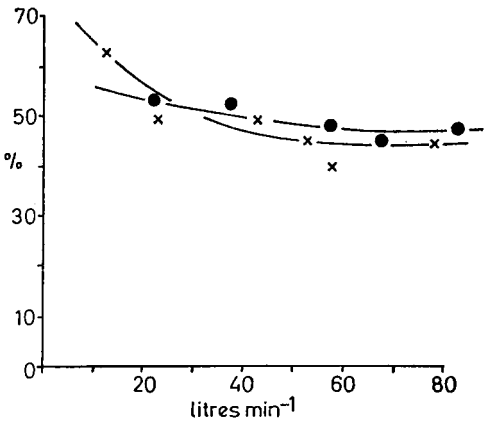

FIG. 2. Effect of air flow rate (litres min^{-1}) on deposition of drug (%) in mouthpiece and throat regions of modified 'Kirk' lung. ●—● salbutamol. ×—× isoprenaline.

the apparatus without loss. The collector (Fig. 1b) is designed such that not only do the particles impinge on the wall but are also subjected to a large centrifugal force, both effects causing them to be deposited. Fig. 3 shows that the amount of material deposited in this region rises rapidly to a maximum as the air flow rate is increased up to 60 litres min^{-1}. As the amount in the collector rises, the amount in the mouthpiece and throat falls, For normal healthy adults the peak inhalation flow rate is in the range 30 to 300 litres min^{-1}, depending on amount of

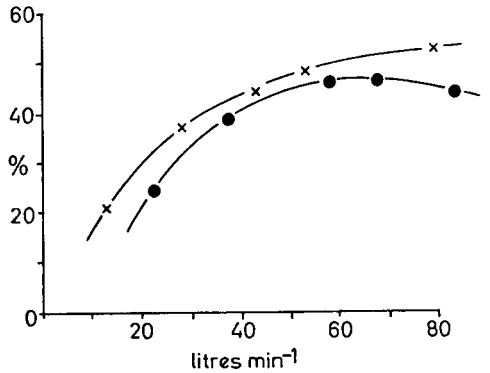

FIG.3. Effect of air flow rate (litres min^{-1}) on deposition of drug (%) in drug collector region of modified 'Kirk' lung. ●—● salbutamol. ×—× isoprenaline

activity (Silverman, Lee & others, 1951). In bronchitic or asthmatic patients, while the tidal flow is lower, the actual inhalation rate is higher—in the range 50 to 400 litres min^{-1} (Coady, Davies & Barnes, 1976). Therefore, it would seem that a flow rate of 60 litres min^{-1}, whilst still probably too low, represents the lowest flow rate likely to be met in practice. The amount of material 'effectively' deposited at this flow rate is about 50% of the total drug available and represents the amount of material which can penetrate into the lung regions and which could be deposited where the bronchii are no longer supported by cartilaginous tissue. Also present in the spray is a range of fine particles which tend to be exhaled. This group of particles is represented by the quantity of material described as 'loss' (Table 1).

Kirk's total filtration approach has established a useful *in vivo/in vitro* approach to the quality control of inhalation aerosols, but we consider that the modified form of the apparatus would improve the technique by taking into account the material which is lost by exhalation. It would enable limits to be placed on oversize and undersize fractions in the spray and would, therefore, lead to an improvement in the efficiency of the pressurized inhalation package as a dose form.

Table 1. *Quantity of drug deposited at various sites in the 'lung' at several flow rates (average of 5 determinations).*

Air flow rate litres min^{-1}	Region of apparatus: Mouthpiece & throat µg	%	Collector µg	%	Loss µg	%
Isoprenaline*						
13	302	63·2	100	20·9	75·5	15·8
28	238	49·8	178	37·3	61·5	12·9
43	235	49·2	214	44·8	28·5	6·0
53	215	45·0	233	48·8	29·5	6·2
58	191	40·0	218	45·7	68·5	14·3
79	215	45·0	251	52·6	11·5	2·4
Salbutamol †						
23	276	53·5	123	23·8	118·5	22·7
38	273	52·8	201	38·8	43·5	8·4
58	231	48·4	239	46·2	47·5	5·4
68	234	45·4	239	46·2	44·5	8·4
84	248	49·9	201	38·8	68·5	11·3

Total delivery µg/5 actuations	µg/actuation found	stated
* 477·5	95·5	80
† 517·5	103·5	100

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