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A novel labelling method for measuring the deposition of drug particles in the respiratory tract

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Summary

Spray drying technique was used for ^{99m}Tc-labelling of disodium cromoglycate particles. ^{99m}Tc was coprecipitated with the drug and nearly spherical radioactive particles were formed with the aerodynamic diameter of 3.8 μm. Labelled particles were inhaled by 7 healthy volunteers using a metering dose aerosol. The deposition of drug particles was monitored by the means of a γ-camera. On average about 9% of the aerosol dose deposited in a whole lung area and about 81% in the mouth, oesophagus and stomach. About 10% of the dose remained in the actuator. The results obtained agree reasonably well with the previously published results of deposition of Teflon particles in the respiratory tract. The novel labelling method used in this study enables evaluation of the deposition of real drug particles in the respiratory tract.

Introduction

Inhalation of drugs has become one of the most widely used drug delivery methods in asthma therapy. Using pressurized aerosols, dry powder inhalators or nebulizers, drug particles or droplets can be administered directly to their site of action in the lungs. It has been, however, widely documented that in inhalation therapy only a small part of the delivered dose reaches the human lungs and especially the alveolary stage of the respiratory tract which is the most effective area for the drug response (Newman et al., 1981, 1984a and b; Hallworth and Malton, 1984).

After the proper delivery of the inhaled dose the most critical parameter with respect to the deposition of inhaled drug particles is the particle size distribution (Gonda and Byron, 1978). The accepted optimum size for inhaled drug particles is between 0.5 and 7 μm (Davies et al., 1976). Particles smaller than 0.5 μm seem to be exhaled and particles larger than 7 μm cannot enter the bronchial stage. Therefore drug particles and droplets in inhalation drug forms have been reduced to the suitable particle size.

Deposition of the inhaled drug particles has been studied with several in vitro and in vivo methods. Perhaps the most frequently used in

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vitro method is based on cascade impaction (Hallworth and Andrews, 1976). This method has been assumed to mimic the function of human lungs if the test conditions are carefully controlled (Davies et al., 1976). Practically all in vivo deposition studies have been done using radiotracer techniques. ^{99m}Tc-labelled Teflon particles have been widely used as model particles in these studies (Newman et al., 1981, 1984a and b). Teflon particles were labelled by the spinning-disc method described by Camner et al. (1971). With this method it has been possible to obtain reliable information from the behaviour of small particles in the human respiratory tract. Although Teflon particles used in these studies had nearly the same particle size as actual drug particles used in inhalation therapy, the chemical and physical properties of the Teflon particles were different from those of drug particles. The use of Teflon particles is also rather unphysiological because of the insoluble nature of this material.

Chemical labelling of the drugs used in a management of asthma is difficult because these molecules rarely contain an element with a suitable radionuclide (Hallworth, 1983). Only one bronchodilator drug, namely ipratropium bromide has been succesfully directly labelled with bromine-77 (Spiro et al., 1984).

Recently Vidgren et al. (1987) have pointed out that spray drying is a possible method of obtaining disodium cromoglycate particles suitable for inhalation therapy. The object of this study was to evaluate if the spray drying method can be used for ^{99m}Tc-labelling of disodium cromoglycate. The deposition of labelled drug particles in the respiratory tract was also studied after dosing from the metering dose aerosols.

Materials and Methods

Spray drying and labelling of drug particles

Disodium cromoglycate (BP 1980, Chemisell, Italy) was dissolved in 50 ml of water to give a 6% w/w solution; 1 ml of 0.9% w/w sodium chloride water solution containing ^{99m}Tc was added to the drug solution. This mixture was spray-dried (Buchi Minispray drier, type 190, F.R.G.) at a feed rate of 60 ml/min. The air input temperature during drying was about 180 °C, and the outlet temperature was about 80 °C. The throughput of air was 2.4 m^3/min and the nozzle air pressure was 800 Nl.

Particle properties

The effective particle density, ρ_t, of the spray dried disodium cromoglycate was measured by an air comparison pycnometer (Beckman, type 930, U.S.A.) using helium as an inert gas. Six determinations were done. The effective particle density with the standard error of the mean was 1.82 ± 0.01.

The dimensions of the particles were studied from the samples delivered from the aerosol container. The arithmetic particle diameter, d_A, was evaluated microscopically measuring the Feret's diameter of 400 particles. The arithmetic diameter with the standard error of the mean was 2.83 ± 0.04 μm. The behaviour of the particles in human respiratory tract is, however, dependent on the arithmetic diameter as well as on the density of the particles. Thus the mass median aerodynamic diameter, d_{MMA}, was calculated using the equation (Newman, 1983)

$$d_{MMA} = d_A\sqrt{\rho_t} \quad (1)$$

The value of this parameter with the S.E.M. for spray-dried disodium cromoglycate was 3.79 ± 0.05 μm. The distribution of d_{MMA} in disodium cromoglycate powder is presented in Fig. 1.

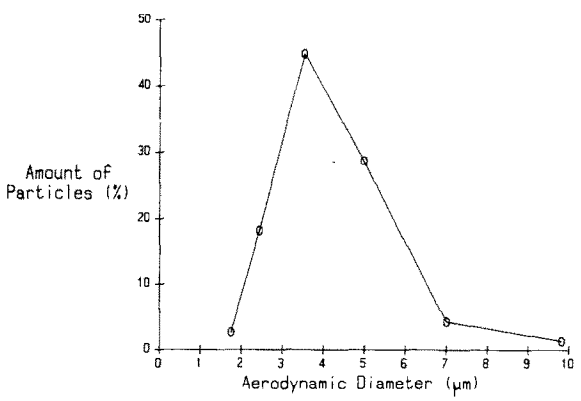

Fig. 1. Distribution of the mass median aerodynamic diameter for ^{99m}Tc-labelled particles of disodium cromoglycate.

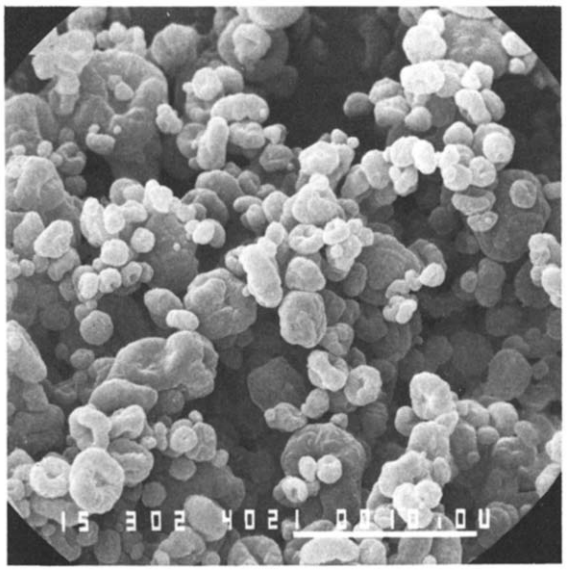

Fig. 2. Scanning electron micrograph from the disodium cromoglycate particles ^{99m}Tc-labelled by the spray-drying technique. Bar = 10 μm.

The shape of the particles was studied from the scanning electron micrographs (Jeol scanning electron microscope, type JSM 35, Japan). Spray-dried particles were nearly spherical (see Fig. 2). Some partially shrunken particles were typically formed during spray drying.

Preparation of the metering dose aerosols

Sorbitan trioleate 100 mg (Span 85, Atlas, Belgium) was dissolved into 20.7 g of liquid propellant dichlorodifluoromethane (Freon P12). Secondly, 62.1 g of liquid dichlorotetrafluoroethane (Freon P114) was added to the mixture of P12 and sorbitan trioleate at a temperature of $-70\,^{\circ}$C. Thirdly, 2.53 g of ^{99m}Tc-labelled disodium cromoglycate was dispersed in the above-mentioned solution using a homogenizer (Ultra-Turrax, type TP 18-10, IKA Werk, F.R.G.). A small amount of the suspension was filtered and the activity of the liquid filtrate was noticed to be negligible. Thus no radioactivity was lost from the drug particles during the preparation process. The samples of 8.28 g of the suspension were filled into metal aerosol containers (Presspart, UK). The containers were closed with 50-μl metering valves (Riker, U.K.). Each delivered dose ($\pm$S.E.M; n = 10) was 1.08 ± 0.02 mg of disodium cromoglycate.

Every volunteer had his own aerosol container for ensuring that the delivered doses were as similar as possible. The activity of one aerosol dose just before the in vivo test was about 400 kBq (10 μCi).

Delivery of the inhalation dose

Seven healthy volunteers took part in the in vivo inhalation test. Before inhalation the lung function was measured and the 80% lung volume of actuation from the maximum vital capacity was carefully trained. It was noticed that all the volunteers were able to repeat this volume with a lower deviation than 5%. The inhalation was done using a velocity of ca. 55–70 liter/min. Inhalation was followed by 5 s of breath-holding.

The aerosol vials were connected with a conventional actuator (Orion Plastic Department, Finland). Just before the γ-camera measurement, 10 doses from the metering dose aerosol were taken separately as carefully as possible by the 80% volume of the breath from the maximum forced vital capacity. The volunteers inhaled the aerosol doses with a carefully controlled closed mouth technique (Pavia et al. 1977). The total activity of the disodium cromoglycate taken by every volunteer was about 4 MBq (100 μCi).

Measurement and calculation of deposition

The measurements of deposition were done with a large field γ-camera (Type 400T, General Electric, WI, U.S.A.) equipped with a low-energy all-purpose collimator. The energy window was 10% for the ^{99m}Tc energy peak (140 keV).

All measurements were done for each person in the anteroposterior and posteroanterior view in the same measurement geometry for 5 min per view in the sitting position. The data were collected to the Gamma-11-system with a PDP11/34 computer (Digital Equipment Corp., MA, U.S.A.) with a 64×64 collection matrix. All results were calculated after correction of the background radiation and time decay of ^{99m}Tc. The geometric mean counts were calculated for the lung region and the results were listed for the actuator and lungs as well as mouth, oesophagus and stomach. For the individual correction of attenuation in

different body thicknesses the point source measurement in opposite site of the subject was done. The correction factor for the dose measured in air was determined with the calibration curve, which was measured in various depths of water for attenuation and scattering of material (Newman, 1983). Ten puffs of aerosol deposit an initial lung burden of 400 kBq (10 μCi) ^{99m}Tc, and the radiation dose to the lung resulting from this amount of activity does not exceed 4 mrad.

Results and Discussion

According to the γ-camera results, the activity of the aerosol dose was relatively small. But using the 10 min time for data collection it was still quite possible to obtain sufficient counts to draw conclusions of the deposition of ^{99m}Tc-labelled particles in different parts of the human body (Fig. 3). The activity of the actuator after dosing was measured. Only a rather small fraction of the dose remained in the actuator (Figs. 4 and 5). This result agrees very well with the previously published results by Newman et al. (1984b) and Sears and Asher (1985). It has been pointed out that the

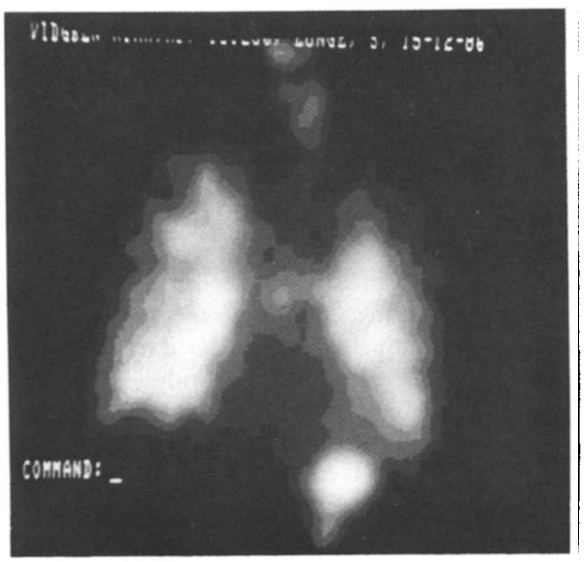

Fig. 3. Typical γ-camera photograph from the deposition of ^{99m}Tc-labelled particles of disodium cromoglycate in the respiratory tract of one of the human volunteers.

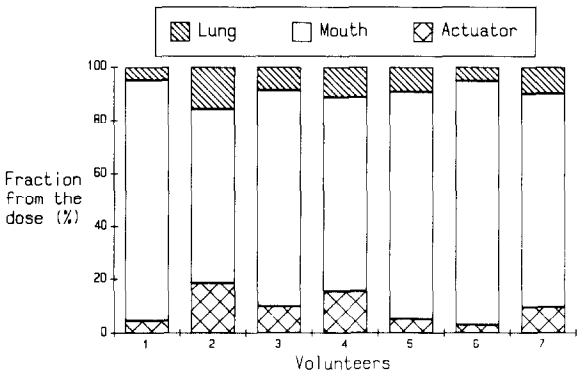

Fig. 4. Fractional deposition of ^{99m}Tc-labelled particles of disodium cromoglycate separately in 7 volunteers after administration from the metering dose aerosol.

inhalation technique affects the deposition patterns of the metering dose aerosols (Sears and Asher, 1985). Individual results point out that relatively large deviations existed between volunteers (Fig. 4). This is due partially to the differences in inhalation techniques and partially to the differences in lung functions.

On the other hand the delivery of aerosol spray by the means of relatively high pressure led to the inertial impaction of drug particles on the mucosa of the mouth and the upper part of the respiratory tract. This is followed by the swallowing of the drug to the stomach. Besides inertial impaction also other factors e.g. gravitional sedimentation

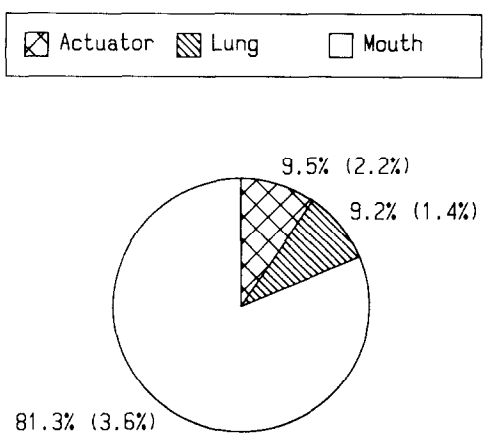

Fig. 5. The mean fractional deposition and the standard error of the mean of ^{99m}Tc-labelled particles of disodium cromoglycate after administration from the metering dose aerosol.

and Brownian diffusion may force the particles to adhere to the mucous membrane of the respiratory tract (Newman et al., 1982). In this study, on average 81.3% of the dose was deposited in the mouth, oesophagus and stomach. The mean share of the dose deposited in the lungs was about 9%. Thus only a very small portion of the drug dose reached the therapeutically important bronchial stage of the respiratory tract.

The results by Newman et al. (1981, 1984a and b) obtained using the labelled Teflon particles are in good agreement with the results of this study. Thus the method used in this study seems to be a reliable method for describing the deposition of particles in the human lungs. This novel labelling method is, however, safer and simpler as well as less expensive to perform. The method of ^{99m}Tc labelling by spray-drying makes it possible to use real drug particles in deposition studies. This method enables the in vivo comparison of different drug forms including dry powder inhalators. It might be possible to label also particles of other antiasthmatic drugs using this method.

The method of labelling drugs by spray-drying cannot be used in studies of the bronchial mucocial clearance of disodium cromoglycate due to the decreasing radioactivity of the lung area as a function of time (Fig. 6). This is either due to the dissolution of drug particles in the mucous membrane or to the loosening of ^{99m}Tc from the particles. ^{99m}Tc leakage from drug particles after 10 min is 38%. This value is several times higher than that of ^{99m}Tc-labelled Teflon particles (Camner et al., 1971). Disodium cromoglycate particles labelled by the spray-drying technique are, however, stable enough for this kind of deposition studies.

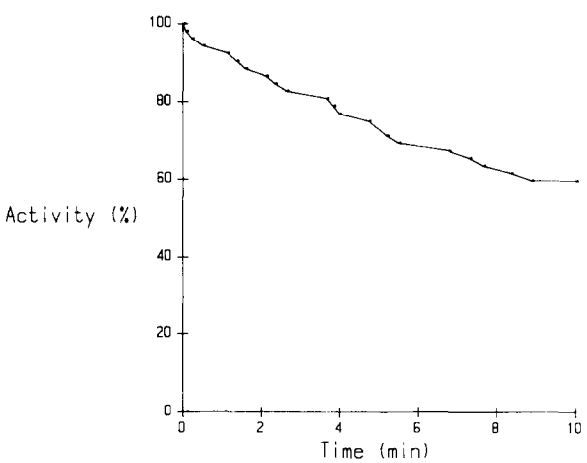

Fig. 6. Time–activity curve of the whole lung area after administration of ^{99m}Tc-labelled particles of disodium cromoglycate from the metering dose aerosol.

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