CHAPTER FIVE

CONCLUSIONS AND SUGGESTIONS FOR FUTURE WORK

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The primary aims of the present study were to examine the *in vivo* deposition of aerosols from metered-dose inhalers and to correlate the findings with *in vitro* aerosol parameters such as particle size. The *in vivo* studies required the establishment of two conscious animal models which were examined using a gamma camera. A major part of the work was concerned with gamma radiolabelling aerosol particles, especially aerosols containing the β_2 adrenoreceptor agonist, salbutamol. This enabled the body distribution of inhaled salbutamol to be studied in rabbits and beagle dogs.

The particle size of the aerosols (generated by an MDI or nebuliser) used in the present study was compared by two methods, cascade impaction and laser light-scattering, and an attempt was made to correlate the results obtained from the two methods to the *in vivo* regional lung deposition patterns. The Andersen Sampler, an eight-stage cascade impactor, was used to measure the particle size distributions of drug and radiolabel from the same sample of aerosol. All formulations used in the *in vivo* studies were measured in this way. The paired measurement of two distributions in a cascade impactor is a technique which is unique to this study. In addition to establishing the validity of a radiolabel in a formulation, this technique was used to study the separation of the excipient, oleic acid, and salbutamol in an aerosol discharged from a metered-dose inhaler. The particle size distributions of excipients in MDI's has not been previously published. Valuable *in vivo* correlations could be made in the future by γ-radiolabelling the oleic acid in the formulation with iodine-123. Dual gamma camera images of the drug and surfactant *in vivo* after administration from an MDI would then enable an estimation to be made of differences in lung deposition sites between the components.

The particle size results from the Andersen Sampler were correlated with those from the PMS laser light-scattering device and with published results, using metered-dose inhalers containing salbutamol. Two different methods were used so that direct comparisons of optical and aerodynamic diameters could be made with this type of aerosol. The laser light-scattering device provided a new and rapid method for determining the particle size distribution of aerosols from MDI's. The first published results of the measurement of non-drug particles in an MDI (Lea et al., 1982) used a microscope method to simply count the number of particles greater than 100μm. The present study uses the light-scattering method to rapidly assess the number of non-drug particles in the size range of the instrument (0.3-20μm) which is more relevant for inhalation studies. It was found that a substantial proportion of particles by number were not drug particles, although they represented a small amount by mass. The PMS device was not used for measurement of radiolabelled aerosols because of the hazards involved in containing the radioactivity discharged from such MDI's.

The radionuclide technetium -99m was used in all the in vivo work in the present study. The use of selenium-75 was considered as most suitable for producing a γ-radiolabelled salt of salbutamol. However, the increased hazards in using such a radionuclide, with a long half life (118 days), prevented its use in the present study. A completely closed administration system would have to be developed before selenium-75 could be employed for this type of study. The technetium complex for all the in vivo work with MDI's used tetraphenylarsonium chloride as the complexing agent. Although this complex successfully radiolabelled a salbutamol formulation for use with beagle dogs, the formulation is potentially toxic and therefore could not be used for extensive studies in man. Extensive human studies might

require reformulation as the aerosols used in the present study are not fully tested toxicologically.

The beagle dog proved to be a useful conscious animal model for studying deposition patterns of metered-dose inhalers. Qualitative differences were shown in regional deposition, and the total lung dose was significantly different for aerosols with different activity median diameters. The lung images obtained with the dog were large enough and detailed enough to be potentially useful in studying regional deposition from different aerosol formulations and from varied delivery devices such as the MDI and nebuliser. Tomographic imaging may provide more detailed images for the assessment of regional lung deposition since the effect of imaging the respiratory airways in two dimensions can be confusing. Further exploration of the dog model could be achieved by following direct comparisons of lung deposition patterns in humans using the same aerosol. Future work using the animal models and systems described could also include comparisons of aerosols with the same AMAD but differing in other properties such as polydispersity and hygroscopicity.

All animals used in this study were physiologically normal, but it would be interesting to study deposition of inhalation aerosols with the γ-camera before and after bronchoconstriction induced by histamine. Correlation of any changes in deposition pattern with the bronchodilator could also be made, to estimate the loaction of drug receptor sites (Newhouse & Ruffin, 1978; Ruffin et al., 1978a). Similarly, the effect on lung deposition of inhaling aerosol from an MDI at the beginning and end of a breath may be studied and compared with the published clinical measurements (Newman et al., 1981). However, a pneumotachograph which activates an aerosol firing device is required for automatic firing of the MDI in co-ordination with inhalation. Carefully controlled administration techniques are needed to avoid rebreathing the aerosol left in the delivery device.

Further correlations using the techniques of conscious animal dosing, aerosol radiolabelling and particle size measurement established in this study should provide invaluable data on the behaviour of an inhalation aerosols at an early stage in its research and development.