BIOPHARMACEUTICAL STUDIES OF INHALATION AEROSOLS

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Two conscious animal models (the rabbit and the beagle dog) have been established for the inhalation of therapeutic aerosols. The *in vivo* aerosol deposition pattern was measured using a gamma camera, allowing repeated evaluation with different formulations in the same subject. Conscious animals were used to avoid anaesthetic effects on respiration and to allow dosing with materials which were not fully tested toxicologically for human use. Techniques were investigated for γ-radiolabelling therapeutic aerosols containing salbutamol with technetium-99m and two methods used for radiolabelling nebulised and metered-dose aerosols. The aerosols were administered via oral delivery devices designed to bypass filtration by the nasal passages. The design of the administration chamber for dogs also allowed co-ordination of firing a metered-dose inhaler with inspiration. Metered-dose inhalers containing salbutamol with different activity median diameters were administered to the dogs, and the gamma camera lung image showed differentiation according to the particle size range of the aerosol, both in terms of total dose delivered to the lung and activity distribution within the lung.

The mass and activity aerodynamic size distributions of the drug and radionuclide in the aerosol were simultaneously measured by an eight-stage cascade impactor, the Andersen Sampler. The dose fraction deposited in the administration chamber *in vivo* was related to the fraction deposited in the glass 'throat' inlet to the impactor. The Andersen Sampler was also used to measure the aerodynamic size distributions of salbutamol and the surfactant (oleic acid), in a Ventolin Inhaler. The results showed that the mass size distribution of oleic acid droplets was finer than that of the drug particles.

Mean aerodynamic diameters of aerosols measured by the Andersen Sampler were related to projected area diameters from a laser light-scattering instrument, the PMS-CSASP-100, and to other published figures. The PMS instrument was also used to measure sub-micron particles in metered-dose inhalers.

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CHAPTER THREE - GAMMA RADIOLABELLING

CONTENTS (contd.)

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ABBREVIATIONS

AGC	-	aerosol generation chamber
AMAD	-	activity median aerodynamic diameter
d_{gn}	-	geometric mean diameter by number
d_{gw}	-	geometric mean diameter by weight
DTPA	-	diethylenetriaminepenta-acetic acid
HSA	-	human serum albumin
IPPB	-	intermittent positive pressure breathing
mbk	-	methyl isobutyl ketone
MDI	-	metered-dose inhaler
MMAD	-	mass median aerodynamic diameter
oxine	-	8-hydroxyquinoline
Ph_4AsCl	-	tetraphenylarsonium chloride
PMS	-	the PMS-CSASP-100 probe and particle size measurement system.
σ_g	-	geometric standard deviation
Tc-Ph_4AsCl	-	complex of tetraphenylarsonium chloride with technetium-99m.
URT	-	upper respiratory tract