CHAPTER 1

INTRODUCTION

Drug delivery to the lungs by inhalation has attracted tremendous scientific and biomedical interest in recent years. Pulmonary delivery has proven especially attractive alternative to oral, transdermal, and parenteral administration for the treatment of local lung disorders including asthma and cystic fibrosis (Anderson et al.,1989) and have potential for the systemic delivery of peptides and proteins (Patton, 1996). Patients with cystic fibrosis (CF) and chronic pulmonary infection with *Pseudomonas aeruginosa (Psa)* have frequent acute exacerbations of respiratory infection characterized by increased sputum production and tenacity, increased sputum purulence, increased frequency and severity of cough, malaise, deterioration of pulmonary function, weight loss, fever, and leukocytosis (Rubio, 1986). Many patients are given long-term treatment with inhaled and/or systemic antibiotics in the hope of maintaining their physical well-being, quality of life, weight, and lung function, as well as to decrease the number of disease exacerbations and hospital admissions (van Klingeren, 1988; Mukhopadhyay et al, 1996 and Ramsey et al, 1999). Antibiotic therapy has become a mainstay of treatment for patients with CF or non-CF bronchiectasis who are infected with *Psa*, and has been credited with the prolonged survival of CF patients (Boat, 1988; Kepron, 1996 and Hoiby et al, 1982). Inhaled antibiotics have been used effectively for ameliorating chronic pulmonary infections in CF, and non-CF bronchiectasis. Inhalation offers the potential benefit of producing high concentrations of antibiotic at the site of infection in the airways, without the risk of systemic toxicity. Thus, inhaled antibiotics have the potential to provide more effective antimicrobial therapy with fewer adverse effects. Traditionally, aerosolized antibiotics have been administered by means of small-volume nebulizers (SVN). Drug administration by SVN is associated with well-documented disadvantages, including extended administration time, high cost, low efficiency and poor reproducibility, risk of bacterial contamination (Eisenberg et al, 1997). SVN have been increasingly replaced by pressurized metered dose inhalers (pMDI) or dry powder inhalers (DPI) because they are much more efficient, provide more rapid and easier drug administration, and are more cost-effective. For antibiotic therapy, which requires delivery of much larger doses of medication to the lungs than in the case of bronchodilators or steroids, DPIs are likely to be more effective than pMDI, since they can potentially deliver up to 20 mg of powder readily, while pMDI cannot efficiently deliver more than 5 mg per puff (Newman et al 1991 and Irani et al, 1972).

DPIs are versatile delivery systems which may require some degree of dexterity to operate. Typically, they dispense a metered quantity of powder in a stream of air drawn through the device by the patients own inspiration and do not require CFC propellants to disperse the drug. A DPI formulation may consist of micronised drug (<5μm) alone, or of drug blended with a larger inert carrier material like lactose (20–100 μm). The small drug particulates will loosely associate with the lactose surface and become detached in the turbulent airflow that results from the patient inhaling through the device to actuate a dose. The smaller drug particulates enter the lung while the larger carrier particles that escape the device deposit mainly in the oropharynx.

Dry powder aerosols of micronized antibiotics has been attempted, but were limited by inefficient delivery devices and/or poorly dispersible lactose formulations (Goldman et al, 1990 and Labiris et al, 1999). Poor dispersibility of micronised formulations is because of their tendency to form aggregate due to hydrophobic or electrostatic interactions between the fine particles. These changes in the particle size and increases in cohesive forces over time tend to provide powders that give undesirable pulmonary distribution profiles upon activation of the device. More particularly, fine particle aggregation disrupts the aerodynamic properties of the powder, thereby preventing large amounts of the aerosolized medicament from reaching the deeper airways of the lung where it is most effective.

Among the factors that can be adjusted to optimize the efficiency of aerosol formulations, particle chemistry and surface morphology (manipulated to reduce particle-particle aggregation or hygroscopicity) and particle solubility (altered to influence the rate of therapeutic release) are well documented (Gonda I & II, 1992). An attractive strategy for preparation of inhalation particles with improved aerosolization efficiency is by diminishing aerosol particle mass density and increasing particle size. To understand the rationale behind therapeutic aerosol particle design, it is helpful to briefly review the concept of aerodynamic diameter and its relation to the pattern of particle deposition in the lungs. Aerodynamic diameter is the geometric diameter a particle appears to possess on the basis of its in-flight speed, were it assumed to be spherical and to possess a mass density of 1 g/cm^3; stated differently, the geometric diameter of a spherical particle possessing unit mass density (1 g/cm^3) is equivalent to its aerodynamic diameter. Because many naturally occurring particles possess a mass density near this value and because sphericity is a

tendency of nature based on surface energetic considerations, such a ''base-case'' particle has proven useful for discussing the sites and extent of aerosol particle deposition in the lungs as a function of particle size.

A more quantitative idea of aerodynamic diameter can be gathered by imagining a spherical particle falling under gravity through air; so long as the characteristic particle size is substantially larger than the mean free path of the surrounding air molecules, it can be shown that the particle will settle with a velocity (v)

$$v = \frac{mg}{3\pi\mu d} \qquad \text{-------- Equation (1.1)}$$

where m is the particle mass, g is the gravitational constant, μ is the viscosity of air, and d is the particle diameter. Expressed in terms of particle mass density (ρ), this gives

$$v = \left(\frac{g}{18\mu}\right)\rho d^2 \qquad \text{---------- Equation (1.2)}$$

Equation 1.2 shows that spherical particles will fall under gravity with a velocity that is proportional to their mass density ρ and the square of their geometric diameter (d^2). If we consider the heuristic definition of aerodynamic diameter provided above, it is possible to rewrite Equation 1.2 in terms of the particle's aerodynamic diameter, as

$$v = \left(\frac{\rho_a g}{18\mu}\right) d_a^2 \qquad \text{---------- Equation (1.3)}$$

where ρ_a = 1 g/cm3, and where we have defined the aerodynamic diameter (da) by the relationship

$$\rho_a d_a^2 = \rho d^2 \qquad \text{---------- Equation (1.4a)}$$

or

$$d_a = \sqrt{\frac{\rho}{\rho_a}}\, d \qquad \text{---------- Equation (1.4 b)}$$

Equation 1.3 shows that a spherical particle of any mass density ρ will settle with a velocity that depends only on its aerodynamic diameter d_a, i.e., is dependent on size

and mass density through the specific relation of Equation 1.4. Modifications to Equation 1.4 arise for nonspherical particles (Gonda I, 1992); these modifications can include more than a single aerodynamic coefficient, particularly in the case of nonisotropic particles (e.g., cylinders), wherein the particles translate with a preferred orientation. Because gravitational settling constitutes one of the principal mechanisms of aerosol particle deposition in the lungs, the concept of aerodynamic diameter becomes a useful intrinsic particle property with which to discuss a particle's expected lung deposition performance following inhalation. Moreover, the second principal mechanism of particle deposition in the lungs, inertial impaction, also depends uniquely on d_a (Landahl, 1950). Aerodynamic diameter has thus been used for several decades to quantify an aerosol particle's inherent propensity to deposit in the lungs, essentially independently of its shape, mass density, and (in principle) geometric size.

The aerodynamic diameter window of 1–3 μm has proven to be optimal for inhalation drug delivery. Particles of mean aerodynamic diameter of 1–3 μm deposit minimally in the mouth and throat and maximally in the lower airways and in the lung's parenchymal region (Altschuler et al, 1957; Clark et al, 1994; Davies et al, 1972; Heyder et al, 1975 & 1984 and Muir et al, 1967). Tracheobronchial deposition, generally not desired for an inhalation therapy, is maximized for aerodynamic diameter between, 8 and 10 μm. Particles possessing an aerodynamic diameter smaller than 1 μm are mostly exhaled, and particles larger than 10 μm have little chance of making it beyond the mouth.

Engineered particles provide a low area of contact and reduced cohesive forces between them. This lower surface energy imparts increase in flowability and fine particle fraction and has been shown to improve peripheral lung deposition by reducing deposits in the extrathoracic and tracheobronchial airways, making them ideally suited for inhaled therapies used in the treatment of diseases involving infection of the airway (CF and non-CF bronchiectasis) without substantial systemic component. Furthermore some of them had shown reduced clearance by alveolar macrophage action, thereby improving the bioavailability of inhaled pharmaceuticals (Vanbever et al, 1999)

Aminoglycosides are considered among the most useful classes of antibiotics for treating *Psa* infections. The major drawback of aminoglycosides is the need for their relatively high-dose intravenous administration, which carries the potential for

systemic toxicity (Chan, 1989; Moore et al, 1987 and Barclay et al 1994). Consequently, when given intravenously in maximum safe doses, only relatively low sputum aminoglycoside concentrations are achievable.

Tobramycin sulfate (TB) and amikacin sulfate (AMK) were selected for the study, because of their relatively low systemic toxicity and minimum inhibitory concentrations. TB is one of the aminoglycosides with the lowest systemic and toxicity, and early empiric studies revealed that aerosol administration of the intravenous formulation to a variety of patients appeared to be well tolerated and it was more active then gentamycin against *Psa.* Efficacy of TB aerosol therapy has been clinically proven and improvement was observed by a substantial reduction in the numbers of *Psa* in the sputum and a decrease in the peripheral blood neutrophil count (Lodge, 1998). AMK, a broad spectrum aminoglycoside effective against *Psa* at lower minimum inhibitory concentrations (MIC_{90}) of 2 μg/ml and retained their activity against gentamycin and TB resistant microorganisms, because of its unique resistance to the aminoglycoside-inactivating enzymes (Chambers et al, 1996). Low sputum level of intravenously administered aminoglycosides and their associated systemic toxicities can be circumvented by direct delivery of effective amount of these antibiotics to the airways.

1.1 RESEARCH ENVISAGED

The research work focuses with an overall objective of delivering effective amount of high dose antibiotics directly into the endobronchial site of infection. New formulation concepts for pharmaceutical development of inhalable antibiotics with improved aerosolization properties are being focused. The proposed plan of work was divided into following specific aims:

I. Literature reviews covering various aspects of particle engineering and their behaviors been explored for pulmonary drug delivery. Selection of drug profiles like TB and AMK, their pharmaceutical development methodologies and techniques of pulmonary administration.

II. Selection of suitable methodology for design and development of aerodynamically light and large particles (ALLP) containing high therapeutic payload of aminoglycoside antibiotics having lower mass density ($\rho < \sim 0.4$ g / cm^3) and large in size (5-30 μm). ALLP will be prepared by spray drying and/or freeze drying process, characterized for traits and topography and their influence on the *in-vitro* aerosol performance will be evaluated.

III. Quantitative aspects of the effects and relationships among various formulation components will be optimized by suitable statistical design on the ALLP produced by selected technology.

IV. Characterization of traits, topography and *in vitro* aerosolization properties of optimized ALLP. Evaluation of ALLP flow and dispersion characteristics, packing properties, influence of humidity and airflow rate on dispersion characteristics of ALLP.

V. Stability studies of potential formulations with respect to potency, degradation, moisture content, particle size, emitted dose, fine particle fraction and the physical changes like caking and discoloration.

VI. Assessment of pulmonary deposition with in lung and pulmonary clearance study of ALLP with respect to conventional lactose base formulation.

VII. Comparative alveolar macrophage uptake study of ALLP with conventional lactose base formulation by bronchoalveolar lavage method.

VIII. Evaluation of pulmonary toxicity of developed formulation in the rat lung.

1.2 REFERENCES

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