Chapter 1

INTRODUCTION

1.1 General Introduction

Tuberculosis (TB) is one of the most significant infections causing human diseases. Although the incidence of TB declined greatly during the twentieth century, it has become a major problem in human immuno-deficiency virus (HIV) patients. The World Health Organization (WHO) estimates that active cases of TB afflict seven to eight million people annually, and lead up to three million deaths per year (Grange and Zumla, 2002 ; Reichman and Hershfield, 2000). Furthermore, a person infected with HIV is ten times more likely to develop TB than one who is HIV-negative. Consequently, the spread of HIV is accelerating the rise in TB case rates (Blanc and Nunn, 1999 ; Grange and Zumla, 2002 ; Reichman and Hershfield, 2000).

The causative organism of TB is tubercle bacilli, named *Mycobacterium tuberculosis*. The current treatment of pulmonary TB involves prolonged oral administration of high doses of combined antibiotics, which are associated with unwanted side effects and poor compliance (Suarez *et al.*, 2001). In addition, oral administration causes a rise in multi-drug resistant TB (Panchagnula and Agrawal, 2004). Effective chemotherapy of TB involves daily administration of one or more drugs for a period of six months or longer. The initial intensive phase of two months requires four drugs (isoniazid, rifampicin, pyrazinamide, streptomycin or ethambutol). The continuation phase can last four to six months, during which rifampicin is

combined with isoniazid. However, the adherence to full treatment is difficult and many patients stop treatment before completing the regimen (Blanc and Nunn, 1999 ; Deol and Khuller, 1997).

Fortunately, there is a bacille Calmette-Guérin (BCG) vaccine (a live attenuated strain of *M. bovis*) which is administered to a hundred million children annually. The efficacy of BCG has been a source of contention since its introduction in the 1920s but it seems to be more effective in some countries than others (Groves, 1997).

Most oral antituberculosis drugs presently in use fail to achieve high drug concentration in the lung. A few reports suggest that high drug concentration in the lung will be obtained after maintaining a high dose oral drug administration for a long period of time (Liu *et al.*, 2003 ; Sharma *et al.*, 2001 and Tsapis *et al.*, 2003). Clinical management of the disease is limited because of toxic side effects. Moreover, there are problems caused by the degradation of drugs before reaching their target site, low permeability and poor patient compliance.

An alveolar macrophage is the first defense mechanism against infection. The tubercle bacilli penetrate inside the macrophages subsequently to be protected through intracellular harboring. The bacilli secrete molecules that present phagosome-lysosome fusion. Due to their very hydrophobic waxy cell wall, bacilli are resistant to digestion by lysosomal enzymes and hence resist the killing effects of the macrophage (Vyas *et al.*, 2004).

The development of antituberculosis drugs delivered directly to the lung is one of the most promising ways. As the dose is reduced, it will cause side effect and adverse drug reaction. Hence, patient compliance is expected. Most importantly,

targeting the drug to the alveolar macrophage may improve efficacy and potentially reduce systemic toxicity. In addition, giving a high local drug concentration may reduce the duration of treatment and prevent possible multi-drug resistance of TB.

1.2 Objectives of the Thesis

The aims of this study were as follows :

1. To study and develop antituberculosis drugs as dry powder inhalers (DPIs).
2. To study the antimycobacterial activity of the DPIs *in vitro*.
3. To evaluate the physicochemical stability of antituberculosis DPIs.

1.3 Structure of the Thesis

In this chapter (Chapter 1), the problems in the TB treatment are addressed. The potential factors to the problems are described and used to define the aim and specific objectives of each chapter. A general review of literature is presented in Chapter 2.

Chapter 3 describes the method development for measuring antituberculosis drugs. Validation methods were established.

Chapter 4 describes the production of rifampicin and isoniazid as DPIs with sugar carriers (trehalose dihydrate, mannose, lactose monohydrate) by physical mixing. In this chapter, the delivery efficiency of DPIs to the lower airways was monitored.

Chapter 5 describes the production of isoniazid by spray drying technique with trehalose dihydrate and lactose monohydrate. The efficacy of DPIs to deliver the drug to the lower airways was performed as previously described in Chapter 4.

Chapter 6 develops encapsulation method of rifampicin with lipid (cholesterol and lecithin) by spraying into antisolvent technique. After DPIs was formulated, the formulation was evaluated for the delivery efficiency to the lower airways.

Chapter 7 describes drug susceptibility testing of selected formulations as compared with standard rifampicin and isoniazid. The conclusion of the thesis is presented in Chapter 8.