Chapter 5

FORMULATION DESIGN OF ANTITUBERCULOSIS DRY POWDER INHALERS BY SPRAY DRYING

5.1 Introduction

Spray drying was explored in the 1980s as an alternative means of making fine particles with desirable flow and dispersion characteristics without the need of using coarse carriers or forming soft pellets (Chan and Chew, 2003). Spray drying is a common practice in powder preparation for a wide range of drugs. Spray dried powder can be produced respirable drug particles and used to deliver particles to the lung via dry powder inhalers (Malcolmson and Embleton, 1998). Although, this is a well-established technology in the food and pharmaceutical industries, recovering micronized spray dried material at an economically acceptable yield is a major challenge, requiring an extremely high-efficiency cyclone. However, this approach has attracted much interest of late because of its potential application in the micronization of biopharmaceutical (peptide and protein) particles for delivery to the systemic circulation via the pulmonary route (Platz *et al.*, 2003).

In addition, micronised but spherical particles can be prepared by spray drying. Spray drying is a process in which a homogeneous aqueous mixture of a drug and a carrier is introduced via a nozzle, spinning disc or an equivalent device into a hot gas stream to atomize the solution from fine droplets. The aqueous mixture may be a solution, suspension, solid or the like, but needs to ensure uniform distribution of

components in a mixture and ultimately the powdered composition. Preferably the aqueous mixture is a solution. The solvent, generally water rapidly evaporates from the droplets producing a fine dry powder having particles 1 to 5 μm in diameter (Platz *et al.*, 2003). Surprisingly, the drug is not degraded when it is exposed to the hot drying gas, and the powders can be prepared for pharmaceutical use. An acceptable purity is defined as less than 5% degradation products and contaminates, preferably less than 2% with the highest acceptance at less than 1%.

The spray drying is done under conditions that result in a substantially amorphous powder of homogeneous constitution having a particle size that is respirable, a low moisture content and flow characteristics that allow for aerosolization. Spray drying also allows a control over particle shape, morphology and density dependent on the spray drying conditions (Steckel and Brandes, 2004). Preferably the particle size of the resulting powder is such that more than 98% of the mass is in particles with a diameter of about 10 μm or less with about 90% of the mass being in particles with a diameter less than 10 μm with about 80% of the mass the particles have a diameter of less than 5 μm. In fact, spray drying has been applied to a variety of substances, such as peptides, antibiotics, vaccines, and carrier particles. One of the principal purposes of aerosolizing spray dried powders is to achieve powder particle diameters of several micrometers with a narrow particle distribution (Sham *et al.*, 2004). In spray drying, a drug solution is atomized to fine droplets which are evaporated in a warm air current to form dry particles. Although the drying air temperature can be relatively high (e.g., > 100°C), the actual temperature of the evaporating droplets is significantly lower due to cooling by the latent heat of vaporization. Thus, thermal degradation of the active ingredient is not so much a

concern as it first appears (Chan and Chew, 2003). In the case of rifampicin, it is thermolabile when the temperature of the drying chamber is set at 80°C (Agrawal *et al.*, 2004). Thus, rifampicin could not be prepared by spray drying.

5.2 Materials

D-(+)-Lactose monohydrate (Fluka, Switzerland)

D-(+)-Trehalose dihydrate (Sigma chemical company, St. Louis, MO, USA)

Isonicotinic acid hydrazide (Sigma chemical company, St. Louis, MO, USA)

Span 80 (Srichand united dispensary, Co. Ltd., Bangkok, Thailand)

5.3 Equipment

Andersen cascade impactor (Atlanta, Georgia, USA)

Laser diffractometer (Mastersizer, Malvern, UK)

Scanning electron microscope (Jeol, Japan)

Spray dryer (Anhydro, Copenhagen, Denmark)

Sputter coater (SPI supplied, USA)

Twin stage impinger (Copley instrument, Nottingham, UK)

Vacuum pump (Gast, USA)

5.4 Methods

5.4.1 Preparation of the formulations

The formulations for spray drying were prepared by dissolving 7.5 g of isoniazid and 12.5 g of carrier in 1000 ml of water. All solutions were processed immediately after preparation. Solutions were spray dried utilizing a spray dryer system equipped with a two-fluid nozzle for atomization. The 1000 ml of water were sprayed prior to atomization. Spray dried powder formulations were collected via a cyclone. These powder formulations are equal to 1250 doses (16 mg per dose) and were stored in a desiccator at room temperature over silica gel. Formulation code is shown in Table 5.1.

Table 5.1 Compositions of dry powder formulations obtained from spray drying technique

Formulation no.	Formulation code	Drug	Carrier
19	INH-1 (sd)	isoniazid	trehalose
20	INH-3 (sd)	isoniazid	lactose

5.4.2 Particle size distribution measurement

Particle size analysis was performed by suspending approximately 100 mg of DPI in chloroform containing 1% w/v of Span 80 which was pre-saturated with the powder under investigation. The suspension was sonicated in an ultrasonic bath for 10 minutes. Then, the experimental were performed according to section 4.4.2 as described before.

5.4.3 Content uniformity of spray dried formulations

This experimental were performed according to section 4.4.6 as described before.

5.4.4 Characterization of particle morphology

Visualization of particle size and morphology of these formulations was achieved by SEM. This experimental were performed according to section 4.4.3 as described before. All micrographs of these particles were taken at an acceleration voltage of 10 keV.

5.4.5 *In vitro* deposition of drugs in spray dried formulations by TSI

In vitro deposition of INH-1 (sd) and INH-3 (sd) formulations were carried out using a TSI. Each deposition experiment involved the aerosolisation of 6 times, each containing a dose of 16 mg powder, equivalent to 6 mg of isoniazid.

16 mg of dry powder formulation was weighed and placed in a glass inhaler device. For each determination, 7 ml of water was placed in the stage 1 and 30 ml in stage 2 of the TSI. The air flow was drawn through the device at a flow rate of 60 l/min for 10 seconds. The inhaler device, the mouthpiece adapter and upper stage (stage 1) were rinsed with water. The same procedure was repeated for the lower stage (stage 2) of the TSI. The eluent was adjusted to the appropriate volume with water. All solutions were analysed for the concentration of isoniazid using HPLC method as described in Chapter 3. Deposition of isoniazid in the lower stage was considered to be the FPD, ED and FPF described in section 4.4.5.

5.4.6 *In vitro* deposition of drugs in spray dried formulations by ACI

The depositions of dry powder formulations were assessed *in vitro* again using an Andersen Mark II cascade impactor. 16 mg of dry powder formulation was weighed by analytical balance and put in a glass inhaler device. This experimental were performed according to section 4.4.7 as described before. The ED, MMAD and GSD were calculated according to the equation in section 4.4.7.

5.4.7 Stability of the spray dried formulations after storage

The spray dried formulations were stored in a desiccator at room temperature. The %content of drugs and MMAD were determined after a storage period of 3 months according to section 4.4.8.

5.5 Results and Discussion

5.5.1 Particle size distribution measurement

Figures 5.1 and 5.2 show particle size distribution of INH-1 (sd) and INH-3 (sd) respectively. The mean of the volume median diameter is 6.48 ± 1.50 μm and 6.08 ± 0.81 μm (mean ± SD, n = 3) of these formulations respectively. A large particle size was obtained by spray drying technique. However, the delivery to lower airway of both formulations must be evaluated by *in vitro*. Particle size distribution of particles is not exclusive factor for influences the deposition pattern in the human lung (Shekunov *et al.*, 2003).

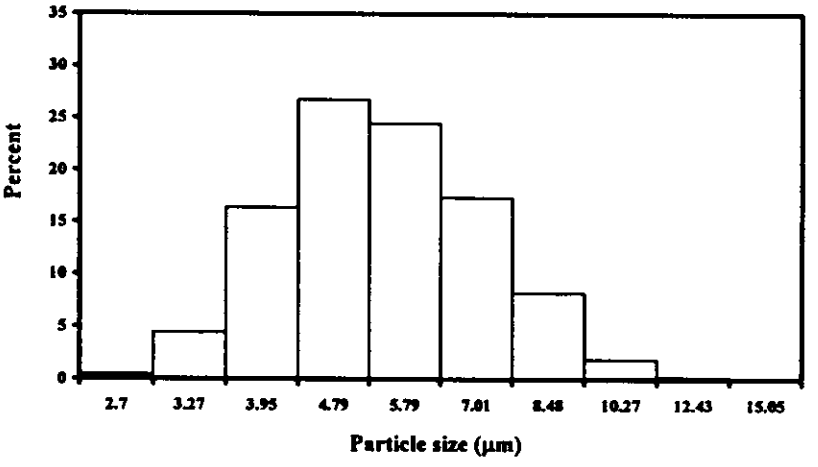

Figure 5.1 Particle size distribution based on volume of INH-1 (sd) formulation using Malvern laser light diffraction technique

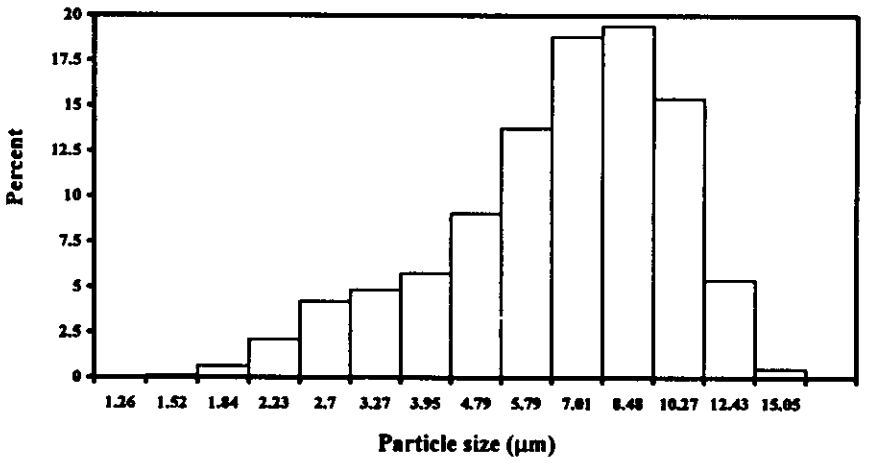

Figure 5.2 Particle size distribution based on volume of INH-3 (sd) formulation using Malvern laser light diffraction technique

5.5.2 Content uniformity of spray dried formulations

Figure 5.3 shows content uniformity of isoniazid in both formulations. High content uniformity (>100%) was obtained from both formulations employing trehalose and lactose as carriers.

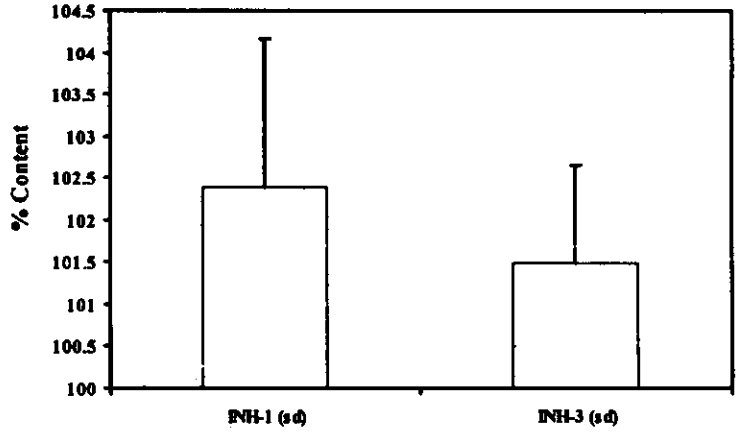

Figure 5.3 Content uniformity of INH-1 (sd) and INH-3 (sd) formulations (mean ± SD, n = 10)

The isoniazid contents of samples varied from 102.39 ± 1.77% for the formulation containing trehalose as a carrier [INH-1 (sd)] prepared from spray drying technique to 101.48 ± 1.18% for the formulation containing lactose as carrier [INH-3 (sd)] prepared by spray drying technique. Spray drying technique gave higher content uniformity than that obtained from physical mixing of formulations because previously collected dry particles after spray drying, the drug and carrier are dissolved and mixed homogeneously.

5.5.3 Morphology of dry powder formulations

Figure 5.4 (A-D) shows morphology of INH-1 (sd) formulation and INH-3 (sd) formulations obtaining from SEM. Both formulations have a spherical particle and uniform shape and size.

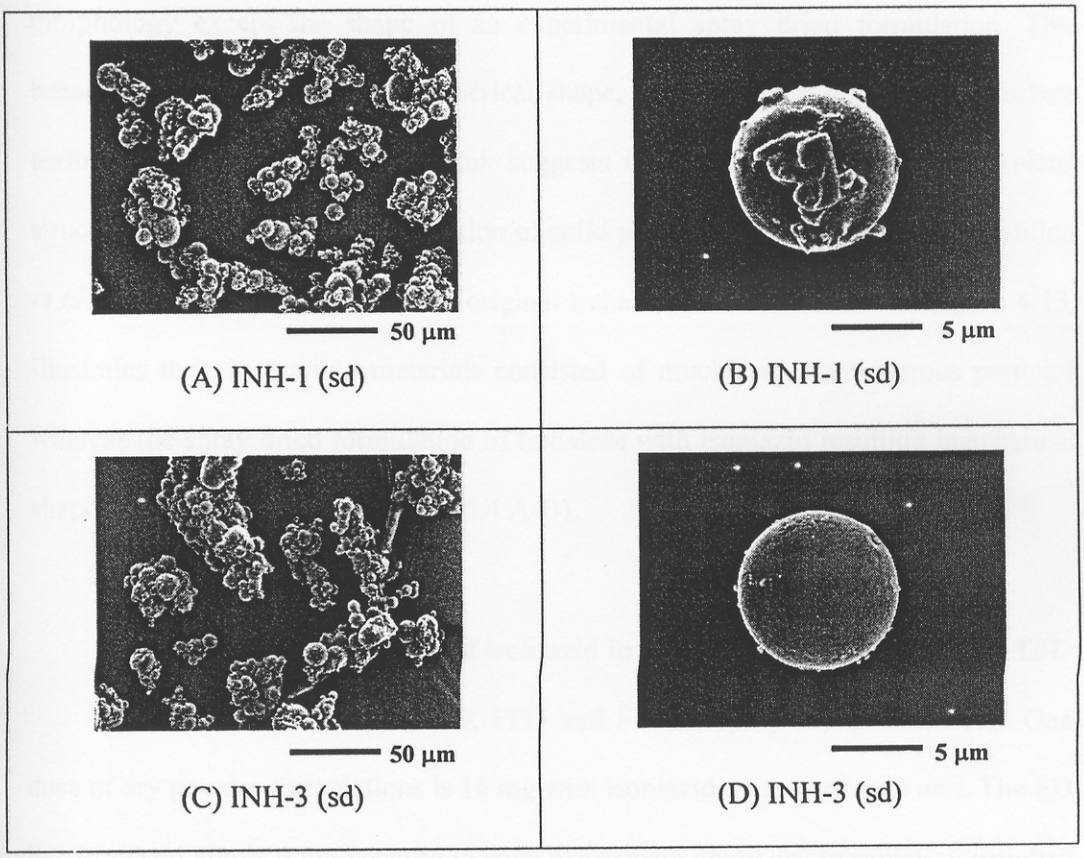

Figure 5.4 Electron micrographs of (A) INH-1 (sd) × 300, (B) INH-1 (sd) × 3000, (C) INH-3 (sd) × 300 and (D) INH-3 (sd) × 3000

The spray dried particles was typically spherical particles with 5-10 µm in size (Figure 5.4). SEM shows that the particle shape of the spray dried formulation varied from spherical shape with rough surface to spherical shape with smooth surface. Figure 5.4 (A-D) also shows that, the number of small particles spherical formulation particles increased by spray drying when compared to isoniazid,

trehalose or lactose particles obtained from the grinding mill [Figures 4.11 (C-D), 4.12 (A-B and E-F), respectively]. Looking at the SEM pictures of the raw material lactose, Figure 4.12 (E-F), it can be seen that the particles do not differ with respect to morphology except the shape of an experimental spray dried formulation. This became conspicuous due to its spherical shape, but still had a very smooth surface texture (Figure 5.4 C-D). This result suggests that lactose might offer the skeletal structure necessary for the formulation of solid particles by spray drying (Bosquillon *et al.*, 2001). A SEM image of the original trehalose material, shown in Figure 4.13, illustrates that the starting materials consisted of much larger and porous particles whereas the spray dried formulation of trehalose with isoniazid resulting in spherical shape with porous particles (Figure 5.4 A-B).

5.5.4 *In vitro* deposition of isoniazid in spray dried formulations by TSI

Table 5.2 shows ED, FPD and FPF of spray dry formulations. One dose of dry powder formulations is 16 mg with isoniazid 6 mg in dosage unit. The ED has isoniazid above 6 mg because in each experiment spray dry formulation weighed more than 16 mg. Both of formulations have high FPF (> 60%).

Table 5.2 Drugs deposition in the TSI after aerosolization of spray dried formulations (mean ± SD, n = 6)

Formulation code	ED (mg)	FPD (mg)	FPF (%)
INH-1 (sd)	6.17 ± 0.40	4.17 ± 0.41	67.53 ± 2.63
INH-3 (sd)	6.87 ± 0.18	4.88 ± 0.16	71.11 ± 0.78

Although our EDs delivery efficiencies were over 100% nominal dose which was related to content uniformity over 100%. Factors accounting for these over 6 mg include thermolabile of sugar carriers during spray drying process and loss of water content of the powder formulations after storage in desiccator. The mean fine particle doses for INH-1 (sd) and INH-3 (sd) were 4.17 ± 0.41 and 4.88 ± 0.16 mg, respectively. The formulation containing trehalose gave a high FPD and FPF than that obtained from formulation containing lactose. The results suggest that these drug-trehalose particles did not aggregate and resulted in good flowability. In all cases, the standard deviations for the ED, FPD and FPF were low and satisfactory according to the pharmacopoeia.

5.5.5 *In vitro* deposition of isoniazid in spray dried formulations by ACI

Figure 5.5 shows particle size distribution of spray dry formulations based on aerodynamic diameter. Figure 5.6 (A) and (B) shows relationship between z value and cut off aerodynamic diameter of the particle that was used to calculate MMAD. The EDs were 5.89 ± 0.65 mg and 5.43 ± 0.55 mg, MMADs were 5.85 ± 1.83 μm and 4.83 ± 2.31 μm, GSDs were 1.53 ± 0.21 and 1.73 ± 0.28 (mean ± SD, n = 6) for the INH-1 (sd) and INH-3 (sd) formulations, respectively. The MMAD obtained by ACI was close to mean volume median diameter that obtained by laser light diffraction technique.

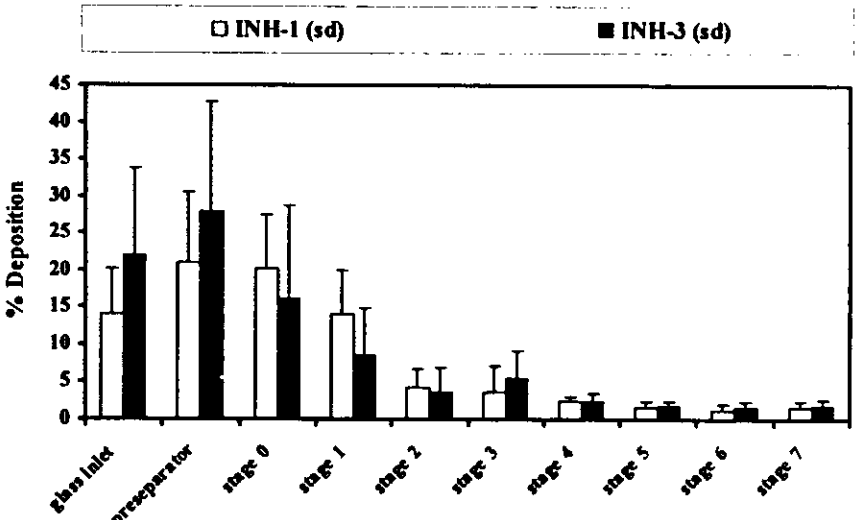

Figure 5.5 Size distribution of isoniazid in spray dried formulations on each stage of the ACI as aerosolized at a flow rate of 60 l/min (mean ± SD, n = 6)

(A)

(B)

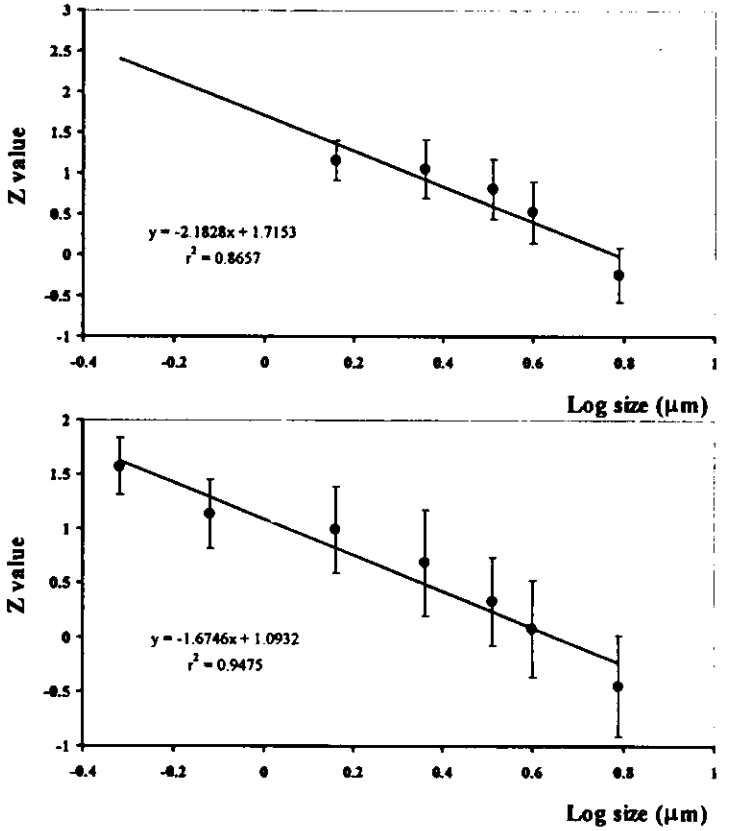

Figure 5.6 Relationship between Z value and cut off aerodynamic diameter (log scale) on each stage of the ACI of formulations (A) INH-1 (sd) and (B) INH-3 (sd)

5.5.6 Stability of the spray dried formulations after storage

The drug contents and MMAD after storage for 3 months are shown in Table 5.3. The initial %content and MMAD obtained from section 5.5.2 (uniformity of dosage unit) and section 5.5.5 (*in vitro* deposition by ACI) are the same.

Table 5.3 Drug contents (mean ± SD, n = 3) and MMAD (mean ± SD, n = 6) of dry powder formulations after storage 3 months at room temperature

Formulation	%content		MMAD (μm)	
	Initial	After 3 months	Initial	After 3 months
INH-1 (sd)	102.39 ± 1.77	103.35 ± 0.95	5.85 ± 1.83	7.87 ± 4.17
INH-3 (sd)	101.48 ± 1.18	103.10 ± 3.58	4.83 ± 2.31	2.12 ± 0.22[#]

[#] $P < 0.05$

From Table 5.3, the contents of INH-1 (sd) and INH-3 (sd) formulations after storage 3 months increased about 1-1.5% from initials. This may result from loss of water because the formulations were stored in a desiccator over siliga gel. The content of both spray dried formulations remained unchange after storage, thus the isoniazid have vary high stability after formulated by spray drying technique. The MMAD of the initial formulation was compared with that of the stored formulations after 3 months. After storage for 3 months, MMAD value of the formulation of isoniazid containing fine trehalose or micronised mannose were significantly larger than the initial values ($P < 0.05$). The significant increase of MMAD after storage was probably due to the formation of particle aggregates. In contrast, the spray dried isoniazid with lactose showed smaller MMAD values after 3 months storage. It may be the result that electrostatic force of the formulation was retained for a long period of time therefore the initial size was large. However, after the electrostatistic force disappeared, the size was small when determined the aerodynamic diameter of particles. Other formulations show that the MMAD values

after 3 months storage are not significantly different ($P > 0.05$) from initial size. The results suggest that these formulations have high physical stability for DPIs.