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Influence of Formulation and Preparation Process on Ambroxol Hydrochloride Dry Powder Inhalation Characteristics and Aerosolization Properties

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The objective of this study is to evaluate the influence of formulation and preparation process on ambroxol hydrochloride (AH) dry powder inhalation (DPI) characteristics and aerosolization properties. Spray-dried samples of AH, AH/leucine, and AH/leucine/mannitol were prepared from their corresponding water solutions under the same conditions to study the influence of the composition, and the AH/leucine/mannitol (2.5/0.5/1 by weight) formulation was used for investigation of the effect of the preparation process. Following spray-drying, the resulting powders were characterized using scanning electron microscopy, laser diffraction, tapped density, and angle of repose measurements, and the aerosolization performance was determined using a twin-stage liquid impinger. AH/leucine/mannitol (2.5/0.5/1 by weight) obtained by cospray-drying improved the AH aerosolization properties. The AH/leucine/mannitol (2.5/0.5/1 by weight) preparation exhibited the following properties: 62.34% yield, 0.34 g/cm^3 tap density, 2.71 μm d_{ae}, 33.45° angle of repose, and 30.93% respirable fraction. The influence of the preparation process on DPI characteristics and aerosolization properties was relatively small, but the influence of the composition was relatively large. Optimization of DPI can be achieved by selecting the most appropriate formulation and preparation process.

Keywords ambroxol hydrochloride; dry-powder inhalation; spray-drying conditions; aerosolization properties; leucine

INTRODUCTION

Inhalation therapy is an attractive and effective therapy for a number of pulmonary diseases. The potential advantages of inhalation therapy have been well known for many years (Dalby & Suman, 2003). Ambroxol hydrochloride (AH) is often used as a mucolytic agent to increase surfactant secretion in the lung (Disse, 1987; Seifart et al., 2005). Inhalation may be able to offer an improvement over current drug delivery strategies. There are a number of marketed AH products available. Oral presentations of AH require substantially higher dose and may be associated with a greater incidence of systemic side effects. Following i.v. administration, absorption is faster than oral but i.v. also requires a substantially higher dose (Von, 1978), and so it will also increase systemic side effects and lead to poor patient compliance. An AH inhalation preparation would overcome some of the drawbacks of the above delivery routes.

Nebuliser, pressurized metered dose inhaler (pMDI), and dry powder inhalation (DPI) systems can all be used to achieve deposition in the target region, but DPI is particularly useful compared with Nebuliser and pMDI because of its better portability and absence of propellant for drug aerosolization (Malcolmson & Embleton, 1998; Timsina, Martin, Marriott, Ganderton, & Yianneskis, 1994). The particle size of the dry powder is a crucial factor in DPI formulation, and an aerodynamic diameter between 1 and 5 μm is required to allow powder deposition in the appropriate area of the lung tissue (Atkins, 2005; Ikegami et al., 2003; Larhrb, Martin, Marriott, & Prime, 2003; Okamoto, Aoki, & Danjo, 2000; Shekunov, Feeley, Chow, Tong, & York, 2003; Zeng, Martin, Marriott, & Pritchard, 2000).

Three methods, that is, air-jet milling, supercritical fluid precipitation (SCFP), and spray-drying, are usually used to produce dry powders for inhalation (Timsina et al., 1994). However, air-jet milling only provides a limited opportunity for control over potentially important particle characteristics (Timsina et al., 1994). Although SCFP is attractive, many compounds are not soluble in the available supercritical fluids, and therefore, SCFP is restricted to marketed DPI products (Timsina et al., 1994). The spray-drying technique has been applied successfully in the pharmaceutical industry since the early 1940s and may meet DPI requirements because it usually produces small spherical particles with a narrow size distribution (Okamoto et al., 2000). In fact, spray-drying has been used by many researchers to generate dry powders suitable for inhalation (Corrigan, Corrigan, & Healy, 2004, 2006; Najafabadi, Gilani, Barghi, & Rafiee-Tehrani, 2004; Okamoto et al., 2000; Surendrakumar, Martyn, Hodgers, Jansen, & Blair, 2003). Carbohydrate and amino acids are often used as excipients for DPI in spray-drying. Lactose, mannitol, and leucine are recog-

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nized as safe and have been widely used in DPI formulations in previous studies (Andya et al., 1999; Codrons, Vanderbist, Ucakar, Précat, & Vanbever, 2004; Corrigan et al., 2004; French, Edwards, & Niven, 1996; Najafabadi et al., 2004). However, lactose is prone to absorb moisture, and therefore, mannitol and leucine were chosen for this study.

The aim of this study is to evaluate the influence of the formulation and preparation processes on DPI characteristics and aerosolization properties.

EXPERIMENTAL MATERIALS

AH was obtained from Beijing Taiyang Ltd (Beijing, China). Leucine, ammonium phosphate dibasic, and mannitol were provided by Tianjun Bodi Ltd (Tianjun, China). Acetonitrile was purchased from Kangkede (Tianjun, China) and was of chromatographic grade.

METHODS

Formulation of the Dry Powders

Dry powders were made with AH, AH/leucine, and AH/leucine/mannitol (Table 1) by spray-drying in order to evaluate the influence of the formulation on the powder characteristics and aerosolization properties. They were dissolved in *ultra pure* water. The pH was then adjusted to 6.0 ± 0.02 by addition of a few droplets of NaOH 0.01 mol/L and passed through a 0.22-μm cellulose filter.

The powders were produced using a Spray Dryer SD-1000 (Eyela, Tokyo, Japan) at low relative humidity (30–40%). Solutions were pumped into the drying chamber at a rate of 1.8 mL/min, an atomizing pressure of 17 Kpa, an airflow rate of 0.60 ± 0.05 m^3/min, and an inlet air temperature of 130°C. The outlet temperature depended on the inlet temperature, the liquid and the gas flow rates, and varied between 75 and 80°C.

To estimate the effect of spray-drying conditions on DPI characteristics and aerosolization properties, AH/leucine/mannitol samples (2.5/0.5/1 by weight) were spray-dried under the following conditions (Table 2).

TABLE 1
Formulation Design

Formulation No.	Composition	Concentration of Spray-Drying Solution (g/100 mL)
1	AH	2.5
2	AH/leucine	2.5/0.1
3	AH/leucine	2.5/0.5
4	AH/leucine	2.5/1
5	AH/leucine/mannitol	2.5/0.5/0.5
6	AH/leucine/mannitol	2.5/0.5/1
7	AH/leucine/mannitol	2.5/0.5/1.5

TABLE 2
Spray-Drying Conditions for AH/Leucine/Mannitol (2.5/0.5/1 by Weight)

No.	Feed Flow Rate (mL/min)	Atomizing Pressure (KPa)	Air Flow (m^3/min)	Inlet Temperature (°C)
1	1.1	17	0.6	130
2	1.8	17	0.6	130
3	2.5	17	0.6	130
4	1.8	15	0.6	130
5	1.8	17	0.6	130
6	1.8	18	0.6	130
7	1.8	17	0.5	130
8	1.8	17	0.6	130
9	1.8	17	0.7	130
10	1.8	17	0.6	110
11	1.8	17	0.6	130
12	1.8	17	0.6	150

All samples were transferred to tight closed amber glass containers and stored in a desiccator over silica gel.

Powder Characteristics

Yield of Spray-Drying Powders

The yields of spray-drying powders were quantified as the percentage of the anticipated yields.

Scanning Electron Microscopy

A small amount of sample was scattered on mutually conductive double-sided adhesive tape placed on an aluminum stub and gold-coated using a JFC-1200 Fine Coater (Jeol, Tokyo, Japan) with a current of 20 mA for 200 s. Scanning electron micrographs were imaged with a scanning electron microscope (SEM) (SSX-550; Shimadzu, Kyoto, Japan) at an accelerating voltage of 15 KV and with an emission current of 170 μA by scanning fields randomly at several suitable magnifications.

Particle Size and Density

The particle sizes of the samples were determined by a Beckman Coulter LS 230. Powders were added carefully into the sample cup. The measurement was then performed for a sample run time of 90 s. Each sample was analyzed in triplicate. The data obtained were expressed in terms of the particle diameter at 10, 50, and 90% of the volume distribution (d[υ,10], d[υ,50], and d[υ,90], respectively) and *the volume mean particle size* (*D*). The span of the volume distribution, a measure of the width of the distribution relative to the median diameter d[υ,50], was derived using Equation 1. A large span is indicative of a more heterogeneous size distribution.

$$\text{Span} = \frac{\text{d}[\nu,90] - \text{d}[\nu,10]}{\text{d}[\nu,50]}, \quad (1)$$

where d[υ,10], d[υ,50], and d[υ,90] are the particle diameter at 10, 50, and 90% of the volume distribution, respectively.

The powder tapped density (ρ) was obtained by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped and the volume reading was taken until little further volume change was observed (British Pharmacopoeia Commission, 2005). Measurements were performed in triplicate.

The theoretical estimates of particles primary aerodynamic diameter were derived from the particle sizing and tapped density data using Equation 2:

$$d_{ae} = \left(\sqrt{\rho/\rho_1}\right)d, \quad (2)$$

where d_{ae} is aerodynamic diameter, ρ_1 = 1 g/cm^3 (Bosquillon, Préat, & Vanbever, 2004), and d is the particle diameter of the volume distribution.

Angle of Repose

The angle of repose was determined by the method reported, that is, the powder is poured through a funnel and forms a cone-shaped pile which makes an angle α to the horizontal (Hickey & Concessio, 1997). Measurements were performed in triplicate.

Aerosolization Properties of the Powders In Vitro

The in vitro deposition evaluation of AH inhalation powder was conducted in a twin-stage liquid impinger (TI) (Figure1) (Geuns, Toren, Barends, & Bult, 1997), using 7 mL of purified water as the dilution solvent in the upper impingement chamber D and 30 mL in the lower impingement chamber H, at a continuous air flow rate of 60 L/min produced by a vacuum pump connected to the outlet F of the impaction apparatus. For each actuation, an approximately half-filled capsule (size 3, loaded with spray-drying powder blends of 24 ± 1 mg) was inserted in the dosage chamber of an Aerolizer® inhaler (Schering Co., Kenilworth, USA) connected to the TI. The pump was switched on and allowed to operate for 10 s.

After 10 actuations for one determination, the apparatus was dismantled. The subsequent steps were as follows:

1. The upper impingement chamber D, the mouthpiece adapter A, throat B, and neck C were washed with purified water into volumetric flasks.
2. The lower impingement chamber H and the coupling E were washed with purified water into volumetric flasks.

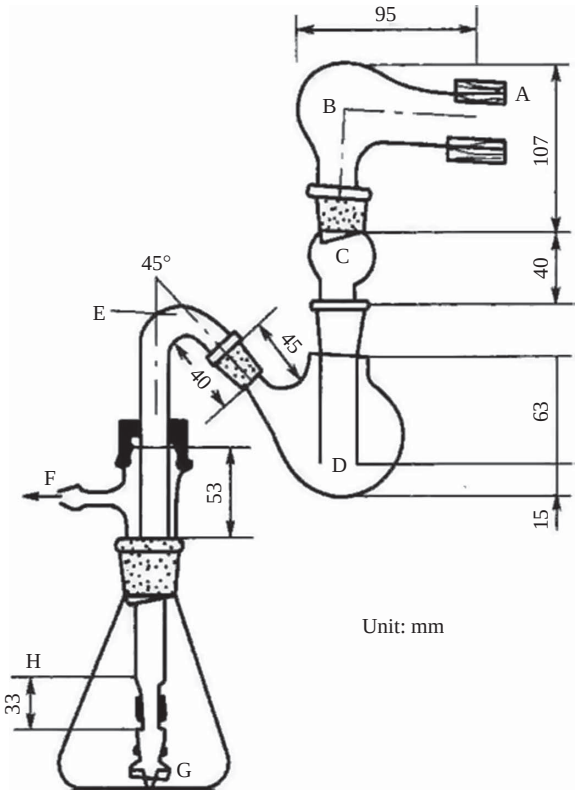


FIGURE 1. Instrument for evaluating in vitro deposition of dry powder inhalations (DPIs).

3. The capsule and the DPI inhaler were washed separately with purified water into volumetric flasks.

The content of AH in each flask was determined by high-performance liquid chromatography (HPLC) assay. Before they were assayed, samples of the solution were passed through a 0.45-μm cellulose acetate filter. These determinations were conducted in triplicate for each preparation.

The deposition in the lower impingement chamber H and the coupling E represented the *repairable* fraction (RF), expressed as a percentage indicating the ratio of the mass of drug recovered from the lower impingement chamber H and the coupling E to the total loaded dose.

HPLC Analysis of Ambroxol Hydrochloride

The HPLC system consisted of a chromatographic pump (PU-1580; Jasco Corporation, Tokyo, Japan), an injector equipped with a 20-μg sample loop, and an ultraviolet detector (UV-1575). AH and dialysates were separated using a chromatographic column (HiQ Sil, 250 mm × 4.6 mm i.d. 5 μm; Kya Tech Corporation, Tokyo, Japan) with a guard column (10 mm × 4.6 mm i.d.) maintained at ambient temperature. The mobile phase consisted of acetonitrile–0.01 mol/L ammonium phosphate dibasic (pH 7.0) (50:50 vol/vol), and the flow rate of

the mobile phase was 1 mL/min. The mobile phase was passed through a 0.45-μm Millipore filter and degassed before use. The UV detector was set at 248 nm and AUFS of the detector was set at 0.0025.

Data Analysis

The rank sum ratio (RSR) method was used to evaluate the effect of the spray-drying composition on the powder systematically using the five indexes, that is, yield, density, d_{ae}, angle of repose, and RF. The high yield and RF, and low density, d_{ae}, and angle of repose are better for DPI. So, the yield and RF are considered as high-optimization indexes. The density, d_{ae}, and angle of repose are considered as low-optimization indexes. The best preparation was identified by Equation 3:

$$RSR_n = \frac{1}{5\times 7}\sum_{j=1}^{5} R_{nj}, \tag{3}$$

where n represents the line, j represents the array, and R_{nj} is the rank of the n line j array indexes.

RESULTS AND DISCUSSION

The dry powder physical characteristics, that is, yield, particle size, angle of repose, tap density, and morphology, were explored by using different excipients and varying the spray-drying parameters. As reported previously, the powder composition most markedly affected the particle characteristics (Andya et al., 1999; Corrigan et al., 2004; Corrigan et al., 2006; Najafabadi et al., 2004; Surendrakumar et al., 2003).

Influence of Composition on DPI Characteristics

As shown in Figure 2, the yield of recovered powder varied considerably. The yields of AH/leucine/mannitol and AH/leucine preparations were high, whereas AH alone exhibited the lowest yield. When the powders were collected, AH/leucine and AH/leucine/mannitol preparations performed well in the receiving flask, whereas AH spray-drying powder alone adhered to the vortex tube. It is possible that the properties of the powders were changed by the leucine, and therefore, the high yield was obtained from the *cospray* solution.

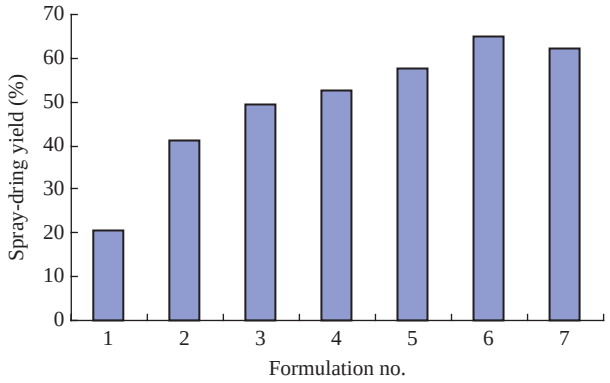


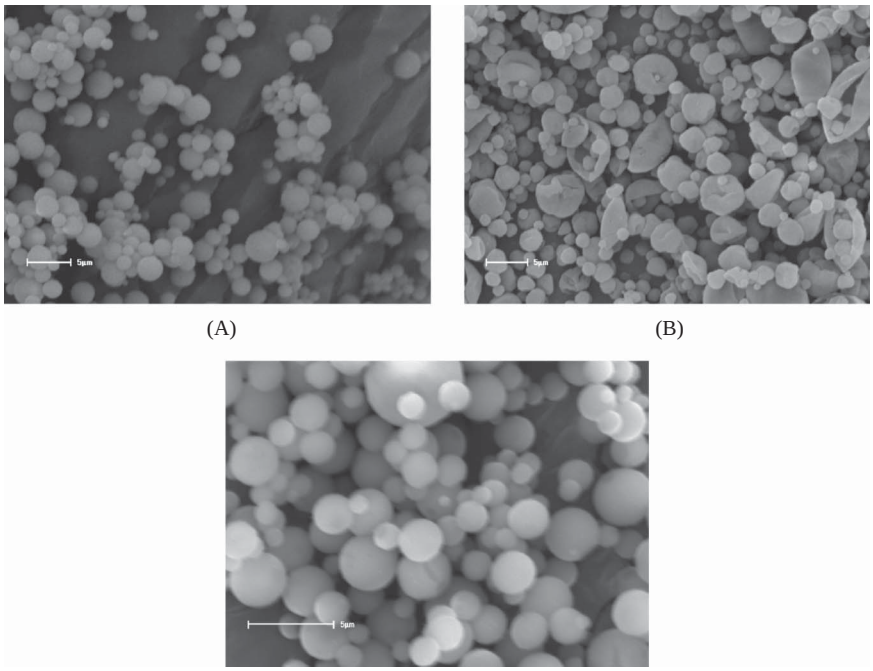
FIGURE 2. Spray-drying powders yield of the different formulation.

The SEM micrographs (Figure 3) showed that the spray-drying powders were amorphous, and powders generated by spray-drying are known to be highly amorphous in nature (Corrigan, 1995). The addition of leucine to the dry powders changed the particle morphology as seen by the SEM from smoothly spherical to extremely porous and fibrous (Figure 3B). Figure 3C showed that AH/leucine/mannitol cospray-drying powder was smoothly spherical. It is likely that leucine exhibited surfactant-like properties (Gliński, Chavepeyer, & Platten, 2000) and it may be that the leucine changed the surface tension properties of the solvent systems. Differences in the surface tension properties of the solvent systems may influence the capacity to migrate to the droplet surface during the spray-drying process and, hence, affect the particle morphology. Although these factors were not investigated during this study, they present the opportunities for further research.

The particle sizing and tapped density data are shown in Table 3. The mean particle size of the powders generated from formulation 2–7 was between 2 and 6 μm, indicating that the powders were of a suitable size to avoid deposition by inertial impaction in the oropharyngeal cavity (Larhrb et al., 2003). The mean particle size of AH spray-drying powder was large, 19.8 μm. However, the scanning electron micrographs (Figure 3A) clearly indicated that the powder was composed of particles approximately 2.5 μm in diameter. This suggests that, because of the cohesion of individual particles to form large aggregates, there was no dispersal during the sizing procedure, so a large size was obtained during particle sizing. As reported, powders generated by spray-drying have a small particle size and thus are often highly cohesive (Clarke, Peart, Cagnan, & Byron, 2002; Irngartinger, Camuglia, Damm, Goede, & Frijlink, 2004). Furthermore, this also suggests that this powder exhibits a poor flow property and is likely to display unsatisfactory aerosolization characteristics.

From Table 3, it can be seen that the mean particle size of powders gradually increases from formulation 2 to 7. So it is supposed that the higher the concentration of the spray-drying solution *is*, the larger the mean particle size of the spray-drying powders *is*. The tap density of the powders *from formulation 2 to 4* fell as the leucine increased (Table 3). As reported elsewhere, the tap density of the powders can be reduced by L-leucine (Lucas, Anderson, Potter, & Staniforth, 1999). However, the density of AH/leucine/mannitol powders is lower than that of AH/leucine. It is possible that the density of the powders was affected by the particle morphology. Thus, it appears that the density of smooth spherical particles is lower than that of porous and fibrous particles.

The d_{ae} of formulations 2–7 was between 1 and 4 μm. This indicates that the powders were of a suitable size for deposition



(A) (B)

(C)

FIGURE 3. (A) Scanning electron micrographs of ambroxol hydrochloride (AH) spray-drying powder, (B) AH/leucine (2.5/0.5 wt/wt), and (C) AH/leucine/mannitol (2.5/0.5/1 by weight).

TABLE 3
Particle Size, Densities, and Angle of Repose of the Spray-Drying Powder (Mean, $n = 3$)

	Particle Size Analysis							
Formulation No.	d[υ,10] (μm)	d[υ,50] (μm)	d[υ,90] (μm)	Span	D (μm)	d_{ae} (μm)	Density (g/cm^3)	Angle of Repose (°)
1	10.22	19.62	35.66	1.30	19.8	17.59	0.79	56.8
2	1.30	2.67	5.32	1.51	2.69	1.94	0.52	53.3
3	2.01	3.98	6.23	1.06	4.06	2.47	0.46	49.78
4	2.27	4.29	7.86	1.30	4.25	2.79	0.43	50.23
5	2.24	4.49	8.03	1.29	4.57	2.74	0.36	40.67
6	2.31	4.64	9.27	1.50	4.66	2.71	0.34	33.4
7	2.63	5.06	10.55	1.57	5.12	3.32	0.42	37.89

in the alveolar region of the lung (Atkins, 2005; Ikegami et al., 2003; Larhrb et al., 2003; Okamoto et al., 2000; Shekunov et al., 2003; Zeng et al., 2000).The d_{ae} of the AH spray-drying powder was fairly large (>5 μm) because of the large particle size observed during particle sizing. This powder would not be deposited often in the lung.

The angle of repose is frequently employed to characterize the particle flow. The smaller the angle of repose *is*, the better the flow property *is* (Hickey & Concessio, 1997). We can see that the flow property of AH/leucine/mannitol(2.5/0.5/1 by weight) preparation is the best while that of the AH spray-drying powder is the worst (Table 3).

Influence of the Powder Composition on Aerosolization Properties

As shown in Figure 4, the amounts of AH deposited at each stage of TI varied for different preparations. This suggests that each preparation has different aerodynamic properties. Figure 4 also lists that the amounts of AH spray-drying powder remaining in the capsule was greater than others. This was attributed to the cohesion of individual particles to form large aggregates that were not dispersed. So, the RF of the AH spray-drying powder was fairly low. The RF of AH/leucine spray-drying powders was higher than that of AH/leucine/mannitol spray-drying powders. This observation is in line with the previously reported data, that

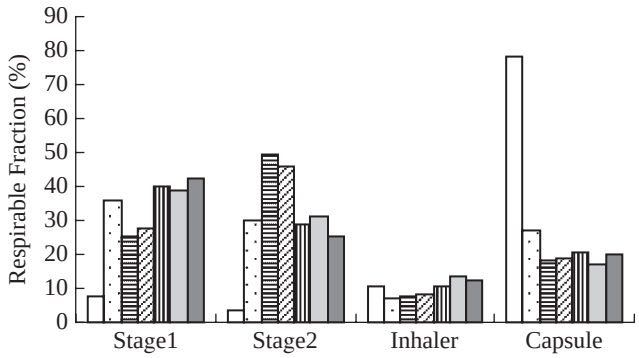


FIGURE 4. Aerosolization properties of the spray-drying powder (mean, $n = 3$). Powders were obtained from formulation 1 (white bars), formulation 2 (dotted bars), formulation 3 (horizontally slashed bars), formulation 4 (diagonally slashed bars), formulation 5 (vertically slashed bars), formulation 6 (light gray bars), and formulation 6 (dark gray bars).

is, the RF of porous and fibrous solid particles were significantly improved compared with spherical particles (Ikegami et al., 2003).

Results of the RSR Test to Evaluate Preparations of Different Composition

As all the indexes were not simply positively correlated or negatively correlated, the RSR method was applied to evaluate all the preparations. From Table 4, we can see that the AH/leucine/mannitol (2.5/0.5/1 by weight) spray-drying powder was relatively optimal.

Influence of the Preparation Conditions on DPI Characteristics and Aerosolization Properties

The spray-drying parameters, feed rate, atomizing pressure, airflow rate, and inlet air temperature were investigated. Because the mean size of the atomized liquid was affected by the gas–liquid relative velocity of the airflow atomizer, but the feed rate was fairly smaller than airflow rate, the feed rate had little impact on the powder properties (data not shown). As shown in Tables 5 and 6, the smaller the d_{ae} of the spray-drying powder *is*, the greater the atomizing pressure and the airflow rate *are*. It is possible that the mean size of the atomized liquid decreased with the atomizing pressure and the airflow rate increased. The density of the spray-drying powder decreased with an increase in the inlet temperature, but d_{ae} increased with it (Table 7). It is likely that the high temperature is associated with a faster drying, which makes the surface of the liquid droplet harden and the residual moisture expand, leading to the formation of hollow particles.

From the above results, the influence of spray-drying parameters on powder properties is relatively small. It is supposed that the spray-drying powder characteristics and aerosolization properties mainly relate to the properties of the spray-drying solution, that is, viscosity and surface tension of the spray-drying solution, *which are related to the composition of solution.* So the spray-drying powder characteristics and aerosolization properties are principally affected by composition of the spray-drying solution.

CONCLUSIONS

The objective of this study was to evaluate the influence of the formulation and preparation processes on DPI characteristics and aerosolization properties. The results show that the spray-drying powder characteristics and aerosolization properties depend on the nature of the composition employed. AH/leucine/mannitol (2.5/0.5/1 by weight) by cospray-drying improved the AH aerosolization property. The effect of the spray-drying parameters on powder properties is relatively small. Optimization of DPI can be achieved by selecting the most appropriate formulation and preparation process.

TABLE 4
Results of the RSR Test

	Yield (%)		Density (g/cm^3)		d_{ae} (μm)		Angle of Repose (°)		RF (%)		
Formulation No.	X_1	R_1	X_2	R_2	X_3	R_3	X_4	R_4	X_5	R_5	RSR
1	20.79	1	0.79	1	17.59	1	56.81	1	3.53	1	0.14
2	40.98	2	0.52	2	1.94	7	53.32	2	30.23	4	0.49
3	52.67	4	0.46	3	2.47	6	49.78	4	49.32	7	0.69
4	49.72	3	0.43	4	2.79	3	50.23	3	45.67	6	0.54
5	57.68	5	0.36	6	2.74	4	40.67	5	28.67	3	0.66
6	62.34	6	0.34	7	2.71	5	33.45	7	30.93	5	0.86
7	64.75	7	0.42	5	3.32	2	37.74	6	25.42	2	0.63

X_1–X_5 is the value of the yield, density, d_{ae}, angle of repose, and RF, respectively. R_1–R_5 is the rank of the yield, density, d_{ae}, angle of repose, and RF, separately.

TABLE 5
The Field, Density, d_{ae}, Angle of Repose, and RF of AH/Leucine/Mannitol (2.5/0.5/1 by weight) Spray-Drying Powder at Different Atomizing Pressures (Mean, $n = 3$)

Atomizing Pressure (Kpa)	Field (%)	Density (g/cm^3)	d_{ae} (μm)	Angle of Repose (°)	RF (%)
15	64.67	0.36	3.15	33.21	30.93
17	63.34	0.38	2.85	32.05	29.72
19	62.75	0.35	2.74	34.62	30.35

TABLE 6
The Field, Density, d_{ae}, Angle of Repose, and RF of AH/Leucine/Mannitol (2.5/0.5/1 by weight) Spray-Drying Powder at Different Airflow Rates (Mean, $n = 3$)

Airflow Rate (m^3/min)	Field (%)	Density (g/cm^3)	d_{ae} (μm)	Angle of Repose(°)	RF (%)
0.5	63.63	0.37	3.29	34.27	30.47
0.6	62.74	0.36	2.82	32.75	30.79
0.7	64.73	0.38	2.63	31.53	31.34

TABLE 7
The Field, Density, d_{ae}, Angle of Repose, and RF of AH/Leucine/Mannitol (2.5/0.5/1 by weight) Spray-Drying Powder at Different Inlet Temperatures (Mean, $n = 3$)

Inlet Temperature (°C)	Field (%)	Density (g/cm^3)	d_{ae} (μm)	Angle of Repose(°)	RF (%)
110	64.35	0.54	2.82	33.21	30.65
130	62.38	0.46	2.93	32.05	29.75
150	62.52	0.34	3.24	34.62	30.67

REFERENCES

Andya, J. D., Maa, Y., Costantino, H. R., Nguyen, P., Dasovich, N., Sweeney, T. D., Hsu, C. C., & Shire, S. J. (1999). The effect of formulation expients on protein stability and aerosol performance of spray-dried powders of a recombinant humanized anti-IgE monoclinal antibody. *Pharm. Res., 16*, 350–358.

Atkins, P. J. (2005). Dry powder inhalers: An overview. *Respir. Care, 50*, 1304–1312.

Bosquillon, C., Préat, V., & Vanbever, R. (2004). Pulmonary delivery of growth hormone using dry powders and visualization of its local fate in rats. *J. Control. Release, 96*, 233–244.

British Pharmacopoeia Commission. (2005). Density of solids: Bulk and tapped density. In *British pharmacopoeia* (Vol. 4, pp. A211–A212, Appendix VQ). London: Her Majesty's Stationery Office Ltd.

Clarke, M. J., Peart, J., Cagnan, S., & Byron, P. R. (2002). Adhesion of powders for inhalation: An evaluation of drug detachment from surfaces following deposition from aerosol screams. *Pharm. Res., 19*, 322–329.

Codrons, V., Vanderbist, F., Ucakar, B., Préat, V., & Vanbever, R. (2004). Impact of formulation and methods of pulmonary delivery on absorption of parathyroid hormone (1–34) from rat lungs. *J. Pharm. Sci., 93*, 1241–1252.

Corrigan, O. I. (1995). Thermal analysis of spray dried products. *Thermochim. Acta, 248*, 245–258.

Corrigan, D. O., Corrigan, O. I., & Healy, A. M. (2004). Predicting the physical state of spray dried composites: Salbutamol sulphate/lactose and salbutamol sulphate/polyethylene glycol co-spray dried systems. *Int. J. Pharm., 273*, 171–182.

Corrigan, D. O., Corrigan, O. I., & Healy, A. M. (2006). Physical, chemical and in vitro deposition properties of salbutamol sulphate/ipratropium bromide and salbutamol sulphate/excipient spray dried mixtures for use in dry powder inhalers. *Int. J. Pharm., 322*, 22–30.

Dalby, R., & Suman, J. (2003). Inhalation therapy: Technological milestones in asthma treatment. *Adv. Drug Deliv. Rev., 55*, 779–791.

Disse, B. G. (1987). The pharmacology of ambroxol—review and new results. *Eur. J. Respir. Dis. Suppl., 153*, 255–262.

French, D. L., Edwards, D. A., & Niven, R. W. (1996). The influence of formulation on emission, deaggregation and deposition of dry powders for inhalation. *J. Aerosol Sci., 27*, 769–783.

Geuns, E. R., Toren, J. S., Barends, D. M., & Bult, A. (1997). Decrease of the stage-2 deposition in the twin impinger during storage of beclomethasone dipropionate dry powder inhalers in controlled and uncontrolled humidities. *Eur. J. Pharm. Biopharm., 44*, 187–194.

Gliński, J., Chavepeyer, G., & Platten, J. (2000). Surface properties of aqueous solutions of L-leucine. *Biophys. Chem., 84*, 99–103.

Hickey, A. J., & Concessio, N. M. (1997). Descriptors of irregular particle morphology and powder properties. *Adv. Drug Deliv. Rev., 26*, 29–40.

Ikegami, K., Kawashima, Y., Takeuchi, H., Yamamoto, H., Mimura, K., Momose, D., & Ouchi, K. (2003). A new agglomerated KSR-592 β-form crystal system for dry powder inhalation formulation to improve inhalation performance in vitro and in vivo. *J. Control. Release, 88*, 23–33.

Irngartinger, M., Camuglia, V., Damm, M., Goede, J., & Frijlink, H. W. (2004). Pulmonary delivery of therapeutic peptides via dry powder inhalation: Effects of micronisation and manufacturing. *Eur. J. Pharm. Biopharm., 58*, 7–14.

Larhrb, H., Martin, G. P., Marriott, C., & Prime, D. (2003). The influence of carrier and drug morphology on drug delivery from dry powder formulations. *Int. J. Pharm., 257*, 283–296.

Lucas, P., Anderson, K., Potter, U. J., & Staniforth, J. N. (1999). Enhancement of small particle size dry powder aerosol formulations using an ultra low density additive. *Pharm. Res., 16*, 1643–1647.

Malcolmson, R. J., & Embleton, J. K. (1998). Dry powder formulations for pulmonary delivery. *Pharm. Sci. Technol. Today, 1*, 394–398.

Najafabadi, A. R., Gilani, K., Barghi, M., & Rafiee-Tehrani, M. (2004). The effect of vehicle on physical properties and aerosolization behavior of disodium cromoglycate microparticles spray dried alone or with L-leucine. *Int. J. Pharm., 285*, 97–108.

Okamoto, H., Aoki, M., & Danjo, K. (2000). A novel apparatus for rat in vivo evaluation of dry powder formulations for pulmonary administration. *J. Pharm. Sci., 89*, 1028–1035.

Seifart, C., Clostermann, U., Seifart, U., Mqller, B., Vogelmeier, C., VonWichert, P., & Fehrenbach, H. (2005). Cell-specific modulation of surfactant proteins by ambroxol treatment. *Toxicol. Appl. Pharmacol., 203*, 27–35.

Shekunov, B. Y., Feeley, J. C., Chow, A. H. L., Tong, H. H. Y., & York, P. (2003). Aerosolization behaviour of micronised and supercritically-processed powders. *J. Aerosol. Sci., 34*, 553–568.

Surendrakumar, K., Martyn, G. P., Hodgers, E. C. M., Jansen, M., & Blair, J. A. (2003). Sustained release of insulin from sodium hyaluronate based dry powder formulations after pulmonary delivery to beagle dogs. *J. Control. Release, 91*, 385–394.

Timsina, M. P., Martin, G. P., Marriott, C., Ganderton, D., & Yianneskis, M. (1994). Drug delivery to the respiratory tract using dry powder inhalers. *Int. J. Pharm., 101*, 1–13.

Von, R. K. (1978). Ergebnisse einer klinischen prüfung mit ambroxol zur frage der postoperativen bronchitisbehandlung. *Arzneim. Forsch., 28*, 934–935.

Zeng, X. M., Martin, G. P., Marriott, C., & Pritchard, J. (2000). The influence of carrier morphology on drug delivery by dry powder inhalers. *Int. J. Pharm., 200*, 93–106.