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Research paper

Aerosolisation of beclomethasone dipropionate using spray dried lactose/polyethylene glycol carriers

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Abstract

The aim of this study was to characterize the physical properties of spray dried lactose in the presence of different polyethylene glycols (PEG 400, PEG 3000 and PEG 6000) and to evaluate their performance as carriers for dry powder inhaler (DPI) formulations. The efficiency of spray dried lactose/PEG carriers in aerosolisation of beclomethasone dipropionate (BD), a model hydrophobic drug, was compared to Pharmatose® 325 M (L325), spray dried lactose alone (SDL), and also a sieved (< 38 μm) fraction of α-lactose monohydrate (SL). In vitro deposition analysis was performed using a twin stage liquid impinger at a flow rate of 60 l/min through a Spinhaler®. The deposition profiles of the drug from binary formulations composed of BD and spray dried lactose/PEG carriers were also compared to ternary formulations containing large and fine lactose carriers. Differential scanning calorimetry and X-ray diffraction data showed the presence of α-anhydrous lactose in spray dried lactose/PEG crystalline powders. Spray drying of lactose in the presence of PEG 400 resulted in the production of a powder (SDL-PEG400) with lower α-lactose monohydrate content, and also smaller particle size distribution than those obtained in the presence of PEG 3000 (SDL-PEG3000) or PEG 6000 (SDL-PEG6000). All formulations showed different deposition profiles, except those containing SDL-PEG3000 or SDL-PEG6000 which exhibited similar data. The fine particle fraction of aerosolised BD varied from 6.26 ± 1.07 (for L325) to 25.87 ± 5.33 (for SDL-PEG3000). All deposition profiles of BD aerosolised from SDL-PEG3000 were significantly higher ($P < 0.01$) than those produced by binary and ternary formulations containing L325, a coarse lactose commercially available for DPI formulations. The differences observed in deposition data for various carriers were interpreted according to their physical properties. It was concluded that particle size distribution, morphology and specific surface texture of SDL-PEG3000 and SDL-PEG6000 were important factors influencing their efficiency as small carriers for DPI formulations.

Keywords: Aerosolisation; Spray drying; Dry powder inhaler; Fine particle fraction; Beclomethasone dipropionate; Lactose; Polyethylene glycols; Crystallinity

1. Introduction

Dry powder inhalers (DPIs) are widely accepted as an alternative to pressurised metered-dose inhalers and nebulisers for pulmonary drug delivery [1]. DPIs present many advantages over other aerosol generating systems. The possibility of generating aerosols from drug particles without the use of volatile propellants makes them environmentally friendly and also easy to operate. They are portable and relatively inexpensive with improved physicochemical stability of the drugs as a result of the dry state in the formulation [2].

DPI formulations consist of micronised drug with an aerodynamic diameter between 1 and 5 μm for deep lung deposition [3,4]. The presence of these small particles with intrinsic high cohesive forces results in poor flow and dispersion properties. So in most commercially available dry powder formulations for inhalation, the drug is blended with and distributed over the surface of a coarse carrier (e.g. Lactose) [5]. The drug detachment from the carrier particles and its subsequent aerosolisation properties depend on

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physicochemical properties of the particles (both the drug and the carrier) and the design of the inhaler. The physicochemical properties of the carrier particles, that are usually the main component of DPI formulations, may have an important role in the delivery of drug particles to the lung. The effect of carrier properties such as particle size distribution [6], morphology [7], surface roughness [8] and electrostatic charge [9] on drug aerosolisation efficiency have been investigated. Various attempts also have been made to modify carrier particle properties to enhance pulmonary delivery efficiency of drug particles [10–12].

Recently, it has been shown that the spray drying of α-lactose monohydrate with polyethylene glycol (PEG) 4000 can influence the crystallinity and polymorphic form of processed lactose [13]. Many reports are available in the literature indicating amorphous nature for spray dried lactose [14,15]. Therefore, it was surprising that the presence of PEG 4000 resulted in the production of crystalline particles during spray drying process. The ability of PEG 4000 to hydrogen bond with water and the reduction in rate of water evaporation during spray drying was assumed to be the reason for this phenomenon [13].

In this study the effect of the type of PEG on the physical properties of α-lactose monohydrate during spray drying was investigated. The potential application of the processed particles as carrier in dry powder formulations for inhalation was also evaluated. Beclomethasone dipropionate (BD) was used as a model hydrophobic drug with high cohesion properties to challenge the efficiency of co-spray dried particles in dispersion and aerosolisation of difficult to formulate drugs.

2. Materials and methods

2.1. Materials

Beclomethasone dipropionate was supplied as micronized particles by Farmabios, Pavia, Italy. Spinhaler® was purchased from local market. Pharmatose® 80 M and Pharmatose® 325 M were supplied by DMV International, Veghel, The Netherlands, and hard gelatin capsule shells (size 2) by Cipla, Mumbai, India. Methanol of HPLC grade and butan-1-ol were obtained form Merck, Darmstadt, Germany. Polyethylen glycols (PEG 400, PEG 3000 and PEG 6000) were purchased from Merck-Schuchardt, Hohenbrunn, Germany.

A sample of Pharmatose® 80 M was dried in an oven at 170 °C for 3 h to produce α-lactose anhydrous (LA) form.

2.2. Preparation of carriers

2.2.1. Spray drying method

One gram of each PEGs was dissolved in 20 ml of distilled water using a magnetic stirrer. The resultant solutions were added separately to aqueous suspensions of α-lactose monohydrate (40 g/60 ml) so that three suspensions of α-lactose monohydrate each containing PEG 400, PEG 3000 or PEG 6000 were prepared. The final volumes of the suspensions were adjusted to 100 ml using distilled water. The suspensions were spray dried using a Büchi B-191 mini spray dryer (BÜCHI Labortechnik AG, Flawil, Switzerland) at an inlet temperature of 140 °C, outlet temperature of 87–89 °C, aspiration setting of 65% and spray flow of 600 Nl/h. A sample of 40 g lactose alone was also spray dried under the same conditions. Immediately after the termination of the process, the particles were packed into tightly closed amber bottles and desiccated over silica gel.

2.2.2. Sieve fractionation

α-Lactose monohydrate (Pharmatose® 80 M) was sieved manually through the 38 μm sieve for 10 min. The fraction collected under the sieve (i.e. <38 μm sample) was retained in tightly closed amber bottles and stored in a desiccator over silica gel.

2.2.3. Preparation of fine lactose

α-Lactose monohydrate (Pharmatose® 80 M) was micronized using an air-jet mill (JSM-80, Esco-Labor AG, Riehen, Switzerland) operating at air and inject air pressures of 7 bar. Fine lactose was collected after five passages through the instrument and was packed into tightly closed amber bottles and stored in a desiccator over silica gel.

2.3. Physical characterization

2.3.1. Particle size determination

Particle size distributions were measured by laser diffraction (Malvern Mastersizer X, Malvern, UK) using a 100 mm lens at an obscuration between 0.19 and 0.21. Samples of lactose and spray dried lactose/PEG were prepared by suspending the particles in butan-1-ol with the aid of sonication in a water bath for 3 min. The suspension of BD was prepared in hexane containing 1% Span 85 after sonication for 3 min. Each sample was measured in triplicate.

2.3.2. Density measurement

A helium pycnometer (Quantachrome Instruments, Boynton Beach, Florida, USA) was used to determine true densities of the powders. Approximately 1 g of each powder sample was used after calibration of the instrument using standard stainless steel spheres supplied by the manufacturer. The mean value of triplicate determinations is reported.

2.3.3. Water content measurement

The water content of each powder was determined using a Sartorius infra-red moisture balance (Sartorius MA 100, Goettingen, Germany) by drying at two different temperatures (110 and 160 °C) in the standard and automatic mode.

Three samples (~2 g) were taken from each powder for each temperature and analyzed separately for their water content.

2.3.4. Scanning electron microscopy

The shape and surface morphology of the particles were studied by a scanning electron microscope (XL 30, Philips, Eindhoven, The Netherlands). Prior to scanning, the samples were coated with a thin layer of gold, using a direct current sputter technique.

2.3.5. Differential scanning calorimetry (DSC)

DSC measurements (PL-DSC, Polymer Laboratories, Surrey, UK) were performed on accurately weighed samples (5–10 mg) at a heating rate of 10 °C/min under nitrogen gas purge.

2.3.6. X-ray diffraction

Powder X-ray diffraction patterns were measured using a Siemens X-ray diffractometer (Siemens 5000, Karlsruhe, Germany) with a Cu Kα source operating at a tube load of 40 kV and 30 mA. Each sample was assessed between 5 and 35° (2θ) with a step size of 0.02°.

2.3.7. Infrared spectroscopy

Infrared spectra of samples were obtained with a Nicolet spectrophotometer (Magna 550, Nicolet Instrument Corporation, Madison, WI, USA) in the near-infrared (4000–6000 cm^{-1}) region using compressed KBr disc technique. The spectra were obtained by averaging 64 scans at a resolution of 4 cm^{-1}.

2.4. Preparation of formulations

BD (0.0108 g) was weighed into a 25 ml stainless steel jar and mixed with carrier (0.7124 g) manually by means of geometric dilution. BD was mixed with spray dried lactose/PEG 400 (SDL/P400), spray dried lactose/PEG 3000 (SDL/P3000) or spray dried lactose/PEG 6000 (SDL/P6000) in a ratio of 1:67.5 w/w using a turbula mixer (Dorsa Novin Afzar, Tehran, Iran). The stainless steel jar was then placed in the mixer and mixing process was continued for 15 min to prepare binary ordered mixtures (Table 1). Pharmatose® 325 M (L325), spray dried lactose (SDL) and sieved lactose (SL) were also used and mixed with BD separately under the same conditions.

To better challenge the efficiency of spray dried/PEG powders as carrier for DPI formulations, two ternary mixtures were also prepared as indicated in Table 1. Jet milled lactose (JL) was used as third component in a concentration of 2.5% (w/w) with respect to BD content. JL was pre-blended with BD before the addition of large carrier to optimize the efficiency of mixing process according to the published data [16].

Six samples, each weighing 29 ± 1 mg equivalent to the filling weight in each capsule, were randomly selected to determine the homogeneity of the mixtures. The coefficient of variation (<6%) in BD content was used to assess the degree of homogeneity.

Table 1
Components employed to prepare the binary and ternary formulations of beclomethasone dipropionate (BD)

Formulations	Components mixed with BD	
Binary mixtures		
BD/L325	Pharmatose® 325M	
BD/SDL-PEG400	Spray dried lactose/PEG 400	
BD/SDL-PEG3000	Spray dried lactose/PEG 3000	
BD/SDL-PEG6000	Spray dried lactose/PEG 6000	
BD/SDL	Spray dried lactose	
BD/SL	Lactose (seived <38 μm)	
Ternary mixtures		
BD/L325/JL	Pharmatose® 325M	Micronized lactose (jet milled)
BD/SDL-PEG3000/JL	Spray dried lactose/PEG 3000	Micronized lactose (jet milled)

All formulations were filled in hard gelatin capsules (size 2) manually with 29 ± 1 mg of powder mixtures, equivalent to 425 ± 5 μg BD.

2.5. HPLC analysis of BD

BD was assayed by HPLC (Waters, Milford, MA, USA) employing a 15 cm × 4.6 mm C-18 μBondapack column according to a validated method reported in previous studies [16] with some modifications. The analysis was performed using a solution of methanol and water (70:30) as a mobile phase in a flow rate of 0.8 ml/min, incorporating dexamethasone phosphate as an internal standard and UV detection at 239 nm. The system was calibrated using standard solutions of BD over the range of 0.1–20 μg/ml ($R^2 = 0.999$).

2.6. Drug deposition studies

The dispersion and deposition characteristics of all powder mixtures were assessed by Spinhaler® connected to twin stage impinger (TSI; Apparatus A, European Pharmacopoeia, 2000, Copley, Nottingham, UK). Powders were dispersed at steady flow rate of 60 l/min. This flow rate was lower than the flow rate of 100 l/min which is recommended by the Pharmacopoeia for the low resistance devices, but has been used widely to characterize and compare the deposition data of DPI formulations aerosolised with low resistance devices [17–20]. The effective cut off diameter of the upper stage of TSI was found to increase when it operated at higher flow rate [21]. Therefore, the deposition experiments were conducted at the flow

rate of 60 l/min (effective cut off diameter of <6.4 μm) under the conditions which have been reported in the literature [16,22,23].

HPLC mobile phase containing dexamethason phosphate as internal standard was introduced to upper stage (stage 1; 7 ml) and lower stage (stage 2; 30 ml) of the TSI. Once the assembly had been checked and found to be airtight and vertical, a Spinhaler® had been inserted into the rubber mouthpiece attached to the throat of the impinger. One capsule was placed in the inhaler and the vacuum pump was switched on. The pump was operated for 5 s so that a steady flow rate of 60 l/min was achieved, and the dose was released. The pump was operated for another 7 s at the established flow rate following the release of the dose and it was then switched off. The operation time of 4 s at 60 l/min allowed the aspiration of 4 l of air in the apparatus. However, for formulations containing SDL or SL, as the carrier, the period of 4 s was not sufficient, because drug/carrier agglomerates blocked the holes of the capsules and a considerable portion of the powder remained in the capsule. Therefore, the operation time was extended to 7 s to empty more powder load from the capsules. All formulations were aerosolised for this period to compare their deposition data under the same condition. Each deposition experiment involved the aerosolisation of five capsules. The inhaler body, capsule shells, stage 1 and stage 2 were separately washed with mobile phase containing internal standard and the volume of the samples was adjusted with the same solvent. The concentration of BD in each sample was analysed by HPLC method.

The total amount (μg) of BD recovered from the inhaler, the capsule shells, the upper and lower stages of TSI was calculated per capsule and defined as recovered dose (RD). Fine particle dose (FPD) was defined as the amount of drug recovered per capsule from the lower stage of TSI. Fine particle fraction (FPF) was calculated as the ratio of FPD to RD and expressed as a percentage. Emitted dose was defined as the total quantity of drug recovered from upper and lower stages of TSI per capsule. The emitted dose percent was calculated as the percentage of emitted dose to RD and dispersibilty was calculated as the percentage of FPD to emitted dose. Statistical analysis was performed using a one-way analysis of variance (one-way ANOVA) with multiple comparison between deposition data using a Tukey honest significant difference test (Statistica, StatSoft, Tulsa, USA).

3. Results and discussion

3.1. Physical characteristics

As shown in Table 2, the particle size distribution of BD, with 90% of particles ($d_{90\%}$) less than 5.7 μm, was suitable for respiratory delivery. The particle size distribution of spray dried carriers was different depending on the feed conditions. Volume median diameter ($d_{50\%}$) and distribution patterns of SDL-PEG3000 and SDL-PEG6000 were quite similar. SDL-PEG400 exhibited smaller $d_{50\%}$ (6.7 μm) than SDL-PEG3000 (9.7 μm) and SDL-PEG6000 (9.4 μm). Such a difference in particle size distribution was interesting since all the samples were spray dried under the same conditions. These results suggested that the physical properties of polyethylene glycols co-spray dried with lactose could affect the particle size distribution of the particles. SDL presented higher proportion of fine particles in comparison with SDL-PEG3000 and SDL-PEG6000. Scanning electron micrographs of spray dried samples demonstrated sphere-like particles (Fig. 1). SDL particles presented spheres with smooth surfaces. The surfaces of spray dried lactose/PEG particles were not smooth and some distortion on the surface of these particles was shown to be identical to that was reported for spray dried lactose/PEG 4000 particles in previous studies [13].

All spray dried samples were shown to have $d_{50\%}$ smaller than L325. L325 particles with a tomahawk shape (Fig. 1) had quite different appearance than spray dried samples. The $d_{90\%}$ of SL (24.1 μm) was greater than $d_{90\%}$ of SDL-PEG3000 (18.8 μm) and SDL-PEG6000 (18.5 μm) but the proportion of fine particles in SL was higher than both spray dried samples. JL with $d_{90\%}$ equal to 13.9 μm was suitable for use as a fine carrier.

Table 2
Particle size distributions and true densities of the materials (mean ± SD, $n = 3$)

Material	Cumulative percent (undersize)			<5.0 μm (%)	True density (g/ml)
	$d_{10\%}$ (μm)	$d_{50\%}$ (μm)	$d_{90\%}$ (μm)		
BD	0.7 (0.1)	1.9 (0.2)	5.7 (0.7)	88.0 (1.2)	ND*
SDL-PEG400	1.5 (0.2)	6.7 (0.6)	13.5 (1.3)	33.5 (2.3)	1.55 (0.02)
SDL-PEG3000	2.1 (0.2)	9.7 (0.9)	18.8 (1.7)	20.9 (1.8)	1.55 (0.04)
SDL-PEG6000	2.0 (0.3)	9.4 (1.1)	18.5 (1.5)	21.7 (1.5)	1.53 (0.03)
L325	6.6 (0.8)	53.5 (4.3)	74.1 (3.8)	8.5 (2.1)	1.54 (0.01)
SDL	1.9 (0.2)	4.5 (0.5)	15.2 (1.5)	43.8 (6.7)	1.48 (0.01)
SL	1.6 (0.1)	9.1 (1.2)	24.1 (1.4)	33.9 (2.2)	1.54 (0.02)
JL	1.3 (0.1)	4.9 (0.3)	13.9 (1.2)	51.0 (3.4)	1.55 (0.01)

*, Not determined.

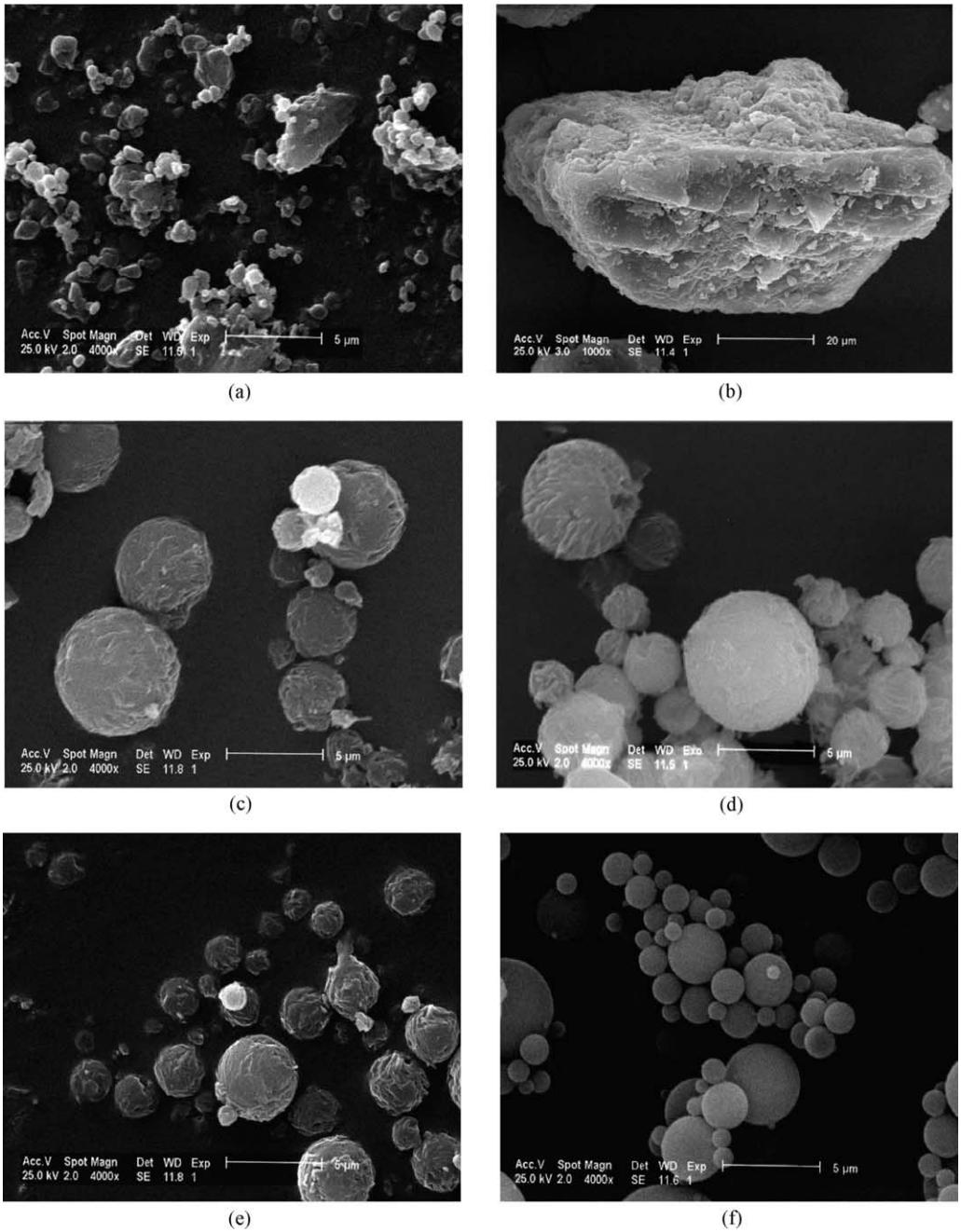


Fig. 1. Scanning electron micrographs of (a) BD, (b) L325, (c) SDL-PEG6000, (d) SDL-PEG3000, (e) SDL-PEG400, (f) SDL.

True densities of all carriers were in the range of about 1.53–1.55 g/ml, except for SDL that was about 1.48 g/ml. These results suggested a solid structure for all materials investigated. L325 is a commercial available α-lactose monohydrate that is used as a coarse carrier in DPI formulations. The presence of α-lactose monohydrate in L325 was supported by a peak at diffraction angle 12.6° in XRD pattern (Fig. 2a). No peak was observed at 10.6° for β-lactose. The DSC scan of L325 showed also the presence of α-lactose monohydrate with two endothermic peaks at approximately 147 and 216 °C due to the loss of crystal water and melting process, respectively (Fig. 3a). The DSC scan of anhydrous lactose (LA) showed only a melting endotherm at 212 °C indicated the presence of α-lactose in the sample (Fig. 3b). XRD profile of this sample was in agreement with this finding.

XRD and DSC scans of SDL, SDL-PEG400, SDL-PEG3000 and SDL-PEG6000 were also included in Figs. 2 and 3, respectively. The XRD data for all spray dried lactose/PEG materials showed a peak at diffraction angle

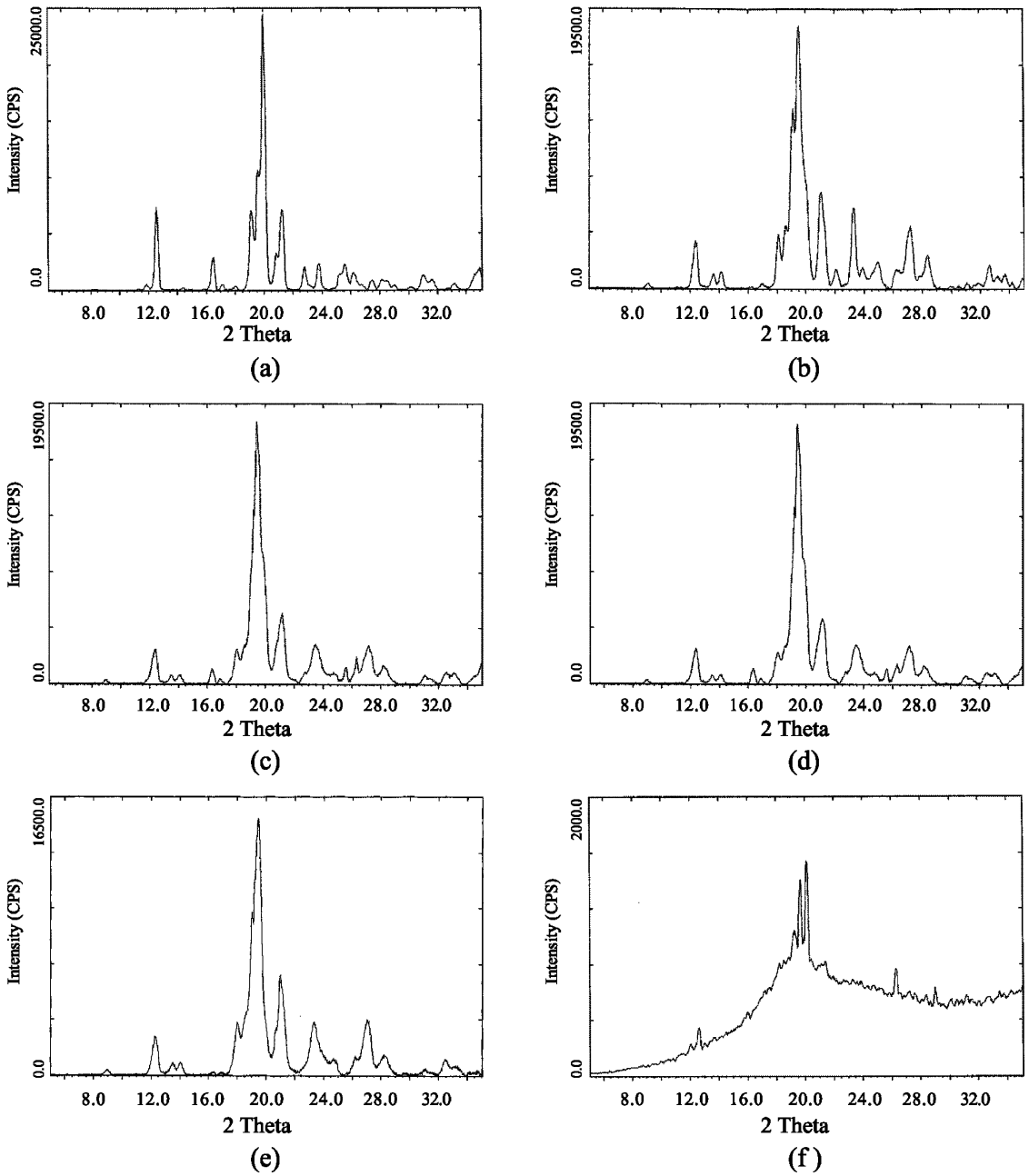


Fig. 2. X-ray diffraction patterns of various lactose samples: (a) L325, (b) LA, (c) SDL-PEG6000, (d) SDL-PEG3000, (e) SDL-PEG400 and (f) SDL.

12.5° (Fig. 2c–e) similar to LA (Fig. 2b). These data confirmed the presence of α-lactose in spray dried lactose/PEG materials. The presence of some small peaks with a large halo in the XRD profile of SDL confirmed that the sample was predominately amorphous.

A slightly broad endotherm approximately at 105 °C in DSC scans of SDL-PEG3000 and SDL-PEG6000 may be related to the presence of some monohydrate in the samples (Fig. 3c and d). DSC scans of SDL-PEG400 and SDL showed no dehydration peak for crystal water (Fig. 3e and f). SDL showed an exothermic peak at about 170 °C, consistent with recrystallization of amorphous lactose. This exotherm was absent in DSC scans of spray dried lactose/PEG samples. The sharp endothermic peaks ranging from 211 to 214 °C for spray dried lactose/PEG samples were attributed to the melting process of α-lactose. No melts were observed at about 230 °C showing the presence of predominantly α-lactose nature for spray dried lactose/PEG materials. This finding was in agreement with previous finding reported for spray dried particles obtained from 40 g/100 ml lactose/PEG 4000 samples [13].

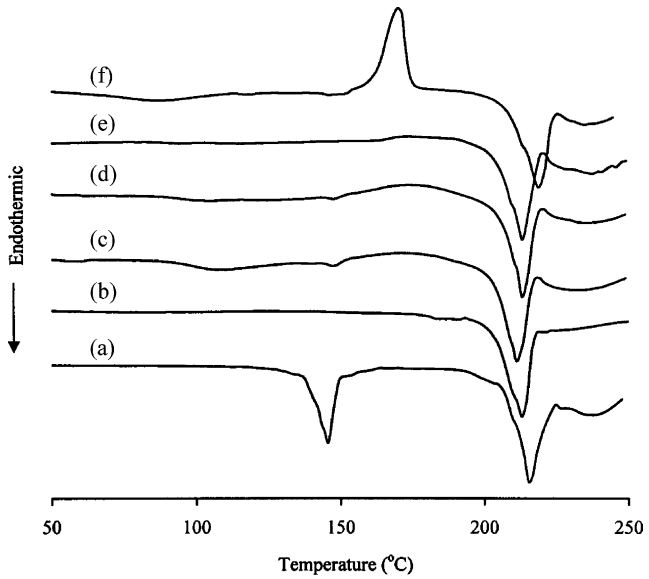


Fig. 3. DSC profiles of various lactose samples: (a) L325, (b) LA, (c) SDL-PEG6000, (d) SDL-PEG3000, (e) SDL-PEG400 and (f) SDL.

Table 3 presented water contents of the materials that were obtained at two different temperatures. The weight loss percentages at 110 °C were attributed to the loss of water adsorbed on the surface of the materials. The presence of PEGs in spray dried lactose/PEG materials probably caused these materials to adsorb more water from the environment, compared to L325. SDL presented high surface moisture content corresponding to its amorphous nature. The weight loss due to the loss of water of crystallization was calculated by subtracting the data obtained at 110 °C from that obtained at 160 °C. This number was divided on molecular weight of water (18 g) to produce the number of moles of water in crystal that was equivalent to the number of moles of α-lactose monohydrate. The percent of α-lactose monohydrate content in each sample are expressed as a percent weight of the analyzed sample (Table 3). The results for L325, SL and JL showed water contents in agreement with theory (5.0% weight loss for water of crystallization). The α-lactose monohydrate content calculated for SDL was close to that published in the literature [24]. Crystallization of lactose with PEG 400 resulted in production of lower content of α-lactose monohydrate compared to those in the presence of PEG 3000 and PEG 6000.

Table 3
Water content of various lactose samples determined by infrared moisture balance technique (mean ± SD, $n = 3$)

Materials	Weight loss (%) at		Weight loss (%) between 110 and 160 °C	α-Monohydrate content (%)
	110 °C	160 °C		
L325	0.52 (0.08)	5.55 (0.04)	5.04 (0.08)	100.78 (1.55)
JL	0.60 (0.02)	5.72 (0.06)	5.12 (0.12)	102.38 (2.41)
SL	0.57 (0.04)	5.59 (0.05)	5.02 (0.04)	100.39 (1.68)
LA	0.40 (0.01)	0.58 (0.06)	0.18 (0.05)	3.50 (0.99)
SDL	2.79 (0.13)	2.97 (0.10)	0.19 (0.04)	3.70 (0.71)
SDL-PEG400	1.66 (0.01)	2.57 (0.06)	0.91 (0.05)	18.22 (0.85)
SDL-PEG3000	1.29 (0.12)	2.84 (0.12)	1.52 (0.19)	30.33 (3.82)
SDL-PEG6000	1.65 (0.07)	3.11 (0.13)	1.47 (0.21)	29.32 (4.08)

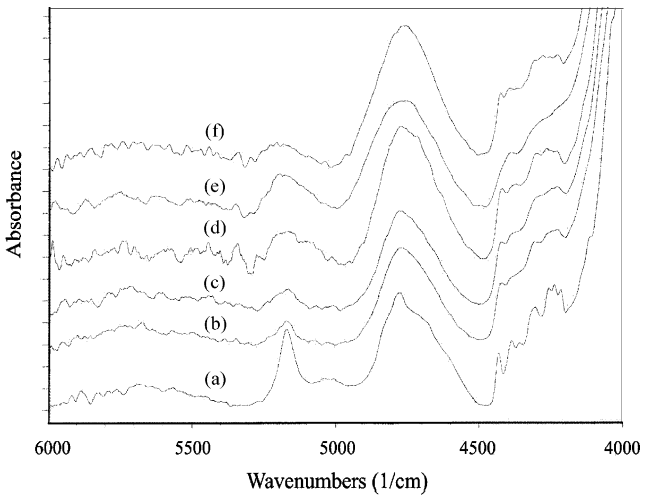


Fig. 4. Infrared spectra of the lactose samples at 6000–4000 cm^{-1} region: (a) L325, (b) SDL-PEG6000, (c) SDL-PEG3000, (d) SDL-PEG400, (e) SDL and (f) LA.

The infrared spectra obtained for different lactose samples are shown in Fig. 4. The water absorption band is often very evident in near-infrared region of the spectra [25]. L325 exhibited a significant water band at 5169 cm^{-1}. The small absorption bands that observed for spray dried powders at this region indicated the presence of lower water content in these materials, compared to L325. These results were in agreement with the results obtained from the other techniques. The similarity in the absorption bands obtained for SDL-PEG3000 and SDL-PEG6000 supported the data acquired from infrared moisture balance technique. The small and wide absorption bands detected for LA, SDL and SDL-PEG400 might be related to a few molecules of water in crystal as well as the water absorbed by these materials from the environment.

3.2. Content uniformity of BD

The recovery of BD from all formulations in content uniformity test was between 92.3 and 103.5% with a coefficient of variation ranging from 2.2% (BD/SDL-PEG3000) to 5.7% (BD/SL).

3.3. In vitro deposition

The recovered dose of BD in in vitro deposition analysis varied from 364 μg for BD/SD-P400 formulation to 419 μg

Table 4
Deposition profiles of BD in a TSI after aerosolisation from of different formulations through a Spinhaler® at a flow rate of 60 l/min (mean ± SD, $n = 3$)

Formulation	FPF (%)	Emission (%)	Dispersibility (%)
BD/SDL-PEG3000	25.8 ± 5.3	91.4 ± 2.1	28.2 ± 4.4
BD/SDL-PEG6000	24.1 ± 5.4	91.9 ± 2.3	26.2 ± 5.3
BD/SDL-P400	14.4 ± 2.0*	82.0 ± 3.9	12.5 ± 2.2
BD/SDL	15.2 ± 3.6*	29.0 ± 1.5**	52.4 ± 9.7**
BD/SL	11.9 ± 2.0**	26.1 ± 2.3**	45.6 ± 5.2**
BD/L325	6.7 ± 1.1**	68.8 ± 3.0**	9.2 ± 1.8**
BD/L325/JL	9.4 ± 1.7**	65.0 ± 3.1**	12.7 ± 2.0**
BD/SDL-PEG3000/JL	24.3 ± 2.6	90.3 ± 1.0	26.9 ± 3.2

* Represents a significant difference ($P < 0.05$) compared with BD/SDL-PEG3000 formulation. ** Represents a significant difference ($P < 0.01$) compared with BD/SDL-PEG3000 formulation.

for BD/SD-P3000 formulation, corresponding to a percent recovery between 85.6 and 98.6%.

No significant difference was observed between deposition profiles of BD aerosolized from formulations containing SDL-PEG3000 or SDL-PEG6000 (Table 4). FPF of the drug from BD/SDL-PEG400 formulation was significantly lower ($P < 0.05$) than the BD/SDL-PEG3000 formulation. A slight, but not significant, difference ($P > 0.05$) was also observed for emission percent and dispersibility of drug from these two formulations. The lower FPF of the drug produced by BD/SDL-PEG400 formulation may be related to the presence of higher fraction of fine particles in SDL-PEG400 powder (Fig. 5). These fine particles had high intrinsic affinity to make agglomerates with drug particles so strong that was not dispersible at the flow rate of 60 l/min. The same results have been also reported for salbutamol sulphate blended with carriers contained large proportions of fine particle [20].

The high emission percents (between 82.0 and 91.4%) of BD from all formulations containing binary mixtures of drug and spray dried lactose/PEG carries suggested high fluidization capabilities of these carriers at 60 l/min.

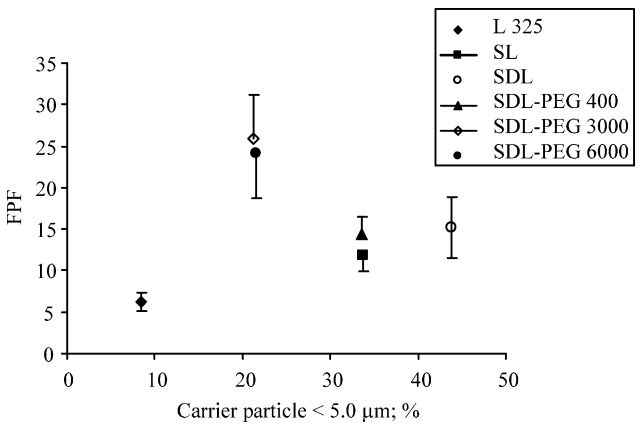


Fig. 5. Relationship between the proportion of fine carrier particles (<5.0 μm) and the FPF of BD aerosolised at 60 l/min via a Spinhaler® using TSI (mean ± SD, $n = 3$).

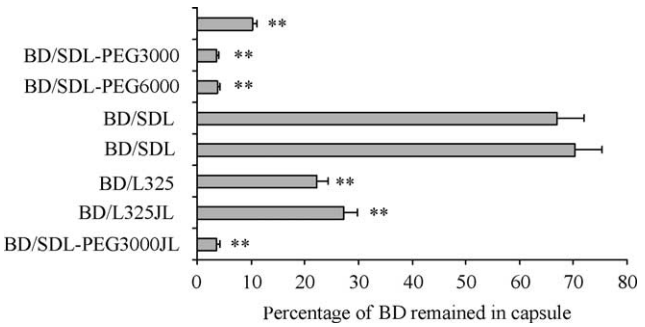
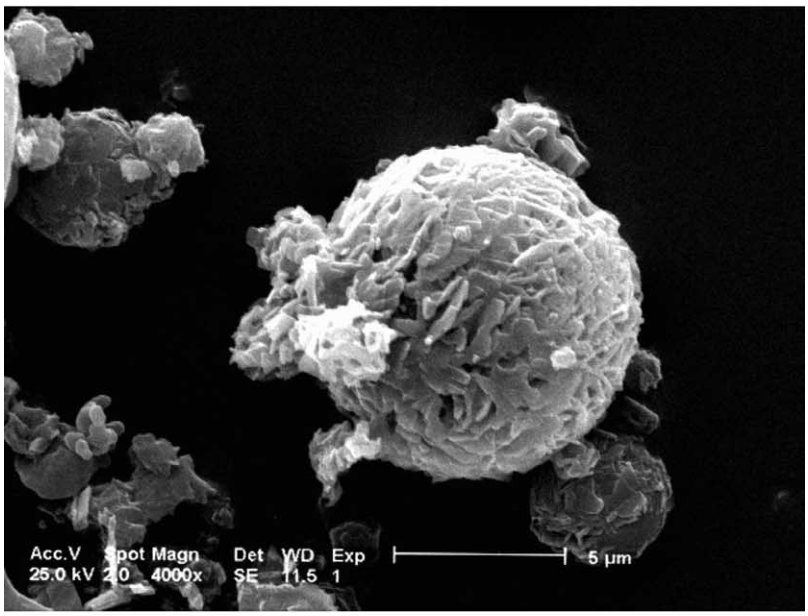


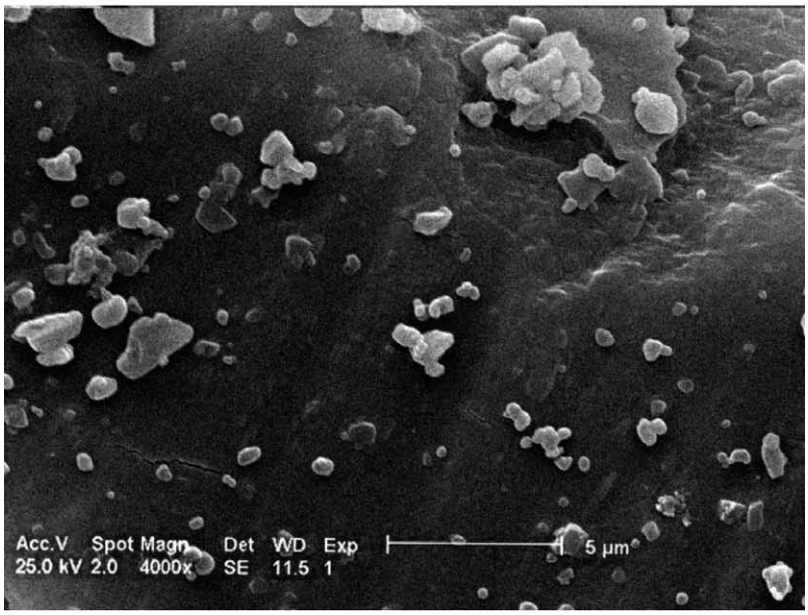
Fig. 6. Percentage of the amount of BD remained in capsules after aerosolisation via a Spinhaler® at 60 l/min using TSI (mean ± SD, $n = 3$). **, Represents a significant difference at $P < 0.01$ compared with BD/SDL.

These findings can be attributed to the spherical nature (Fig. 1) and thus appropriate flow properties of these spray dried particles. Although SDL particles were spherical in shape, their emission from the inhaler was significantly lower ($P < 0.01$) than all spray dried lactose/PEG carriers (Table 4). The difference in behavior for SDL was attributed to the high aggregation tendency of these predominantly amorphous and smooth particles. Like SDL-PEG400, the presence of a higher proportion of fine particles in SDL sample also influenced its performance as a carrier. As shown in Fig. 6, a significantly higher ($P < 0.01$) proportion of the drug remained in the capsules after aerosolization of BD/SDL formulation, compared with formulations containing spray dried lactose/PEG as carriers. It seemed that large agglomerates of SDL and BD particles could not pass through small holes in the capsule shells during aerosolisation process. So the lower proportion of emitted dose decreased the FPF of BD from BD/SDL formulation. SDL particles with their smooth surface and spherical shape would present reasonably low surface roughness. The high dispersibility of fine drug particles from the surface of SDL particles is shown in Table 4. The effect of roughness value on FPF and dispersibility of drug has been published in pharmaceutical literature [7,8]. In contrast, all spray dried lactose/PEG particles presented higher surface roughness than SDL, as it was shown qualitatively by scanning electron micrographs (Fig. 1). Thus, the significantly lower ($P < 0.01$) dispersibility of BD after aerosolisation of the formulations containing spray dried lactose/PEG carriers (compared to BD/SDL formulation) was consistent with previous studies [7,8].

It seemed that creation of the asperities of about 1 μm (Fig. 7) on the surface of particles that was induced by the presence of PEGs during crystallization of lactose in spray drying process, decreased the aggregation tendency of these particles. Generally, it is believed that particulate interactions will increase by interlocking of the asperities on their surfaces [26]. This mechanical interlocking will cause particles to come into close contact and hence, van der Waals forces will be dominant at decreased separation distance. However, it has been shown that small asperities



(a)



(b)

Fig. 7. Scanning electron micrographs showing the presence of BD particles on the surface of (a) SDL-PEG3000 and (b) L325.

of the order of 1 μm on the surface of particles are likely to increase the separation distance of approaching particles, thereby limiting particulate attraction due to van der Waals forces [2].

Since the ideal diameter for pulmonary deposition is between 1 and 5 μm, it can be postulated that a large proportion of BD particles ($d_{10\%} = 0.73$ μm) was not entrapped within the spray dried lactose/PEG carrier surface asperities that were smaller than 1 μm (Fig. 8a). The more drug particles entrapped into the asperities, the higher drag force would require to detach them from the carrier surface. This hypothesis was substantiated by the data obtained for L325. Deposition profiles of the drug from the formulation containing BD and SDL-PEG3000 were significantly higher ($P < 0.01$) than binary mixture containing L325 as a coarse carrier. The presence of large asperities on the surface of L325 is clearly shown in Figs. 1b and 7b. The low FPF (6.7) of the drug from BD/L325 formulation was in part attributed to the portion of BD particles entrapped into L325 large surface asperities. The interaction of this portion of drug is

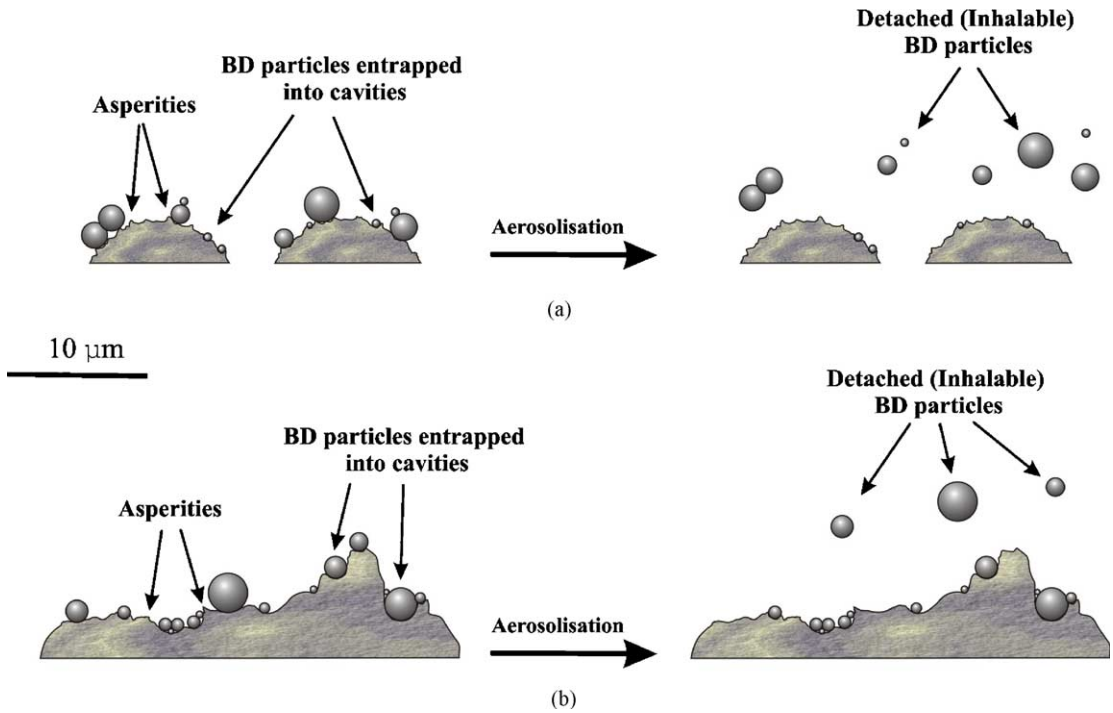


Fig. 8. Schematic representation of the role of carrier surface asperities on the drug entrapment and its fluidization capabilities: (a) BD/SDL-PEG3000, (b) BD/L325.

several orders of magnitude greater than can be achieved by van der Waals forces [2]. Therefore, this portion of drug particles could not detach from the surface of carrier by the air stream produced during aerosolisation process (Fig. 8b).

The application of smaller particle size carriers was previously shown to improve the FPF [27,28]. Thus, the higher aerosolisation capabilities of BD from SDL-PEG3000 particles may be due, in part, to the smaller particle size distribution of SDL-PEG3000 than L325 (Table 2). To better understand the importance of the role of particle size distribution in the efficiency of SDL-PEG3000 as a carrier in DPI formulations, a fraction of α-lactose monohydrate (SL) passed through a 38 μm sieve was collected. $D_{50\%}$ for SL (9.1 μm) was close to SDL-PEG3000 (9.7 μm). However, FPF and emission percent of BD aerosolized from SL were significantly lower ($P < 0.01$) than SDL-PEG3000 (Table 4). Similar to SDL-PEG400 and SDL, The presence of a higher proportion of fine particles resulted in the production of lower deposition of the drug aerosolised from SL. BD/SL formulation produced higher but not significant ($P > 0.05$) FPF of the drug than BD/L325 formulation. The small difference in FPF of the drug between BD/SL and BD/L325 may be related to the presence of cohesive forces between BD micronized particles. The highly cohesive nature of BD fine particles can be shown in Fig. 1 as drug agglomerates and also was reported previously in the literature [16].

Addition of ternary components to mixtures of drug and coarse carrier has been shown to improve the efficiency of aerosolization from DPI formulations [7,8,29]. In this study, BD was blended with JL before the addition of L325 or SDL-PEG3000 to promote the efficiency of mixing process according to previous report [16]. However, the addition of JL to formulation containing L325 as the coarse carrier resulted only in slight but not significant differences ($P > 0.05$) in the deposition profiles of BD, compared to BD/L325 formulation. No significant difference ($P > 0.05$) was observed between the deposition profiles of BD from BD/SDL-PEG3000 and BD/SDL-PEG3000/JL formulations.

4. Conclusions

Under the conditions used, the presence of all PEGs during spray drying process caused lactose to crystallize mainly to α-anhydrous form. The amount of α-lactose monohydrate in the products varied depending on the type of PEG presented. The type of PEG used also influenced particle size and particle size distribution of the spray dried powders.

Spray drying of lactose alone resulted in the production of a predominantly amorphous powder consisting of spherical particles with smooth surfaces. PEGs changed the surface texture of spray dried particles from lactose suspensions and caused the creation of asperities

(about 1 μm) on the surface of these particles. The difference in size of asperities on the surface of the carriers is likely to influence the deposition profiles of drug. The asperities on the surface of spray dried lactose/PEG particles were so small that can entrap only a small fraction (particles <1 μm) of micronized BD particles. Therefore, the possibility of detachment of BD particles from the surface of spray dried lactose/PEG carriers increased during aerosolisation process, compared to the commercially available lactose (L325).

The smaller particle size distribution of SDL-PEG3000 and SDL-PEG6000 compared to L325 was another factor influencing the deposition of the drug. The addition of fine lactose to binary blend of the drug and large carriers showed no significant improvement in the deposition of the drug.

Particle size distribution analysis showed the lowest proportion of fine particles (<5.0 μm) for SDL-PEG3000 and SDL-PEG6000 powders, compared to the other small carriers used in this study. The existence of a large amount of fine carrier particles was found to be an important factor in the reduction of FPF. It is believed that fine carrier particles had high affinity to make agglomerates with the drug particles. At high concentration of fine carrier particles this intrinsic affinity would play a significant role in dispersion of the drug. The results obtained in this study revealed the importance of the combined effects of particle size distribution, morphology and surface texture characteristics of SDL-PEG3000 and SDL-PEG6000 on their performance as carriers for DPI formulations.

The effect of the type and concentration of PEGs on the stability of spray dried lactose/PEG materials remains to be investigated. Further studies are also required to evaluate the consistency of deposition profiles of drug from binary or ternary formulations containing these materials as carriers.

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