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The influence of lactose carrier on the content homogeneity and dispersibility of beclomethasone dipropionate from dry powder aerosols

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Abstract

Dry powder formulations for inhalation usually comprise a mixture of coarse lactose (CL), employed as a carrier, and micronized drug. It was the aim of this study to determine the effects of fine lactose (FL), blended as a tertiary component on the mixing homogeneity and dispersibility of a model hydrophobic drug, beclomethasone dipropionate (BDP). BDP particles (volume median diameter (VMD) 4.6 μm) existed mainly as agglomerates, the majority of which were not dispersed into primary particles after aerosolization at a high shear force (4.7 psi). The resultant particle size distribution of BDP was multi-modal with VMD varying between 4.7 and 30.2 μm. Ternary interactive mixtures were prepared to consist of CL, FL and BDP with a fixed ratio of lactose to BDP of 67.5:1 w/w, but two concentrations of FL, i.e. 2.5 and 5%, w/w. The mixing was carried out using different sequences of adding the three components for two mixing times (15 and 60 min). Binary mixtures composed of CL and BDP were prepared for both mixing times as the controls, and these exhibited a coefficient of variation (COV) in BDP content $\leq 5\%$. Addition of FL to the binary formulations greatly reduced the content uniformity of BDP if the final powder were prepared by first mixing CL with FL before mixing with the drug (COV > 20%, after mixing for 15 min). However, the mixtures, prepared using other mixing sequences, had a similar uniformity of BDP content to the binary mixtures. All ternary mixtures containing 2.5% FL consistently produced a significantly higher (ANOVA $P < 0.01$) fine particle fraction (FPF, 3.1–6.1%) and fine particle dose (FPD, 13.6–30.1 μg) of BDP than the binary mixtures (FPF, 0.3–0.4%; FPD, 1.6–2.1 μg) after aerosolization at 60 l min^{-1} via a Rotahaler into a twin stage liquid impinger. The mixing sequences exerted a significant ($P < 0.05$) effect on the dispersion and deaggregation of BDP from the formulations prepared

Abbreviations: BDP, beclomethasone dipropionate; CL, coarse lactose; COV, coefficient of variation; ED, emitted dose; FL, fine lactose; FPD, fine particle dose (also referred to as respirable dose) is the mass of drug particles smaller than 6.4 μm per capsule after tests using a twin impinger; FPF, fine particle fraction (also referred to as respirable fraction) is the % of drug particles smaller than 6.4 μm after tests using a twin impinger; GSD, geometric standard deviation; TI, twin stage liquid impinger; TOF, time of flight; VMD, volume median diameter.

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using a mixing time of 15 min but such an effect disappeared when the mixing time was lengthened to 60 min. The dispersibility of BDP was always higher from the ternary mixtures than from the binary mixtures. BDP delivery from dry powder inhalers was improved markedly by adding FL to the formulation, without substantial reduction in the content uniformity of the drug.

Keywords: Dry powder inhalers; Lactose; Beclomethasone dipropionate; BDP; Ternary mixtures; Mixing homogeneity; Aerodynamic particle size; Dry powder aerosols

1. Introduction

Inhaled corticosteroids are recommended to be initiated at an early stage in the treatment of all asthmatic patients (British Asthma Guidelines Coordination Committee, 1997; Higgins, 1997) with higher initial dosages being subsequently tapered to the lowest effective dosage (Keeley and Rees, 1997). However, there are concerns regarding the safety of corticosteroids inhaled at high dose (Dluhy, 1998) since drugs such as beclomethasone dipropionate (BDP) administered in this manner have been found to induce systemic side effects such as adrenocortical suppression, skin changes (thinning, bruising) and cataract formation. Ideally, therefore all of the administered dose of corticosteroid should be delivered to the site of action in the respiratory tract so as to obtain the localized therapeutic effects whilst minimizing the amount gaining access to the systemic circulation. The pressurised metered dose inhaler (pMDI) is the most widely used device for administering corticosteroids to the respiratory tract but the chlorofluorocarbon (CFC)-containing pMDIs are gradually being phased out in order to comply with the United Nations Environmental Programme (Timsina et al., 1994). Thus, there has been a resurgence of interest in employing dry powder inhalers (DPIs) in pulmonary drug delivery but DPIs are notorious for the relatively low delivery efficiency of drugs to the lung. For example, the Rotahaler, Spinhaler and Diskhaler were reported to deliver only about 10% of the total administered dose to the lower airways (Pauwels et al., 1997). The majority of the drug is deposited in the upper airways and most of this is eventually swallowed and absorbed systemically via the gastrointestinal tract (Gupta and Hickey, 1991). Thus, the optimization of drug delivery from DPIs to the lower airways will not only increase the therapeutic effects but also reduce any possible side effects. This is of particular clinical significance for BDP, which was found to produce very low respirable fraction after delivery from DPIs (Pauwels et al., 1997). Most dry powder formulations for inhalation comprise fine drug blended with a coarser carrier. α-Lactose monohydrate has been employed most frequently as the carrier and it is usually fractionated so as to have a specific size range such as 63–90 μm for this purpose (Timsina et al., 1994). On inhalation, the drug particles must be dissociated from the carrier and dispersed into the air stream, which then carries the air-borne particles into the lung. The drug particles are usually present in low concentrations, with a drug to carrier ratio of 1:67.5 w/w, being typical (Kassem, 1990). Therefore, the carrier forms an integral component of the formulation and any change in the physico-chemical properties of the carrier particles has the potential to alter the drug deposition profile. A number of previous studies have reported improvements which can be made to the amount of respirable fraction of β_2-agonist, such as salbutamol sulphate, delivered from a DPI by means of manipulating the powder formulation. These have included smoothing the carrier surface (Ganderton, 1992), reducing the particle size of the carrier (Ganderton and Kassem, 1992; French et al., 1996; Steckel and Müller, 1997) and the use of ternary materials in the powder formulation (Staniforth, 1996). Addition of fine lactose (FL) to powders employing coarse lactose (CL) as carrier was also found to improve the dispersion and deaggregation of both salbutamol sulphate (Zeng

et al., 1996) and spray dried bovine serum albumin (Lucas et al., 1998). Although most formulations employ unmodified lactose that contains a proportion of fine lactose, the concentration and particle size of FL have to be carefully controlled in order to achieve satisfactory and reproducible pharmaceutical performance from a specific device (Zeng et al., 1998, 1999). For example, increasing the concentration and/or reducing the particle size of FL would be expected to improve the dispersion of drugs but this would have a detrimental effect on the powder flowability, mixing homogeneity and long-term stability of the powder formulation. Optimal particle size and concentrations of FL would appear to be a function of the device, the drug, CL and the specific requirements for a particular formulation. Given the wide variety of available devices and therapeutic purposes of inhaled drugs, it is likely to be unrealistic, if not impossible, to identify a single acceptable concentration and/or particle size of FL. Nevertheless, these early studies provide detailed insights into the role of FL in determining powder performance, which could supply the industry with general guidance for the development of lactose-based dry powder aerosols. However, all these earlier reports were focused on the effects of FL on the dispersion and in vitro deposition of hydrophilic drugs with little attention being paid to the effect of FL on drug content homogeneity, which is essential to achieve uniform metering doses by the patients. In addition, previous work has not considered the role of FL on the performances of hydrophobic drugs. Therefore, it was the aim of the present study to investigate the effects of FL on mixing homogeneity and dispersibility of a model hydrophobic drug, BDP. The Rotahaler was selected as the model device since it is one of the most widely employed DPIs for BDP delivery to the lung.

2. Materials and methods

Micronized beclomethasone dipropionate and Ventolin Rotahaler were supplied by Glaxo-Wellcome Research and Development, Ware, UK. Regular lactose (Lactochem®) was obtained from Borculo Whey, Chester, UK. Hard gelatin capsule shells (Size 3) were purchased from Farillon, Essex, UK. Butan-1-ol and cyclohexane, both of Reagent grade, were obtained from BDH Laboratory Supplies, Poole, UK and Sigma-Aldrich, Dorset, UK, respectively. Methanol of HPLC grade was obtained from Rathburn Chemical, Walkerburn, UK.

2.1. Preparation of coarse lactose (CL)

The 63–90 μm size fraction of lactose was obtained using an air jet sieve (Alpine, Ausberg, Germany). Regular lactose (100 g) was first sieved through a test sieve with an aperture width of 90 μm (Endecotts, London, UK) for 15 min and the sieved powder was then passed through a 63 μm sieve for a further 15 min. The powder fraction that was retained on the 63 μm sieve constituted CL that was used in the formulations. It was allowed to dry in a vacuum oven at 50°C for 24 h and then transferred to a sealed jar before placing in a desiccator over silica gel until required for further investigation.

2.2. Micronization of lactose

Fine lactose was prepared by micronization using an air-jet mill (JM-80, M & M Fryma, Herts, UK) operating at an air pressure of 15 bar. Thus, the lactose (<63 μm) was fed into the milling chamber via a feeding funnel and the sample collected after one passage through the jet mill was then dried in a vacuum oven at 50°C for 24 h. The collected sample was then placed in a desiccator over silica gel until required for further investigation.

2.3. Particle size measurement by laser diffraction

A small amount of lactose powder (about 5 mg) was dispersed in 5 ml butan-1-ol with the aid of sonication (Sonic water bath-Model F5100b, Decon Laboratories, Hove, UK) for 1 min. The particle size was measured by laser diffraction (Series 2600c, Malvern Instruments, Malvern, UK) using a 100 mm lens, an independent particle size model and obscuration between 0.16–0.18. Each sample was measured in triplicate.

A 63 mm lens was employed to measure the particle size of BDP which had been dispersed in cyclohexane using two protocols. The first involved dispersing BDP in cyclohexane containing 1% Tween 80 with the aid of sonication for 1 min. The suspension was then added dropwise to the measuring cell containing approximately 5 ml of cyclohexane until the obscuration reached a level between 0.16–0.18. In the second protocol, BDP was suspended in cyclohexane containing 1% Span 85 and sonicated for 5 min. The suspension was then filtered to obtain a clear BDP-saturated cyclohexane solution, which was employed to disperse BDP powder both initially as well as in the measuring cell. The size of the dispersed BDP particles was then measured under similar conditions as described before. Each sample was measured in triplicate.

2.4. Particle size measurement by time-of-flight technique

Particle size of BPD was also measured using an Aerosizer with an Aero-Disperser (API Aerosizer Mach-2, Amberst Process Instruments, MA). A small amount of powder (about 5 mg) was placed in the sample cup of the Aero-Disperser. Particle size measurement was carried out at a medium feed rate, high shear force and a sample run time of 300 s. Time-of-flight (TOF) data were processed with the operating software package Version 10.09 for API Aerosizer Mach-2. The density of BDP was taken as 1.105 g cm^{-3} and the volume distributions were recorded. BDP sample was analyzed four times.

Table 1
Mixing sequences employed to prepare the interactive mixtures composed of beclomethasone dipropionate (BDP), coarse (CL) and fine lactose (FL)

Formulations	Mixing sequences	
	Initial blend[a]	Final component[b]
Control	BDP+CL	
CL/FL/BDP[c]	CL+FL	+BDP
CL/BDP/FL[c]	CL+BDP	+FL
BDP/FL/CL[c]	BDP+FL	+CL

[a] Components mixed for 15 or 60 min.

[b] Final component mixed with initial blend for further matched 15 or 60 min.

[c] The sequence of lettering used in abbreviating the composition of each formulation indicates the sequence in which the individual components were blended; All ternary mixtures contained CL, FL and BDP in one of two ratios: 64.1:3.4:1 or 65.8:1.7:1, w/w.

2.5. Characterization of particle shape

The particle shape of the carrier and the drug was assessed by scanning electron microscopy (SEM). Double-sided adhesive tape was placed on an aluminium stub and after stripping off the protective covering, a small amount of particles was scattered on the stub and dispersed by tapping lightly on the edge of the stub with a spatula to break up any agglomerates. The particles were then coated with approximately 15–20 nm gold using a sputter coater (Polaron E5100, Polaron Equipment, Watford, UK) with an electrical potential of 2.0 kV and a current of 20 mA. Several photomicrographs were produced with a Philips SEM501B scanning electron microscope (Einhoven, Holland) by scanning fields, selected randomly, at several magnifications.

2.6. Preparation of powder formulations

All powder mixing was carried out using a Turbula® mixer (Glen Creston, Stanmore, UK) set at an operating level of 2 with an average rotation speed of 90–95 rpm.

Six formulations were prepared, containing CL, FL and BDP in two different ratios namely 64.1:3.4:1 and 65.8:1.7:1 w/w, and using different sequences of powder component addition (Table 1). The first two components (Table 1) were mixed for a predetermined period of time (either 15 or 60 min). The third component was added and the powder blended for a further same matched period of time (i.e. either 15 or 60 min). A formulation composed of CL and BDP only in a ratio of 67.1:1, w/w, was also prepared for all mixing times (i.e. 15 or 60 min) as the control. All blends containing BDP were filled in hard gelatin capsules (size 3) manually such that each capsule contained 33 ± 1 mg of the powder.

2.7. HPLC analysis of BDP

BDP was analyzed by HPLC employing a mixture of methanol and water (70:30) as a mobile phase running at a flow rate of 0.8 ml min^{-1} and UV detection at 239 nm. The HPLC system consisted of a pump (CM 4000 Multiple Solvent Delivery System, LDC Analytical, FL), a multiple wavelength UV detector (SpectroMonitor 3100, LDC Analytical Inc., Florida, USA) and a 15 cm (4.6 mm id) ODS column (Waters, Milford, MA). The retention time for BDP was approximately 4 min. The HPLC system was calibrated with standard solutions ranging from 0.1 to 20.0 μg ml^{-1} before each analysis. The samples (50 μl) were injected accurately in triplicate and the mean peak area was employed to calculate BDP concentrations from reference in the calibration curve.

2.8. Measurement of content uniformity

The content homogeneity of BDP in each formulation was examined by analyzing the quantity of BDP in 33 ± 1 mg of samples from each powder formulation; this weight of sample being equivalent to the filling weight in each capsule. Six samples were taken from six spots of each blend (top left front, top right back, top centre, bottom left back, bottom right front and bottom centre) and BDP content was assayed by the HPLC as described above. Both the % recovery and coefficient of variation (% CV) of BDP content were calculated, the latter being employed to assess the mixing homogeneity of the drug.

2.9. Particle size measurement of aerosolized BDP

Aerodynamic particle size of BDP was determined using a twin stage liquid impinger (TI, Apparatus A, British Pharmacopoeia, 1998) after aerosolization of five capsules, each containing a nominal dose of 33 ± 1 mg powder, equivalent to 482 ± 15 μg BDP, at 60 l min^{-1} via a Rotahaler.

HPLC mobile phase (7 ml) was introduced in stage 1 and 30 ml of the same solvent in stage 2 of the TI. The capsule to be tested was placed in a Rotahaler, which had been fitted into a moulded rubber mouthpiece attached to the throat piece of the impinger. Once the assembly had been checked and found to be airtight and vertical, the vacuum pump was switched on. After the pump had run for 5 s, the dose was released. The pump was allowed to run for another 7 s at 60 ± 2 l min^{-1} following the release of the dose and it was then switched off. The capsule shells were removed from the inhaler device and the test was repeated until five capsules had been actuated in the same manner. The inhaler body, capsule shells and mouthpiece were washed five times with the mobile phase and the washing solution was made up to 100 ml with the same solvent. The sample thus obtained was used to measure the amount of drug retained in the inhaler device. The same process was carried out for both the upper and the lower stages of the twin-impinger. All the samples obtained were analyzed for the concentration of BDP using the HPLC method as described above.

Fine particle dose (FPD), denoted as the quantity (μg) of drug per capsule that deposited in the lower stage of the TI (cut-off diameter < 6.4 μm) after aerosolization, was determined. Recovered dose (RD) was taken as the total quantity of drug recovered per capsule after each actuation whilst emitted dose was that emitted from the inhaler device. Percentage emission was calculated as the ratio of emitted dose to total dose. Fine particle fraction (FPF) was the ratio of FPD to RD whilst dispersibility was the percentage of FPD to emitted dose. All data were analyzed by ANOVA using a Minitab™ for Windows Version 10.2.

3. Results and discussion

3.1. Particle size and morphology of BDP and lactose

CL was shown to have a volume median diameter (VMD) of 87 μm with a geometric standard deviation (GSD) of 2.2 whilst the FL exhibited a VMD of approximately 7 μm with GSD of 1.9 μm. The CL showed a multi-modal particle size distribution with two small peaks at approximately 8 and 25 μm (Fig. 1), suggesting that after

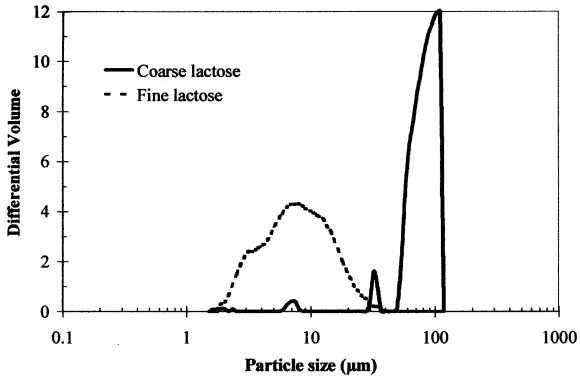

Fig. 1. Particle size distribution of coarse lactose and fine lactose, measured by laser light diffraction.

air-jet sieving, the CL still retained a small portion (approximately 1.5% v/v < 10 μm) of fine lactose. A normal distribution was seen for the particle size of FL (Fig. 1).

The CL crystals were tomahawk-shaped (Fig. 2), which is the shape of lactose crystals grown to maturity (Van Kreveld and Michaels, 1965). FL exists as polydisperse particles with a size typically in the 0.5–20 μm (Fig. 2). A degree of aggregation was clearly shown to be present in FL but absent in the large coarse particles. Interestingly, the finer BDP particles appeared to be essentially spherical whereas the larger BDP particles were less regular in shape.

BDP showed a VMD of 11.0 μm after dispersal in cyclohexane with 1% Tween 80 (Fig. 3). This value of 11 μm for the VMD of the micronised BDP was considered to be very high, especially since SE micrographs indicated visually that there was a high portion of particles present with optical diameters within the range 1–5 μm (Fig. 2). SE micrographs clearly showed that majority of BDP particles formed aggregates, which may not be deaggregated in this dispersing solvent (Cyclohexane with 1% Tween 80), leading to the particle size being overestimated. However, the BDP-saturated cyclohexane with 1% Span 85 resulted in a smaller particle size of BDP (Fig. 3) with VMD of 4.6 μm which was supported by visual estimation of the SE micrographs, suggesting that such a dispersion medium is able to disperse the majority of BDP agglomerates into primary particles.

The size distributions of BDP measured by an Aerosizer (Fig. 4) were found to highly variable. The measured geometric mean diameter varied from 4.7 μm for Run 2 to 30.2 μm for Run 3 although all measurements were conducted under similar conditions. Such a variation in the particle size after aerosolization of BDP particles in an airstream is not surprising, given the cohesive nature of these particles as seen in both SE micrographs and laser diffraction measurement. Multiplets can be clearly seen in the histograms, which showed that less than half of the aerosolized particles existed as primary particles. These results strongly suggest that BDP particles are highly cohesive and very difficult to disperse in an air stream.

3.2. Content uniformity

The average recovery of BDP of all formulations was approximately 98% (Table 2), suggesting that the overall mixing, sampling and analysis were satisfactorily accurate. The coefficient of variation (% CV) in BDP content within each formulation was a function of the components present, the mixing sequence employed and the mixing time (Table 2). The binary mixtures generally showed a smaller % CV in BDP content after mixing for 15 min than for 60 min but both mixing times resulted in a uniform mixing of the drug with % CV < 5%. However, the mixing times required for the preparation of a uniform ternary mixture were shown to be dependent largely upon the mixing sequences of the three components but also to a lesser extent upon the concentrations of FL. For example, the formulations prepared by premixing CL with BDP before mixing with FL were shown to have a similar uniformity of BDP content ($P > 0.05$) to that of the binary mixtures when matched mixing times were employed. A relatively high uniformity of BDP was also achieved within the ternary mixtures prepared by mixing FL with BDP before blending with CL since this formulation exhibited a % CV of BDP content less than 6.4%. The ternary mixture prepared by mixing FL with CL before blending with the drug was shown to be the least uniform in BDP content, with % CV of over 20% being

detected after a mixing time of 15 min. Increasing the mixing time to 60 min reduced the % CV of BDP content to less than 10%, indicating that a longer mixing time is required to produce a uniform distribution of the drug within such a mixture. The % CV of BDP mixed in the sequence CL/FL/BDP was found to be greater at the higher FL concentration (Table 2). However, overall when the FL concentration was increased from 2.5 to 5%, there was no significant (ANOVA $P > 0.05$) effect on the % CV of the drug.

As mentioned above, fine particles of BDP are highly cohesive. They will adhere to large lactose particles only if the shear force introduced during the mixing process overcomes the intrinsic cohesiveness. Visual examination of the SE micrographs (Fig. 2) shows that the BDP fine particles alone formed aggregates whilst after blending with CL, the majority of them were adhered to the surface of the coarse lactose. Drug uniformity within such interactive mixture has been reported to be a function of both the cohesive forces

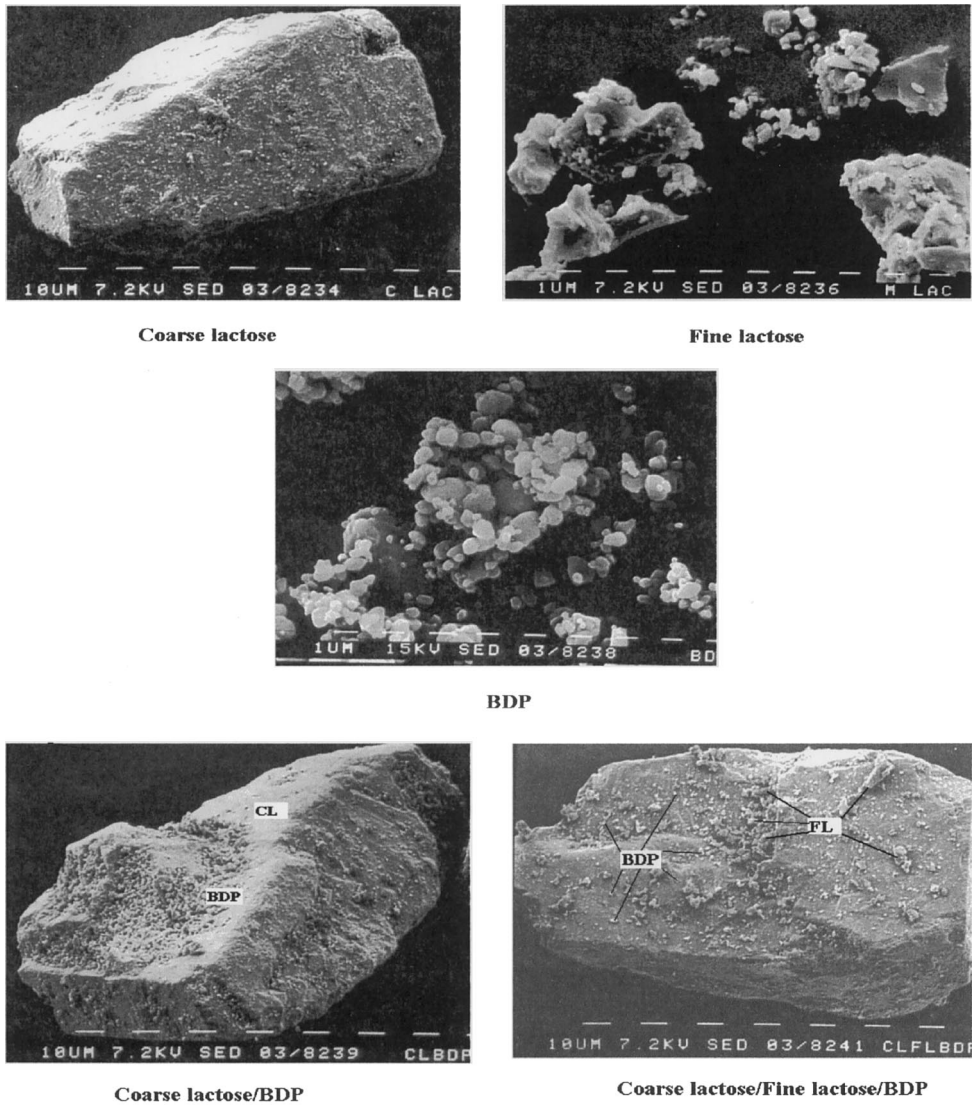

Fig. 2. Scanning electron micrographs of the various samples investigated.

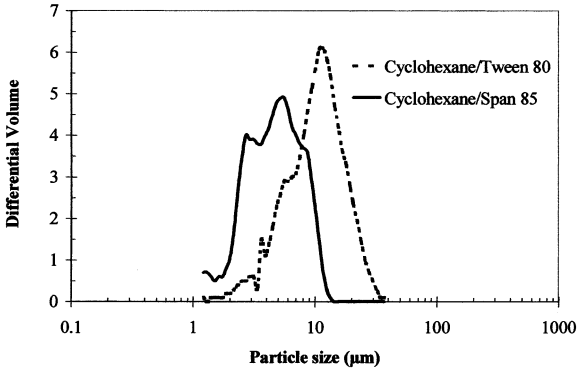

Fig. 3. Particle size distribution of BDP, measured by laser diffraction after dispersing in two media.

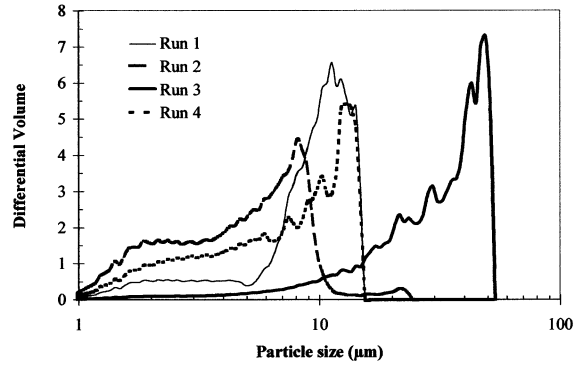

Fig. 4. Particle size distribution of BDP measured by Aerosizer with an Aerodisperser at a medium feed rate, high shear force and a sample run time of 300 s.

among the fine particles and their adhesive forces to the coarse carrier (Staniforth and Rees, 1982). In order to obtain a uniform, stable ordered mixture, it is generally required that the adhesive forces exceed the cohesive forces. Otherwise, the fine particles will be dislodged from the carrier particles during the vibrations encountered in nearly every powder handling process, resulting in a heterogeneous mixture. Since BDP particles are adhered directly to CL in the binary interactive mixtures, the interparticulate forces acting between these two components may be sufficient to maintain a uniform distribution of the drug within the mixture. The situation would be expected to be more complicated in the ternary mixtures as compared with that within the binary mixture. The mixing uniformity of a drug in a ternary mixture would be expected to depend upon both the cohesiveness of the third material and the mixing sequences of the three components. The ternary mixtures prepared by adding FL to the preformed CL/BDP mixture exhibited a similar uniformity of BDP to that of the binary mixture. This was in agreement with a previous report where addition of a small amount of a third, cohesive material (talc) to a preformed binary mixture composed of prednisolone (1%) and lactose–starch granules (425–850 μm) was shown to have little effect on the drug homogeneity (Soebagyao and Stewart, 1985). If the drug particles were first allowed to adhere onto the coarse carrier, the adhesion forces may have been so tenacious that the subsequently added FL may not result in substantial displacement of the drug particles from their adhesion sites on the coarse carrier particles. However, if CL is first blended with FL before mixing with the drug, some of the strong binding sites on CL would have been covered or saturated by FL. This would be expected to reduce the efficiency of CL to break up the drug aggregates during the mixing process. Thus, a longer mixing time (60 min) would then be required to achieve a uniform mixing of such interactive mixtures. If BDP is first blended with

Table 2
The % recovery of BDP obtained from the binary and ternary mixtures (mean (CV), $n = 6$)

Mixing time (min)	Control (%)	FL (% w/w)	CL/BDP/FL (%)	CL/FL/BDP (%)	BDP/FL/CL (%)
15	102.7 (1.1)	2.5	90.7 (3.0)	97.0 (20.6)	93.8 (2.3)
60	88.2 (5.1)		101.6 (3.4)	106.4 (4.1)	103.2 (5.6)
15		5.0	104.5 (2.6)	109.1 (22.0)	90.5 (6.4)
60			92.0 (3.5)	104.0 (9.8)	99.4 (2.0)

Table 3
Deposition profiles of BDP in a TI after aerosolization of different formulations prepared with a mixing time of 15 min at 60 l min^{-1} via a Rotahaler (mean ± SD, $n = 5$)

Formulations	FPD (μg)	FPF (%)	% emission
CL/BDP	1.6 ± 1.7	0.3 ± 0.3	69.8 ± 6.8
CL/BDP/FL	13.6 ± 4.4	3.1 ± 1.0	66.2 ± 4.9
CL/FL/BDP	21.7 ± 4.8	4.9 ± 0.8	64.0 ± 3.5
BDP/FL/CL	30.1 ± 3.9	6.4 ± 0.9	65.5 ± 6.0

FL, then under such conditions a randomized mixture is likely to result due to the similar particle size and density. FL may be regarded as a bulking and dispersing agent for BDP with the added FL disrupting the drug-drug particle interactions by providing alternative adhesion sites. After mixing with CL, the drug particles may subsequently adhere to the coarse carrier as individual particles or as multiplets comprising BDP and FL, resulting in a similar mixing uniformity of the drug to that of the binary mixture.

3.3. The particle size of aerosolized BDP from different powder formulations

The various formulations prepared with a mixing time of 15 min produced different FPF and FPD of BDP ($P < 0.01$) but a similar drug emission ($P > 0.05$) (Table 3). All formulations containing FL resulted in significantly higher ($P < 0.01$) FPF and FPD of BDP than the control. For example, the control produced a FPF (0.3%) and FPD (1.6 μg), which were increased by over ten times if FL was added to the formulations. The relatively low delivery efficiency of BDP from the control formulation suggests that the energy input generated by the air stream through the device was not sufficient to dissociate the majority of the drug particles from their adhesion sites on the CL and/or to deaggregate any drug agglomerates. This is likely to be attributable to the highly cohesive nature of the drug particles, a conclusion supported by the results obtained using the Aerosizer.

Of the three ternary mixtures, formulations BDP/FL/CL and FL/CL/BDP produced higher FPF and FPD values than formulation CL/BDP/FL. For example, formulation BDP/FL/CL resulted in a FPD of BDP of 30.1 ± 3.9 μg, which was over twice that (13.6 ± 4.4 μg) produced by formulation CL/BDP/FL. Addition of FL to powder formulations has been shown previously to improve the dispersion and deaggregation of salbutamol sulphate and spray dried albumin particles, resulting in higher FPF and FPD of the drug (Zeng et al., 1996, 1998; Lucas et al., 1998). These previous workers suggested that such an effect is partly due to the coverage of binding sites on CL by FL. If this is so, then the mixing sequence of the various components would be expected to affect the drug dispersion by altering the particulate interactions between the drug and coarse carrier. It can be seen from the SE micrographs (Fig. 2) that BDP particles are concentrated at some specific regions of the carrier surface, especially the surface cavities, whilst other regions have relatively fewer adhered drug particles. In the presence of FL, these strong binding sites on the coarse lactose particles may have been covered or saturated by the fine lactose, leading to the drug particles being adhered less strongly to alternative binding sites. Thus more drug particles would be expected to dissociate from the coarse carrier on suspension in the airstream, resulting in higher fine particle fractions of the drug. However, if the drug was first blended with CL before mixing with FL as in the case of CL/BDP/FL, more drug particles might be expected to adhere directly to CL than in formulations FL/BDP/CL and CL/FL/BDP. On this basis it might be predicted that the drug dispersion from the former formulation would be lower than from the latter two formulations. However, some redistribution of BDP and FL at adhesion sites on the surface of CL would appear to have occurred in formulation CL/BDP/FL during powder mixing since this formulation still produced significantly higher FPF and FPD of drug compared to the binary formulation. It has been reported previously that mixing sequence influences the particle size distribution of aerosolized salbutamol sulphate from ternary mixtures containing drug, CL and FL (Zeng et al., 1999). It was found in that study that, in contrast to the results obtained with BDP, that the maximum

drug FPF and FPD were obtained when the formulation was made by pre-blending FL with CL before mixing with salbutamol sulphate. In contrast, for those formulations of BDP, produced by using 15 min blending times, it was the formulation prepared by pre-blending the drug with FL prior to adding the CL which resulted in the highest FPF (or FPD) after aerosolization (Table 3). It is possible that the FL in the pre-blend increases the FPD of BDP by disrupting aggregates of the highly cohesive drug thereby promoting the liberation of individual drug particles.

The formulations prepared by mixing for 60 min (Table 4) may appear to produce a similar particle size distribution of aerosolized BDP to those that resulted after aerosolizing the same powders blended for only 15 min. Again, the ternary interactive mixtures containing FL produced a significantly higher FPF or FPD ($P < 0.01$) than the binary mixture. The FPD or FPF of BDP from the former formulations was over seven times that of the latter. However, in contrast to the formulations prepared by mixing for 15 min, the mixing sequences did not show any significant effect ($P > 0.05$) on the particle size distribution of aerosolized BDP from the formulations prepared by mixing for 60 min. During the prolonged mixing, the interaction between the three components may have tended towards an equilibrium with redistribution of drug and FL between CL occurring. The significance of the initial mixing sequences therefore diminishes as mixing time is increased.

Table 4
Distribution of BDP in a TI after aerosolization of different formulations prepared with a mixing time of 60 min at 60 l min^{-1} via a Rotahaler (mean $\pm$ SD, $n = 5$)

Formulations	FPD (μg)	FPF (%)	% emission
CL/BDP	2.1 ± 1.3	0.4 ± 0.3	69.2 ± 4.0
CL/BDP/FL	16.4 ± 4.5	4.1 ± 1.1	68.9 ± 3.3
CL/FL/BDP	26.9 ± 3.1	5.5 ± 0.7	69.1 ± 1.5
BDP/FL/CL	20.5 ± 6.2	4.2 ± 1.2	64.7 ± 4.2

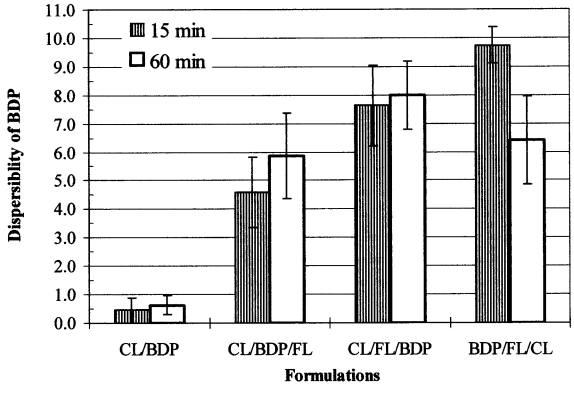

Fig. 5. The dispersibility of beclomethasone dipropionate from the binary mixture and the ternary mixtures containing 2.5% fine lactose after aerosolization at 60 l min^{-1} via a Rotahaler (error bars denote standard deviation, $n = 5$).

All ternary formulations were shown to produce much higher dispersibility of BDP than the binary mixtures (Fig. 5), confirming that the addition of FL improved the dispersion and deaggregation of BDP. The drug dispersibility was shown to follow a similar trend to that of either FPF or FPD in terms of the significance of mixing sequences. Drug dispersibility from formulations prepared with a mixing time of 15 min was affected significantly ($P < 0.01$) by mixing sequence but insignificantly ($P > 0.05$) from the same formulations prepared with a mixing time of 60 min. No significant difference ($P < 0.05$) was observed for the dispersibility of BDP from the same formulations prepared using the same mixing sequences but different mixing times. The exception to this finding was for the BDP/FL/CL mixture, which showed a substantial reduction in drug dispersibility when the mixing time was prolonged from 15 to 60 min. Such a difference in drug dispersibility may be largely attributable to the redistribution of different particles between aggregates. As mentioned before, pre-blending FL with the drug will result in a randomized distribution of the drug with FL and/or generate aggregates of FL and drug alone. Such a state of interaction between CL, FL and the drug is likely to be unstable and during a prolonged mixing, the three components are likely to reorientate so as to produce a more stable interactive system. In such a system, more drug particles may be expected to adhere to the coarse lactose, leading to less drug particles being dispersed from the powder.

4. Conclusions

Adding fine lactose to the preformed binary mixtures composed of coarse lactose and micronised beclomethasone dipropionate had no significant effect on the mixing uniformity of the drug. In contrast, if beclomethasone dipropionate was incorporated into a binary mixture containing the coarse and fine lactose, then the homogeneity of the drug within the ternary mixtures appeared to be reduced. The presence of fine lactose (2.5% w/w) in the powder formulations was shown to increase the dispersion and deaggregation of beclomethasone dipropionate in an air stream, leading to a much-improved FPF or FPD of the drug. The sequence in which the various components of the ternary mixtures were blended together was shown to affect the FPF and FPD of the drug, when mixing time was limited to 15 min. However, the influence of mixing sequences was diminished if the ternary mixtures were prepared by extending the mixing time to 60 min. Regardless of the mixing sequence and time, fine lactose improved the dispersibility of BDP without reducing drug emission from the device. The clinical implications of this are extremely important for BDP since the large, non-dispersed particles are likely to impact on the oropharyngeal area, from where they are swallowed and absorbed. An increase in the dispersibility of the aerosolized drug reduces the amount of drug present in association with large particles and may tend to reduce any side effects associated with uptake of the inhaled beclomethasone dipropionate that deposits in the mouth and back of the throat. Therefore, the delivery efficiency of beclomethasone dipropionate by dry powder inhalers can be improved by means of controlling the particle size distribution of the carrier and preparative conditions. Such an approach to improve deeply inspirable fraction of hydrophobic drug may provide an optimal drug delivery to the lung in conjunction with modifying the surface properties of the drug particles.

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