Particle Interactions Involved in Aerosol Dispersion of Ternary Interactive Mixtures

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Purpose. To investigate the mechanism of action of ternary components within dry powder aerosols.

Methods. Ternary interactive mixtures were prepared containing salbutamol sulphate (SS), coarse lactose carriers and either micronized lactose (ML) or micronized glucose (MG). *In vitro* drug and excipient aerosol deposition was performed using a twin-stage impinger (TSI) at 60 L/min with a Rotahaler device. Adhesional properties of the lactose carrier were examined using an atomic force microscope (AFM) colloidal probe technique.

Result. The fine particle fraction (FPF) from ternary mixtures were dependent upon carrier type ($p < 0.001$), ternary concentration ($p < 0.001$) and ternary component type ($p < 0.05$). Ternary mixtures produced higher FPF than binary mixtures, except those containing Superfine (SF), which was attributed to the high proportion of intrinsic fine carrier particles. The higher FPF obtained from ternary mixtures was independent of the mixing order ($p = 0.08$). Increased adhesion force was observed on the carrier surface following the addition of ternary components ($p < 0.001$).

Conclusion. The results confirm that ternary components increase aerosol deposition of powder mixtures. Some results were not entirely consistent with the saturation of active site theory and a hypothesis involving competitive and multilayer adhesion was proposed and requires further testing.

KEY WORDS: ternary interactive mixtures; dry powder inhaler; atomic force microscopy; lactose; salbutamol sulphate.

INTRODUCTION

Interactive mixtures (1), consisting of micronized drug particles that adhered to the surface of coarse carrier particles, have been employed in dry powder inhaler (DPI) formulations to provide respirable drug particles (below 5 μm aerodynamic diameter) with good flow properties. Drug redispersion from the interactive mixture is required for lung deposition (2). The addition of ternary components to interactive mixtures has been investigated to improve the efficiency of lung deposition from DPI formulations. Ternary mixtures produced higher *in vitro* aerosol deposition for salbutamol sulphate (2,3), bovine serum albumin (BSA) (4) and beclomethasone (5), compared with binary mixtures. Increasing ternary concentration increased fine particle fraction (FPF) (3,6). Differences were not observed between the ternary components examined: micronized lactose and PEG 6000 (4) or micronized lactose and magnesium stearate (3). Smaller ternary components produced higher *in vitro* drug deposition (7). However, the mechanism of action of ternary components within DPI formulations has not been fully elucidated.

The saturation of active sites on the carrier particle has been proposed as the mechanism for increased drug deposition, whereby the adhesion of ternary components onto active (high adhesion) sites leaves passive (low adhesion) sites for drug adhesion (2). The reduced adhesion between drug and carrier particles was suggested to increase drug detachment. Adhesion force measurements have not previously been undertaken to confirm this hypothesis or to identify the existence of active sites. Indirect adhesion measurements have been examined in bulk ternary systems using sieving (8,9) and centrifuge techniques (10); however, no direct adhesion measurements have been performed on the carrier particles following the addition of ternary components. The mechanism of action of ternary components remains speculative and indirectly interpreted from the order of mixing of ternary components or by visual examination. Conflicting results were obtained from the order of mixing (4,7). Lucas and coworkers (4) found that the aerosol deposition was independent of mixing order and observed the presence of small drug-containing aggregates, termed 'multiplets,' indicating that drug redistribution from the lactose carrier to the ternary components. In contrast, higher drug deposition was observed when mixing the ternary component and carrier before the drug was added, suggesting saturation of active sites on the carrier (7). Electrostatic interactions have also been proposed to influence the location of drug detachment (11).

The objectives of this study are to examine the *in vitro* drug deposition from ternary interactive mixtures and to investigate the mechanism of action of ternary components in drug deposition. In this study, ternary mixtures are defined as interactive mixtures containing micronized drug particles, coarse lactose carriers and an added excipient component. Although lactose was already present as the coarse carrier in the binary mixture, the addition of micronized lactose was considered to produce a ternary mixture. Micronized glucose was used as an alternate ternary component. Factors examined included carrier type, ternary component type and concentration. The mechanism of action of ternary components on drug deposition was investigated by examining particle interactions within the powder formulation using three methods. First, the order of mixing of ternary components was examined. Second, concurrent determination of drug and excipient deposition enabled examination of particle interactions between drug and fine excipient particles (intrinsic or externally added ternary particles). Third, the adhesional properties of the lactose carrier surface were determined using an atomic force microscope (AFM) colloid probe technique.

MATERIALS AND METHODS

Materials

Micronized salbutamol sulphate (SS) (Glaxo Wellcome, Australia) was the model drug. Five grades of coarse lactose carriers were employed: Superfine (SF), 100 Mesh (100 M) (New Zealand Milk Products Pty. Ltd., Australia); and Pharmatose DCL 11 (DCL 11), Pharmatose 125 Mesh (125 M) and

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Pharmatose 325 Mesh (325 M) (DMV International, The Netherlands). The ternary component consisted of either micronized lactose (ML) (Microfine, Borcula Whey Products Ltd., U.K.) or micronized glucose (MG) (Ajax Chemicals, Australia), prepared by jetmilling (Chrispro jetmill 75P).

Methods

Particle Size Analysis

Particle size distributions were determined using laser diffraction (Mastersizer S, Malvern Instruments, UK). Ethanol was used as the dispersant for lactose and glucose samples and a 0.5% w/w lecithin in 2,2,4-trimethylpentane solution was used as the dispersant for SS. Samples were sonicated for 3 min immediately prior to measurement. The mean particle size distributions (n = 5) were characterized by the median diameter ($d_{50\%}$) and the percentage of particles below 5 μm.

Interactive Mixtures

Binary and ternary interactive mixtures were prepared using a modified blending technique (12). Batches (5 g) containing 1–10% w/w drug and 0–10% w/w ternary component were vigorously hand-shaken in a glass test-tube containing three ceramic beads for a total duration of 5 min. The ceramic beads (approximately 10 mm diameter) aided the break up of drug agglomerates. Three different mixing orders were employed: Method A where both SS and ternary component were placed between two layers of carrier powder and shaken for 5 min (this method was employed unless otherwise stated), Method B where the ternary component and carrier were blended for 2.5 min, then SS was added and blended for a further 2.5 min and Method C where SS and carrier were blended for 2.5 min, then the ternary component was added and blended for a further 2.5 min.

The homogeneity of each blend was determined using twenty random samples (150 mg), dissolved in 0.1 M hydrochloric acid. The amount of SS in each sample was determined by UV assay at a wavelength of 276.2 nm (Cecil CE6600 UV spectrophotometer, UK). An acceptable degree of homogeneity was achieved with a mean drug content within 10% of the theoretical value and coefficient of variation (CV) less than 5%, which indicated that 95% of samples would fall within 10% of the mean (13).

Scanning Electron Microscopy (SEM)

Surface morphology of ternary interactive mixtures were examined visually by SEM (Hitachi S-570, Japan). Samples were glued onto aluminium stubs, gold-coated (BAL-TEC SCD 005, Japan) and viewed using a 10 kV current.

In Vitro Aerosol Deposition

In vitro aerosol deposition was determined using a twin-stage impinger (TSI) (Copley, UK) using a Rotahaler (Glaxo Wellcome, Australia) at 60 L/min. Purified water was placed into stages 1 and 2 (7 mL and 30 mL, respectively). The theoretical aerodynamic cut-off diameter is 6.4 μm. Powder blends (20 mg) were loaded into hard gelatin capsules (size 3, Fawns and McAllan Pty. Ltd., Australia). Single capsules were actuated for 4 seconds (4 L volume) for each measurement (n = 5). All deposition studies were conducted in an air-conditioned laboratory (21 ± 3°C and 52 ± 12% RH). The amount of SS and excipient remaining in the inhaler and deposited in stages 1 and 2 were determined.

SS was analyzed by HPLC (Waters μBondapak; 125 Å, 10 μm, 3.9 × 300 mm, MA) using a flowrate of 1 mL/min. The mobile phase consisted of a 2:1 (v/v) mixture of 0.2% w/v ammonium acetate and methanol. An injection volume of 100 μL was used. SS was quantified at 276 nm using peak area with external standards. Linearity was observed between 0.04–20 μg/mL with a LOD and LOQ of 0.02 and 0.04 μg/mL, respectively.

Lactose and glucose were analyzed by HPTLC using step-wise methanol-water-chloroform development with 2 M acetic acid pre-conditioning (AMD 2, Camag, Switzerland). Samples and standards were applied to silica plates (Silica gel 60 F_{254}, 20 × 10 cm, Merck, Germany) using a rate of 0.1 μL/sec under nitrogen flow (Linomat IV, Camag, Switzerland). Post-chromatographic derivatization using aniline-diphenylamine (ADP) detection solution (115°C, 15 min) produced blue-coloured zones (14). Lactose and glucose were quantified at 630 nm using peak height (TLC Scanner 3, Camag, Switzerland). The non-linear calibration curve (Michaelis-Menten 2) was obtained between 10–500 ng with LOD and LOQ determined as 10 ng and 20 ng, respectively.

The emitted fraction (EF) was defined as the amount of drug delivered from the inhaler, expressed as a percentage of the recovered dose. The fine particle mass (FPM) was defined as the amount of drug deposited in stage 2. The fine particle fraction (FPF) was defined as the amount of drug deposited in stage 2, expressed as a percentage of the emitted dose. Statistical analysis was performed using a one-way analysis of variance (ANOVA) (Sigmastat, Jandel Scientific, CA) at a 5% significance level. Multiple comparison was performed using a Tukey test. However, randomization of the powder blends could not employed.

Adhesion Force Measurement

The adhesion force on the carrier surface was measured in air by atomic force microscopy (Dimensions 3100, Digital Instruments, CA) at ambient conditions (20–25°C and 40–50% RH) using a colloid probe technique. The colloid probe consisted of a silica sphere (10 μm diameter, Kunishima Kikai Ltd., Japan) attached to a silicon nitride cantilever (Type NP-S, Digital Instruments, CA; spring constant, k = 0.42 N/m). Full details are provided elsewhere (15). Briefly, individual adhesion forces between the colloid probe and carrier surface were measured. Log-normal distributions for each sample were obtained (n > 50), characterized by the geometric mean adhesion force and geometric standard deviation (GSD). Statistical analysis was performed using either a Mann-Whitney rank sum test or Kruskal-Wallis one-way analysis of variance on ranks (Sigmastat, Jandel Scientific, CA) at the 5% significance level. Multiple comparison was performed using the Dunn's test.

RESULTS

Particle Size Distribution

The size distribution of SS particles was appropriate for respiratory delivery and aerosol deposition into the lower

stage of the TSI (Table I). The particle size distribution of lactose carriers varied with $d_{50\%}$ ranging from 35.4 (SF) to 124.8 μm (DCL 11) and the proportion of fine particles (below 5 μm) ranging from 0.6% (DCL 11) to 12.1% (SF) (Table I). Little difference was observed in the size distribution of the ternary components (ML and MG).

Interactive Mixtures

The production of interactive mixtures was confirmed by SEM where drug and ternary component association with the coarse carrier surface was observed (Fig. 1). Particle adhesion on the carrier was non-uniform and characterized by aggregation, with an increasing degree of aggregation occurring with higher ternary concentrations. Acceptable homogeneity was obtained from all binary and ternary mixtures, with the accuracy within 10% of the theoretical value (majority of values falling within 3%) and CV below 3%. Homogeneity determinations using sample sizes of 20 mg were undertaken for a limited number of mixtures, with the accuracy well within 10% of the theoretical value and CV below 4%.

In Vitro Drug Deposition

The recovery of SS ranged between 81.6–98.8%, which was within the acceptable range for mass balance (75–125%) (16).

Significant differences in the emitted fraction (EF) from ternary mixtures were observed for the carrier type ($p < 0.001$) (Fig. 2A). Higher EF was obtained for DCL 11 mixtures ($p < 0.05$), but differences were not observed in EF between the other carriers. Significant differences were not observed in the EF with increasing ternary ML concentration in powder mixtures containing 125 M ($p = 0.806$), DCL 11 ($p = 0.425$), SF ($p = 0.518$) and 100 M ($p = 0.314$) carriers. Although a reduced EF was observed with increasing ternary ML concentration in the 325 M mixtures ($p = 0.015$), differences were not observed between the ternary and binary mixtures.

The effect of ternary component on EF was examined in ternary mixtures containing 325 M and SF carriers (Fig. 3A). The EF was independent of the ternary component type (either ML or MG) in 325 M and SF mixtures ($p > 0.05$ each). Increasing MG concentration reduced EF in 325 M mixtures ($p = 0.002$), with differences not observed in SF mixtures ($p > 0.05$). The EF was independent of the mixing order of ternary mixtures ($p > 0.053$) (Fig. 4).

The fine particle fraction (FPF) from ternary mixtures

Table I. Particle Size Distribution of Salbutamol Sulphate, Coarse Lactose Carriers and Ternary Components Determined by Laser Diffraction (Mean, n = 5)

Sample	$d_{50\%}$ (μm)	Size <5 μm (%)
SS	1.3	97.8
SF	35.4	12.1
100 M	103.8	6.2
DCL 11	124.8	0.6
125 M	67.2	2.8
325 M	54.3	10.0
ML	4.0	60.5
MG	4.4	56.9

Fig. 1. Scanning electron micrograph of 325 M ternary interactive mixtures of 5% w/w SS and (A) 1% w/w ML, (B) 5% w/w ML and (C) 10% w/w ML (magnification ×200).

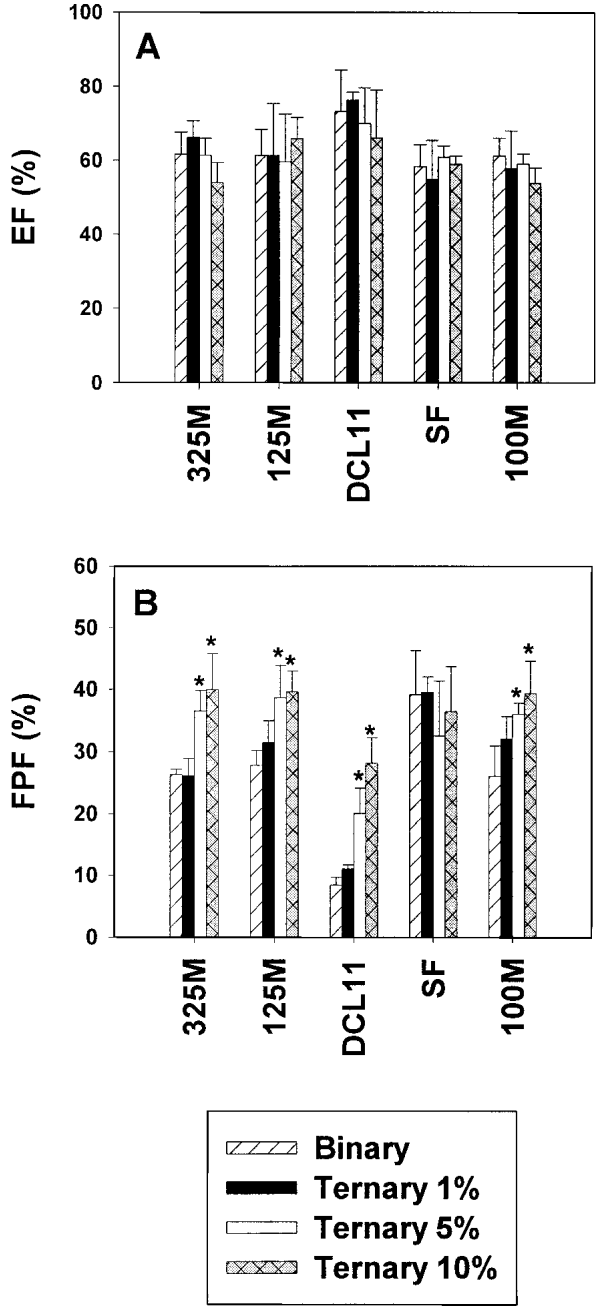

Fig. 2. (A) Emitted fraction and (B) Fine particle fraction of binary and ternary mixtures containing 5% w/w SS and 1–10% w/w ML (Mean + standard deviation, n = 5), where * represents a significant difference ($p < 0.05$) compared with the binary mixture.

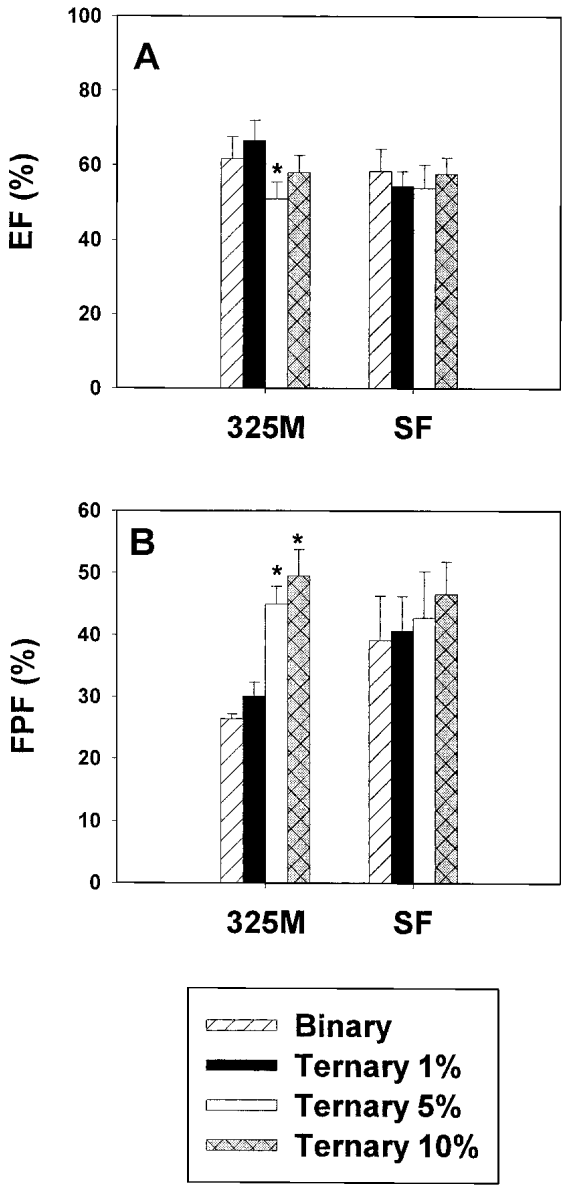

Fig. 3. (A) Emitted fraction and (B) Fine particle fraction of binary and ternary mixtures containing 5% w/w SS and 1–10% w/w MG (Mean + standard deviation, n = 5), where * represents a significant difference ($p < 0.05$) compared with the binary mixture.

was dependent upon the carrier type ($p > 0.001$), ternary concentration ($p < 0.001$) and ternary component type ($p < 0.05$). Apart from SF ($p = 0.378$), increasing ternary ML concentration increased FPF for all carriers ($p < 0.001$) (Fig. 2B). Ternary mixtures containing 5% and 10% ML concentrations produced significantly higher FPF values ($p < 0.05$) compared with binary mixtures for 325 M, 125 M, DCL 11 and 100 M. High FPF were observed for all mixtures containing the SF carrier, but increasing the ternary concentration did not significantly affect the FPF.

The effect of ternary component on FPF was examined in ternary mixtures containing 325 M and SF carriers. For both carriers, ternary mixtures containing MG resulted in higher FPF than ternary mixtures containing ML. Increasing the MG ternary concentration increased the FPF in 325 M mixtures ($p < 0.001$) (Fig. 3B), with significant differences between the binary and ternary 5% and 10% MG mixtures ($p < 0.05$ each). For 325 M mixtures, ternary MG produced significantly higher FPF than ternary ML at both 5% and 10% ternary concentrations ($p < 0.05$). Although MG produced higher FPF than ML in SF ternary mixtures ($p = 0.015$), differences were not observed in FPF with increasing ternary MG concentration ($p > 0.05$) (Fig. 3B).

Difference in FPF were not observed due to the mixing order of the ternary mixtures of 5% SS–5% ML–325 M ($p = 0.080$) (Fig. 4), with all ternary mixtures producing higher FPF than binary mixtures ($p < 0.05$ each).

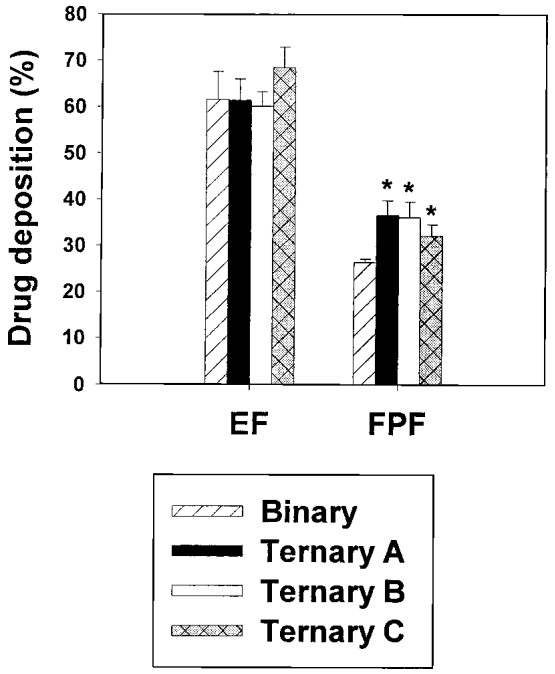

Fig. 4. *In vitro* drug deposition of 325 M ternary mixtures containing 5% w/w SS and 5% w/w ML, prepared using different mixing methods (Mean + standard deviation, n = 5), where * represents a significant difference ($p < 0.05$) compared with the binary mixture.

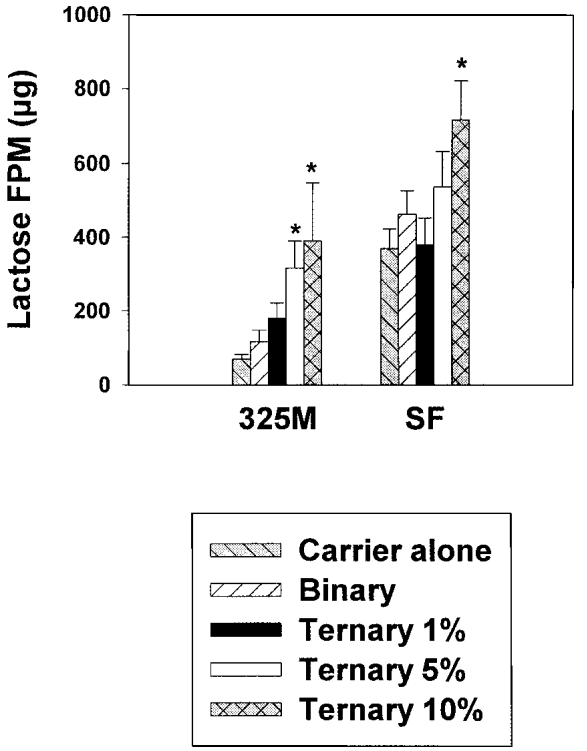

Fig. 5. Lactose fine particle mass of ternary mixtures containing 5% w/w SS and 1–10% w/w ML (Mean + standard deviation, n = 5), where * represents a significant difference ($p < 0.05$) compared with the binary mixture.

In Vitro Excipient Deposition

The lactose FPM was normalized for an initial lactose mass of 20 mg to enable direct comparison between groups (lactose alone, binary and ternary mixtures). The lactose FPM of SF carrier alone was significantly higher than that obtained for 325 M alone ($p < 0.001$) (Fig. 5). Not surprisingly, higher lactose FPM was observed with increasing ternary ML concentration for both carriers ($p < 0.001$ each) (Fig. 5). Increasing ternary MG concentrations produced no difference to the lactose FPM ($p > 0.05$) in SF mixtures (Fig. 6A). Significant differences were observed in lactose FPM ($p < 0.001$) in ternary SS-MG-325 M mixtures (Fig. 6A). Compared with the binary mixture, a reduced lactose FPM was observed in the 325 M carrier alone ($p < 0.05$) and an increased lactose FPM was observed in the ternary 10% MG mixture ($p < 0.05$). As expected, increased glucose FPM were observed with increasing ternary MG concentrations for both SF and 325 M mixtures ($p < 0.001$ each) (Fig. 6B).

Adhesion Force Distribution

Significant differences ($p < 0.001$) were observed in the adhesion force determined on the carrier surfaces of 325 M and SF, following the addition of ML and MG (Fig. 7). Higher adhesion forces were observed following the addition of 1 to 10% ML and MG, compared with 325 M carrier alone ($p < 0.05$ each). Similarly, increased adhesion force was observed with the addition of 5 and 10% ML to SF carrier ($p < 0.05$). In addition, higher adhesion force was observed for SF carrier alone compared with 325 carrier alone ($p < 0.0001$; Mann-Whitney Rank Sum test).

DISCUSSION

Visual examination by SEM confirmed the preparation of binary and ternary interactive mixtures. Although non-uniform adhesion of drug and ternary components and particle aggregation was observed on the coarse carrier surface, a high level of homogeneity was obtained, consistent with minimal segregation (1,8). In addition, the high RD in the aerosol study further confirms that homogenous mixtures were produced.

The EF of ternary mixtures was dependent on carrier type ($p < 0.05$). The higher EF obtained from DCL 11 mixtures (Fig. 2A) was attributed to the larger carrier size and spherical nature enhancing fluidisation and entrainment due to better flow properties. Differences in EF were not observed between binary and ternary mixtures. The EF of ternary mixtures were independent of ternary component type or order of mixing, supporting previous findings (4,5). However, reduced powder emission was observed with ternary mixtures in other studies (3,7).

The fine particle fraction (FPF) from ternary mixtures was dependent on carrier type ($p < 0.05$), ternary concentration ($p < 0.05$) and ternary component type ($p < 0.05$). Ternary mixtures produced higher FPF than binary mixtures for all carriers, except SF (Fig. 2B and 3B). Apart from SF mixtures, increasing ternary concentration increased FPF. The high FPF obtained from the binary and ternary mixtures containing the SF carrier was consistent with previous studies where smaller carrier size (17–20) and increased proportion of fine particles (21–23) increased the FPF. Lower FPF values obtained from DCL 11 mixtures were attributed to the large

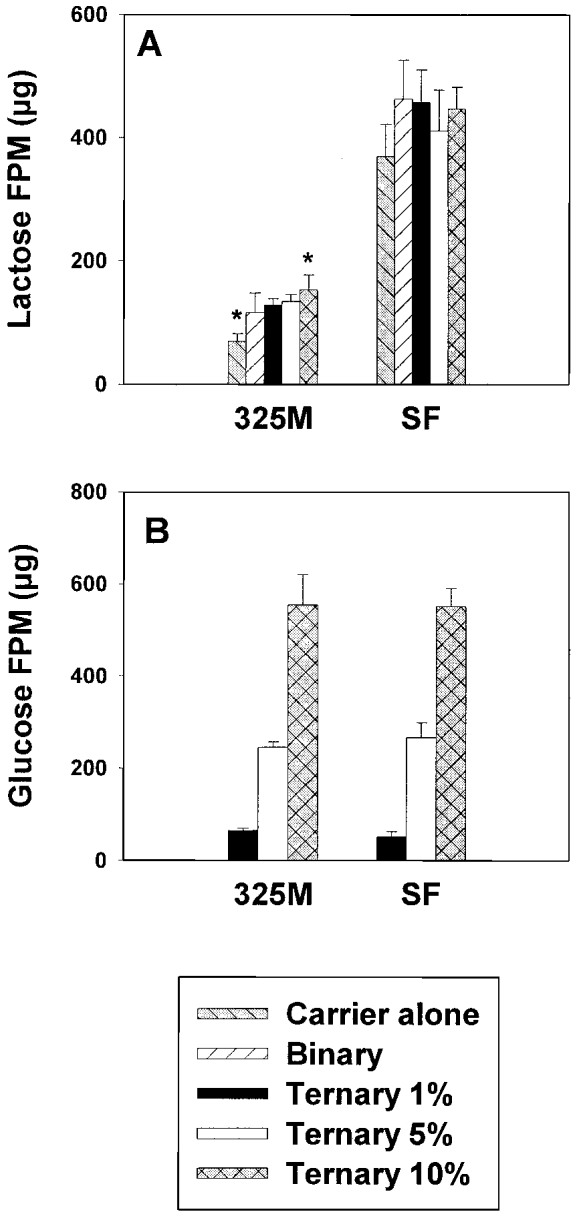

Fig. 6. (A) Lactose and (B) glucose fine particle mass of ternary mixtures containing 5% w/w SS and 1–10% w/w MG (Mean + standard deviation, n = 5), where * represents a significant difference ($p < 0.05$) compared with the binary mixture.

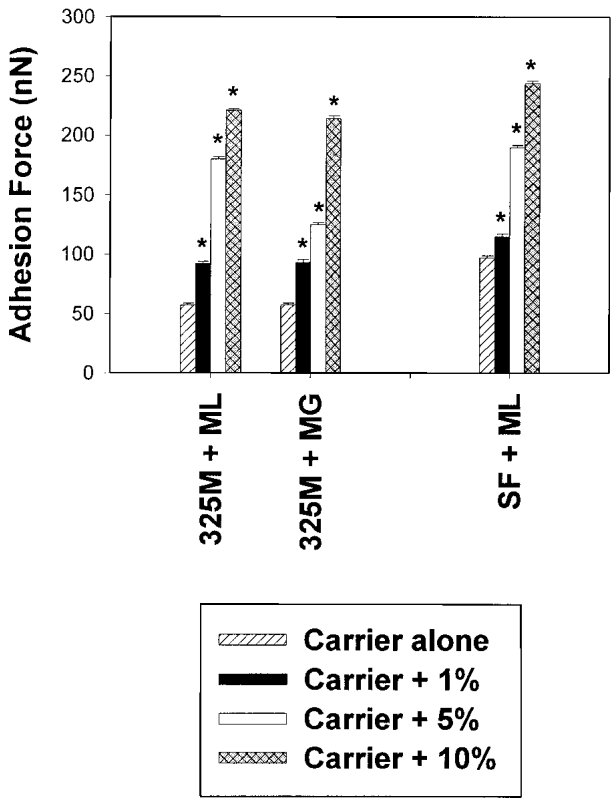

Fig. 7. Adhesion force of lactose carrier before and following the addition of ternary components (Geometric mean + standard deviation, n > 50), where * represents a significant difference ($p < 0.05$) compared with the carrier alone.

carrier size and low proportion of fine particles. Interestingly, increasing ternary concentration generally increased the FPF to a maximal level (around 40%), similar to that obtained for SF mixtures. A maximal FPF level was observed in previous studies using BSA (4) and SS (3). The deaggregation efficiency of the inhaler device dictates the FPF obtained. Use of an inhaler device with greater deaggregation efficiency may further increase FPF from ternary mixtures. The maximal FPF value observed with the other carriers was not attained with the DCL 11 carrier. A FPF of 28.1% was achieved with the 10% ternary ML concentration. Ternary concentrations in excess of 10% were not determined.

Higher FPF were obtained in ternary mixtures using MG than ML for both 325 M and SF carriers. The difference in FPF due to ternary component type is in contrast with previous studies, using ternary components of micronized lactose and magnesium stearate (3) or micronized lactose and PEG 6000 (4).

The independence of mixing order on FPF observed was consistent with some previous studies. The FPF were independent of the mixing sequence of mixtures containing BSA, coarse and micronized lactose (4) and from ternary mixtures containing SS, coarse and intermediate-sized lactose (3). In contrast, higher FPF obtained by adding SS to pre-blended coarse and micronized lactose was attributed to the occupation of active carrier sites by the ternary component (3).

The *in vitro* excipient deposition examined the interparticulate interactions between SS and fine excipients (intrinsic and ternary). The higher lactose FPM observed for the SF carrier compared with 325 M ($p < 0.001$) was related to the higher proportion of intrinsic fine particles present (Table I). However, incomplete detachment and dispersion of fine particles from the carrier surface occurs due to the weaker dispersion forces achieved during aerosolization. The addition of ternary ML increased the lactose FPM for both carriers ($p < 0.001$), as expected due to the greater proportion of fine lactose particles present in the powder mixtures. Similarly, the addition of ternary MG increased the glucose FPM for both carriers ($p < 0.001$). However, an increase lactose FPM was observed in the 325 M carrier with the addition of SS particles ($p < 0.05$) and a further increase was observed with the addition of ternary MG ($p < 0.05$). The increased detachment of fine lactose particles indicated that the addition of SS and MG particles produced a destabilization between the intrinsic fine lactose particles and the 325 M carrier surface.

Although the detachment force may not be indicative of the force experienced by drug particles (15), the AFM colloid probe technique enabled direct measurement of the adhesional characteristics on the carrier surface before and after the addition of ternary particles (ML or MG). Ternary particles were mixed with SF and 325 M carriers using the same mixing technique used for interactive mixtures for aerosol studies, without the addition of SS. The direct measurement of adhesion on the lactose carrier surface before and after the addition of ternary components by AFM showed the existence of a log-normal distribution of adhesion forces. This was consistent with a previous study (15) and demonstrated the existence of a continuum of surface energy sites.

The increased adhesion force observed on the carrier surface following the addition of ternary components was likely to be caused by the higher surface energies of the adhered ML or MG particles produced by their high-energy comminution (24). The attachment of these micronized particles onto the carrier surface may provide high-energy adhesion sites, with higher adhesion observed as the concentration of adhered particles increased. Triboelectric charging may occur during the mixing process due to increased particle contact, resulting in increased electrostatic forces and higher adhesion forces on the carrier surface; however, some charge decay is likely to have occurred prior to the adhesion measurements. In addition, increased surface roughness caused by the fine particles adhered to the carrier surface may contribute to the higher adhesion, due to increased contact area between the probe and surface (25,26).

Previous studies suggested that the effect of ternary components on increased drug dispersion may be explained by the saturation of active sites on the carrier surface by ternary components, thereby allowing easier detachment of drug particles (2,3,7). However, the results obtained in this study using interactive mixtures containing SS as a model drug at concentrations higher than commercial formulations were not entirely consistent with this mechanism for the following reasons.

First, in order for saturation of active sites to occur, some of the ternary lactose and glucose particles are required to occupy these high-energy adhesion sites on the carrier surface in place of drug particles. Thus, order of mixing should influence the FPF because either fine lactose/glucose or drug particles would be bound to the high-energy sites on the lactose carrier surface depending on which fraction was mixed first. However, in this study, the FPF obtained for ternary mixtures of 5% SS–5% ML–325 M was independent of the mixing order (Fig. 4). Similar observations were made in some other studies (3,4).

Second, the saturation of active sites on the lactose carrier by the ternary component was proposed to leave low-adhesion/passive sites for drug adhesion; however, the AFM study demonstrated higher surface energy adhesion sites on the carrier surface after the addition of ternary fine lactose and glucose particles. The surface adhesion characteristics increased with increasing concentration of fine lactose and glucose particles and the increased surface adhesion characteristics were likely to be associated with the presence of these fine ternary particles. SS particles would be likely associated with the high energy, fine ternary particles rather than low energy sites on the carrier surface.

Third, the presence of SS in a binary mixture was observed to increase in lactose FPM compared with that of the lactose carrier alone. The lactose FPM increased from 370 to 460 μg and 70 to 120 μg for SF and 325 M carriers, respectively. The presence of SS therefore displaced the intrinsic fine lactose from the carriers probably by preferentially occupying the carrier adhesion sites or by some interaction between the fine lactose and SS particles. This observation was inconsistent with the saturation of active sites since the intrinsic fine lactose would be expected to occupy active sites on the carrier surface, leaving passive sites for SS adhesion.

Definition of the mechanism by which the addition of fine carrier particles increased the drug FPF in these dry powder formulations is not conclusive. Some observations from this study are inconsistent with saturation of active sites. However, while the results of this study have not been able to clearly define the mechanism by which ternary components increase drug dispersion, they allow the development of hypotheses involving competitive and multilayer adhesion. Competitive adhesion and redistribution processes, previously shown to influence homogeneity and drug segregation within ternary interactive mixtures (27), may provide an explanation for the observations in this and previous studies. Competitive adhesion uses the concept of a distribution constant to define the interaction of a material with other substances present in the powder mixture. SS could be distributed between the large carrier particles and the fine excipient particles to produce an equilibrium mixture where SS was associated with sites on the large carrier surface and with sites on the fine excipient particles. In addition, the degree of surface saturation may influence the dispersion processes. At high drug and fine excipient concentrations, it is likely that the surface adhesion sites are saturated and more complex adhesion processes are likely, involving aggregation and multilayer formation. In fact, the SEMs in this study clearly show networks of particle multilayers on the surface of the large carrier particles. The presence of the multilayer associations, probably consisting of drug and fine excipient particles, may allow greater drug detachment from the carrier surface due to the increased detachment mass. These hypotheses require further testing.

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