International Journal of Pharmaceutics 416 (2011) 129–135

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

The influence of drug loading on formulation structure and aerosol performance in carrier based dry powder inhalers

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ARTICLE INFO

Article history:
Received 6 April 2011
Received in revised form 31 May 2011
Accepted 12 June 2011
Available online 17 June 2011

Keywords:
Active sites
Dry powder inhaler
Spherical carrier
Inhalation medicine
Powder blending

ABSTRACT

Previous studies have reported that carrier:drug ratio and carrier size influence the aerosol performance of dry powder inhalation systems. These previous studies were complicated by the heterogeneous nature of the carriers used, making it difficult to define an explicit relationship between parameters and performance. Here, the authors studied the influence of drug loading and carrier size on drug aerosol performance using homogeneous spherical model carriers. Different formulations containing drug (salbutamol sulphate) and carriers (polystyrene beads with median diameters of 82.8 μm, 277.5 μm and 582.9 μm, respectively) were prepared by varying the ratio of carrier to drug (from ~5:1 to ~85:1). The surface morphology of the carrier particles and force of adhesion were investigated using atomic force microscopy, while the aerosol performance was evaluated using a multi-stage liquid impinger. The carrier surface morphology for all carrier sizes was homogenous with root-mean square roughness values ≤112 nm. No significant difference in the force of adhesion between salbutamol sulphate and the three carrier sizes was observed. Significant differences in aerosol performance of salbutamol sulphate (measured as fine particle dose (FPD) and fraction (FPF) ≤ 5 μm) from the carriers were observed. Specifically, as carrier size increased FPF decreased. In comparison, as drug loading increased there was no change in FPF until a critical threshold was exceeded. Such observations suggest that: (A) aerosolisation performance is governed by carrier collisions and (B) when homogeneous carriers are used, the aerosol performance remains constant with respect to drug concentration, until the formulation transitions from an ordered mix to an agglomerated and/or segregated powder bed.

1. Introduction

Dry powder drugs which are used in inhalation therapy are generally low dose (i.e. 10 s or 100 s of μg) and have an aerodynamic diameter ~<5 μm. Consequently, these highly cohesive powders are commonly blended with a diluent and flow aid, such as coarse α-lactose monohydrate (which generally has a diameter of at least one order magnitude greater than that of the drug). When the drug is adhesive in nature these blended systems form an ordered mix (Hersey, 1975), where the smaller drug particles are preferentially adhered to the coarse material. When this occurs the dry powder formulation is often referred to as a carrier based system. During the inhalation manoeuvre, the energy imparted by the patient fluidises the carrier and the drug particles are liberated and inhaled. While the mechanism of drug particle liberation is not clear (although there is mounting evidence pointing towards carrier–carrier collision in the turbulent airstream (Ooi et al., 2011)), these systems are generally poor performing (it is not uncommon to have respirable drug fractions <40% (Smith and Parry-Billings, 2003)) and are highly sensitive to changes in morphology (Kawashima et al., 1998), chemistry/polymorphism (Traini et al., 2008), dose (de Boer et al., 2005; Dickhoff et al., 2003, 2005; El-Sabawi et al., 2006; Young et al., 2005a), and carrier diameter (Dickhoff et al., 2003; Donovan and Smyth, 2010; Guenette et al., 2009; Islam et al., 2004a; Ooi et al., 2011).

1.1. Theoretical considerations

Since the carrier used in these types of formulation are produced by bulk precipitation followed by size classification, the surfaces are heterogeneous, containing pits and crevices, different crystal facets and variable surface chemistry. It follows that the surface will contain regions of high and low adhesion which, during the dynamic process of blending, will result in the drug being deposited in areas with high adhesion; historically referred to as 'active sites'. Where the adhesion force is much greater than the energy imparted during inhalation, particles will remain adhered to the surface. Subsequently, at low drug loadings the aerosolised drug concentration

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doi:10.1016/j.ijpharm.2011.06.020

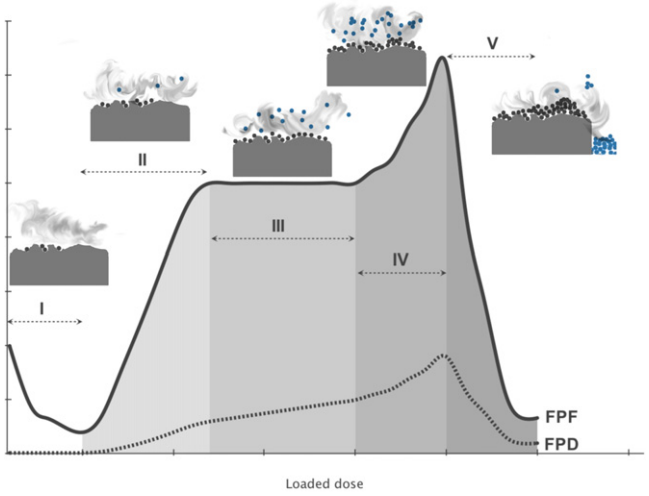

Fig. 1. Theoretical blend structure and influence on fine particle dose and fraction as a function of drug–carrier loading. (I) High adhesion site filling (adhesion ≫ aerosol energy), (II) filling of intermediate sites (adhesion ~ aerosol energy, (III) region of constant aerosol performance (adhesion ≪ aerosol energy), (IV) transition stage between (monolayer/multilayer particulate system with mixture of individual and agglomerated particles) and (V) multi-layer particle formation and formulation segregation.

will remain low. As the drug loading increases, the higher adhesion sites are preferentially filled followed by lower adhesion regions, resulting in a relative increase in aerosolised drug dose. These two potential mixing effects may be referred to as Type I and II regions and their effects on the aerosolised drug dose and fraction is hypothesised in Fig. 1. Indeed, previous studies have demonstrated the transition between Type I and II regions via dose titration of drug with carrier at high carrier:drug ratios (Young et al., 2005a). Furthermore, a study using an etched lactose carrier showed a reduction in this Type I region, suggesting a decrease in areas of high adhesion (i.e. surface crevices) resulted in higher performance at low drug loadings (El-Sabawi et al., 2006). As the drug loading is increased, it is envisaged that many of the remaining areas on the carrier surface will have significantly lower adhesion forces and constant aerosol performance will be reached (Type III regions where increased drug loading will result in a concurrent increase in aerosolised dose and constant aerosolised fraction; Figure 1). Indeed, previous studies have suggested a plateau in aerosol performance at higher drug loadings; however, this also appears to be dependent on the carrier size (de Boer et al., 2005; Dickhoff et al., 2003, 2005; Young et al., 2005a). As the drug loading is increased further it would be likely that multiple agglomerate systems are formed, as the available space on the carrier will approach a monolayer. As this Type IV region occurs, a further increase in performance would be expected to be observed since the 'effective' mass of the attached drug particles is increased due to multiplet formation. Finally, at very high drug loadings (Type V) it is envisaged that the formulation begins to fail due to mass agglomeration and formulation segregation.

It is important to note, that most pharmaceutical systems may also contain a significant amount of excipient fines of a similar size to that of the drug. The presence of these fines underpins the theoretical basis of agglomerate theory (Jones and Price, 2006), where micro-agglomerates are a dominating factor. Interestingly, the hypothetical model proposed here would take into account the agglomerate theory since the relatively high levels of fines studied in works by Adi et al., 2008; Islam et al., 2004b; Louey and Stewart, 2002; Young et al., 2007 would most likely place their formulations in a Type IV region.

1.2. Methodological approach

As part of an ongoing study, the authors focused on the blend structure and performance of an inhalation system containing model carriers with well-defined morphology and size. Polystyrene carriers of different sizes were used since they contained homogeneous and equivalent physico-chemical surfaces. These carriers were then blended with micronized drug in different ratios and the aerosolisation properties determined. Since the carriers had well defined surfaces it would be envisaged that the formulations would be devoid of Type I and II regions, studied previously. This allowed a fundamental study of carrier:drug ratio and carrier size effects without the complication of additional variables.

2. Materials and methods

2.1. Materials

Salbutamol sulphate was supplied by S & D Chemicals (Sydney, Australia) and was micronized using an air jet mill with N_2 gas supply, at a feed pressure 250 kPa and a grinding pressure of 680 kPa (Air Impact Pulveriser, Trost Equipment Corporation, USA). Model polystyrene sphere carriers (Dynoseeds® TS-80, TS-230 and TS-500) were supplied by Microbeads AS (Skedsmokorset, Norway) and used as received. Water was purified by reverse Osmosis (MilliQ, Molsheim, France) and all solvents were of analytical grade (Sigma, Sydney, NSW, Australia).

2.2. Preparation of carrier blends

Different formulations containing drug (salbutamol sulphate) and carrier (polystyrene beads) were prepared by varying the ratio of carrier to drug, with ratios used ranging from ~5:1 to ~85:1. Blends were prepared by hand; via geometric mixing using a spatula in a mortar receptacle, followed by Turbula mixing at 46 rev min^{-1} for 30 min (Bachofen AG Maschinenfabrik, Basel, Switzerland). All prepared blends were stored in tightly sealed containers at 25 °C and 45%RH for a minimum of 24 h prior to use.

Homogeneity of each blend was tested by sampling ten aliquots (50 ± 1 mg) from across the powder bed. Samples were dissolved into known volumes of mobile phase and analysed for salbutamol sulphate concentration by high performance liquid chromatography (HPLC, method described in Section 2.3).

2.3. Physico-chemical characterisation

The micronized salbutamol sulphate and carrier particle size distributions were measured by laser diffraction in isopropyl alcohol or water, respectively (Malvern Mastersizer 2000 equipped with small volume dispersion cell, Malvern, Worcestershire, UK). Approximately 10 mg samples of salbutamol sulphate or polystyrene carrier were dispersed in 15 ml and sonicated for 5 min prior to analysis before transferring drop wise to the dispersion cell until an obscuration between 2% and 5% was achieved. Refractive indices of 1.52 for salbutamol sulphate, 1.39 for isopropyl alcohol, 1.59 for polystyrene and 1.33 for water were used. Each measurement consisted of 2000 sweeps and each sample was tested in triplicate.

The surface morphology of the carrier particles and force of adhesion between drug and carrier was reported previously (Ooi et al., 2011). Briefly, morphology was determined using conventional tapping mode AFM while particle adhesion was achieved using colloid probe AFM. Individual micron sized salbutamol sulphate drug particles ($n = 3$) were attached to the apex of tipless cantilevers and the force of adhesion on each carrier measured over 10 μm × 10 μm areas ($n = 4096$ measurements per run).

The morphology and structure of each carrier:drug blend was investigated using field emission scanning electron microscopy at 5 keV. (SEM; Zeiss Ultra Plus, Carl Zeiss GmbH, Oberkochen, Germany). Prior to study, samples were deposited on sticky carbon tabs and gold coated (10 nm thickness) using a sputter coater (Edwards E306A Sputter Coater, UK).

Salbutamol sulphate drug concentrations, collected from *in vitro* deposition or content uniformity measurements, were quantified using HPLC. The system used was a Shimadzu Prominence UFLC system, consisting of an SPD-20A UV–vis detector, LC-20AT liquid chromatograph and SIL-20AHT autosampler (all Shimadzu Corporation, Japan) with a Waters Nova-Pak C18 4 μm 3.9 mm × 150 mm column (Waters Corporation, MA, USA). The mobile phase consisted of methanol:water at a ratio of 60:40 with 1% (w/v) sodium dodecyl sulphate (SDS). A flow rate of 1 ml min^{-1} and injection volume of 100 μl was used, which gave a retention time of 10 min (with peaks detected at a wavelength of 276 nm). Linearity was confirmed between 0.1 μg ml^{-1} and 100 μg ml^{-1} ($R^2 = 1$).

2.4. In vitro aerosol performance

The influence of carrier to drug ratio on the aerosolisation performance of salbutamol sulphate was conducted using a Multistage Liquid Impinger (MSLI) (Copley Scientific, Nottingham, UK). Methodology followed that of the British Pharmacopeia, detailed in Appendix XII C (2010 edition), allowing for quantitative analysis of the size–mass distribution of dry powder inhalable aerosols. Measurements were made at a constant flow rate of 60 l min^{-1} (set using a TSI 3063 calibrated flow meter; TSI Instruments Ltd., Bucks, UK), established using a GAST rotary vein pump and solenoid timer (Copley Scientific, Nottingham, UK). 20 ml of mobile phase was added to each stage of the MSLI. 50 ± 1 mg of each blend was placed into the sample compartment of a Rotahaler® DPI (GSK, UK) device, which was connected to a mouthpiece adapter inserted into the USP induction port of the MSLI before the apparatus was actuated for 4 s.

Following actuation, the four stages of the MSLI, Rotahaler®, mouthpiece adapter, induction port and filter stage were washed into suitable volumetric flasks using mobile phase and the salbutamol sulphate concentrations analysed by HPLC. Each blend was tested in triplicate, with tests performed in a randomised order, at room temperature and humidity of 21 °C and 45% RH.

3. Results and discussion

3.1. Physico-chemical characterisation

The physical properties of the polystyrene carriers have been studied previously and important parameters reported are summarised in Table 1. The particle size distributions of the polystyrene carriers and the micronized salbutamol sulphate are shown in Fig. 2. The median diameter ($d_{0.5}$) for the TS-80, TS-230 and TS-500 carriers were 82.8 μm, 277.5 μm and 582.9 μm, respectively. In comparison the $d_{0.5}$ the micronized salbutamol sulphate was 3.90 μm, approximately an order of magnitude less than the carrier diameter.

Table 1
Basic physical properties of the polystyrene carriers as measured previously (Ooi et al., 2011).

ID	TS-80	TS-230	TS-500
D_{10} (μm)	60.8	169.5	427.2
D_{50} μm	82.8	277.5	582.9
D_{90} μm	112.6	300.8	801.2
Density, ρ (g cm^{-3})	1.04 ± 0.01	1.05 ± 0.01 g cm^{-3}	1.03 ± 0.01
Roughness, R_{RMS} (nm)	112.0 ± 9.6	49.0 ± 3.0	109.67 ± 6.4

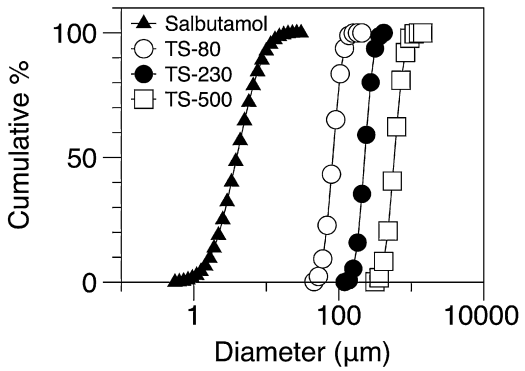

Fig. 2. Particle size distribution of the micronized salbutamol sulphate and polystyrene carriers.

The morphology the polystyrene carriers were smooth (≤112 nm) with coefficients of variations ≤9% for all samples ($n = 5$ for each carrier). It would be expected that the combination of a smooth surface with high homogeneity would result in relatively consistent adhesion values between the drug and carrier, across its surface. Indeed, colloid probe force measurements indicated normally distributed adhesion force values (as opposed to the wide log-normal distributions observed with heterogeneous surfaces (Young et al., 2009)) and a similar profile for each carrier type (Fig. 3). In general a mean adhesion force of 30.7 ± 15.4 nN was reported for the 3 drug probes across all 3 carriers. Statistical analysis of all three drug probes on each carrier surface suggested no significant difference in adhesion, suggesting that particle adhesion to each of the carriers in the formulated blends would be similar.

3.2. Blend homogeneity

Content uniformity of the blends is a good indicator of blend homogeneity and should be discussed with respect to the carrier:drug ratio studied, as well as carrier size. In general, the coefficient of variation (CV) was <10%. However, there was a trend for increasing CV with increased carrier size and higher drug loadings. For example the CV of the 50:1 carrier:drug blends were 4.7, 5.6 and 10% for the TS-80, TS230 and TS-500 carriers. In comparison, decreasing the ratio by a factor of 10 to 5:1 the CV increased to 9.54, 12.39 and 13.17% for TS-80, TS230 and TS-500 carriers (only at the highest drug loading was the CV ≥ 10%). Such observations suggest that, as the relative number of drug particles per carrier increases, it becomes increasingly difficult to make a homogeneous blend. Subsequently, at very high drug loadings the powder bed may contain localised pockets of drug material, possibly as segregated agglomerates.

3.3. Formulation entrainment efficiency

This study utilises a Rotahaler device. This device has a low-pressure drop and relies on airflow entrainment of a powder bed that rests at the base of the device. Subsequently, the initial aerosolisation and 'removal' of the powder from the device will play a major role with respect to the ultimate performance. When considering removal efficiency and aerosolisation performance it is also important to discuss this in terms of the device used. The removal of powder from the Rotahaler will be relatively fast and particle wall collisions will be low. In comparison, devices that incorporate pierced, spinning capsules and/or high-pressure drops may increase collision events with the device and internal sheer forces on the powder.

In order to compare formulation variables such as drug–carrier loading or carrier size it is important to consider the removal effi-

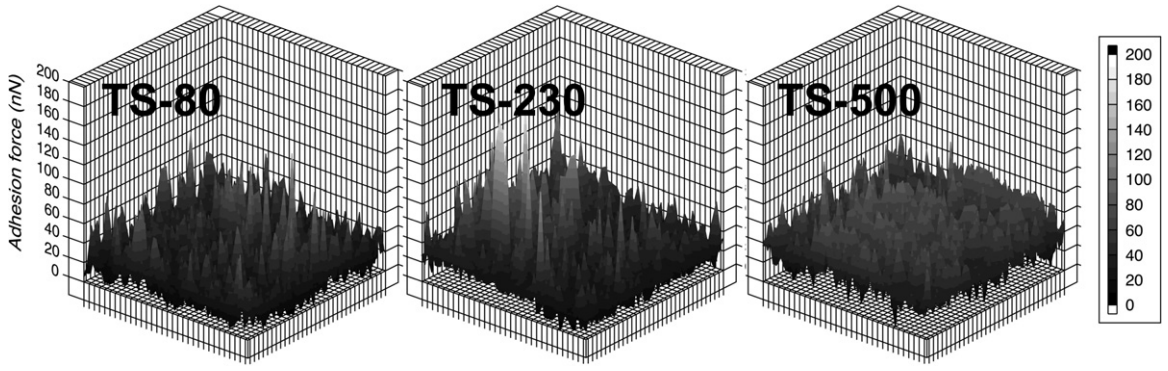

Fig. 3. Representative force of adhesion profiles (x and y axis represent 10 μm × 10 μm) of salbutamol sulphate colloid probe on each of the carrier particles.

ciency of the bulk formulation from the device. For example, if one formulation has a hypothetical drug emitted dose of 100% while a second formulation only has an emitted dose of 10%, one can conclude that the formulation variables studied have a significant impact on the powder bed entrainment mechanism within the device. In such cases, one must be careful since it becomes difficult to study the mechanism of drug aerosolisation due to, for instance, the majority of the carrier remaining in the device. To confidently compare variables such as carrier size and carrier:drug ratio it is important that the removal efficiency of the formulation from the device remains relatively constant. Fig. 4 is a plot of the emitted dose vs. loaded dose of all carrier:drug ratios for all carrier sizes. Emitted dose was defined as drug recovered from all stages of the MSLI and USP induction port while loaded dose was drug recovered from all MSLI stages, USP induction port and device components. Analysis of the data, suggested that for all carrier sizes there was a linear relationship between emitted dose and loaded dose ($R^2 \geq 0.973$), suggesting that regardless of the carrier:drug ratio, the same percentage of drug exited the device (either attached too or liberated from the carrier surface). Interestingly, the slope of emitted dose vs. loaded dose increased slightly with increasing carrier size (slope values of 0.617, 0.697 and 0.754 were observed for TS-80, TS-230 and TS-500 carriers, respectively). Such observations suggest that as the carrier size increased a concurrent increase in device emptying was observed from ~62% to ~75% for the carriers studied). This is presumably due to an increase in the carrier removal rather than drug liberation from the carrier surface, since the aerosol performance in the larger carriers was less.

3.4. Influence of carrier size on aerosol performance

As the carrier size increases, the number of carrier particles per formulation-mass will decrease; and the number of drug particles per carrier will increase. Furthermore, this increase in carrier size will result in an increase in momentum and reduced number of carrier–carrier and carrier–device collisions. The increase in momentum for larger carriers is likely to be the reason for the moderate increase in formulation removal efficiency. However, it is unlikely to be responsible for drug liberation and aerosolisation efficiency since the increase in carrier size was met with a concurrent decrease in drug aerosolisation performance for all formulations. A plot of the fine particle fraction (FPF; percentage of drug particles with an aerodynamic diameter ≤5 μm per total loaded dose) as a function of carrier diameter, for all carrier:drug ratios is plotted in Fig. 5. It can be seen in Fig. 5 that FPF decreased for all formulations as carrier size increased. Regression analysis of the data suggested this to be linear for all formulations, excluding the highest drug loading (5:1 blend), with similar slopes being observed (Table 2). It is proposed that for most formulations, the relationship between aerosol performance and size may be due to the number of carrier collisions rather than the force of collisions, with the smaller carriers being more numerous and having a greater powder density in the fluidised bed. The number of carriers per formulation will vary based on the size and drug formulation ratios, however, the number of particles will range from 100 s to 100,000 s between the two extremes. Direct calculation of the number of collisions is extremely difficult since one must consider each collision as a discrete process occurring in a airflow which is being modified via the position of particles in the powder bed. Future studies should consider computational fluid dynamic simulations coupled (two-way) with a discrete element model; however, currently this is beyond the limitations of conventional computational code.

It is important to note that the effect of press-on-forces during the blending process must be considered as a factor influencing

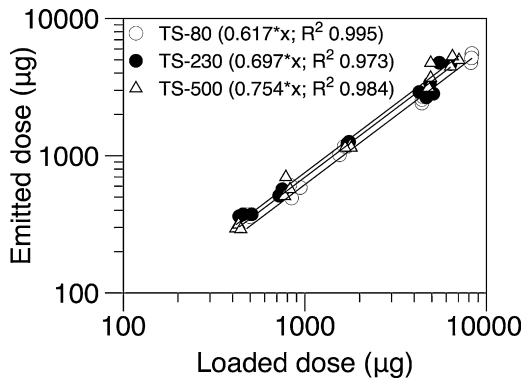

Fig. 4. Plot of emitted vs. loaded dose (including linear regression) for each carrier type.

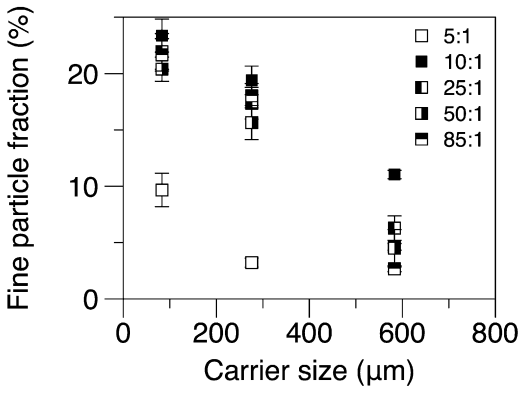

Fig. 5. Plot of fine particle fraction vs. carrier diameter for each formulation (formulation ratios are approximate to allow comparison).

Table 2
Regresion analysis of FPF vs. carrier diameter.

Nominal carrier:drug ratio	Regression analysis (y, FPF in %, x, carrier diameter in μm)	Regression coefficient (R^2)
85:1	$y = 26.39 - 0.039x$	0.978
50:1	$y = 23.62 - 0.032x$	0.995
25:1	$y = 23.62 - 0.032x$	0.995
10:1	$y = 25.75 - 0.025x$	0.997
5:1	$y = 8.586 - 0.087x$	0.651

aerosol performance. However, recent studies by Ooi et al. (2011) have suggested that press on forces may not play such a large role since the effect of carrier density on aerosolisation performance indicated no significant differences.

3.5. Influence of loaded dose on fine particle dose

Fine particle dose (FPD) is defined as the mass of particles with an aerodynamic diameter ≤5 μm, calculated from the MSLI mass deposition data. A plot of FPD vs. loaded dose for the TS-80, TS-230 and TS-500 carrier sizes is shown in Fig. 6A–C respectively. Analysis of the data suggests that in each formulation there was an increase in FPD as loaded dose was increased, up to a point before a decrease was observed. Analysis of the TS-80 and TS-230 suggested this increase to be linear up to ~10:1 carrier ratio formulation (where R^2 and slopes were $R^2 = 0.99$; $b = 0.23$ and $R^2 = 0.99$; $b = 0.19$ for TS-80 and TS-230, respectively). Such observations highlight two critical aspects with respect to these formulations. Firstly, the difference in slope between TS-80 and TS-230 indicate that TS-80 has a greater aerosol performance than TS-230. Secondly, the high regression coefficient across this range suggests the aerosolisation efficiency of each formulation remains constant with respect to carrier:drug ratio. Analysis of the TS-500 carrier formulation showed similar results, however, a lower regression coefficient (due to due deviation from linearity at a higher drug loading) and smaller slope (i.e. lower aerosol performance) were observed ($R^2 = 0.95$, $b = 0.10$).

3.5.1. FPD at low drug loadings and the presence of 'active sites'

Previous reports have suggested that, in conventional lactose based carrier systems, non-linearity between FPD and loaded dose is observed at high carrier:drug ratios (i.e. at low drug loading) (El-Sabawi et al., 2006; Young et al., 2005b). Such observations have been attributed to the presence of 'active sites', where increased drug loading results in little or no increase in FPD. These 'active sites' may be morphological or chemical features on the carrier surface where drug preferentially adheres during the blending process. The adhesion of particles in these areas is greater than that energy input during inspiration and therefore the particles remain attached. Subsequently, little or no increase in FPD is observed until areas of high adhesion are overcome. A later study showed that this region of non-linearity in FPD could be reduced if the lactose surface irregularities were removed (El-Sabawi et al., 2006). In the current study, linear regression of FPD vs. loaded dose at low drug loadings resulted in high R^2 values with the intercept passing through zero. This observation substantiates the theory of preferential drug adherence via 'active sites' since the model carriers were free from surface irregularities and had a low variation in drug–carrier adhesion, measured via colloid probe microscopy.

3.5.2. FPD at high drug loadings and the presence of agglomerated drug

At high drug loadings non-linearity occurs with respect to loaded dose. In an ideal ordered mix, where drug–carrier adhesion is constant across the carrier surface, a linear increase in drug loading should be met with a concurrent increase in FPD.

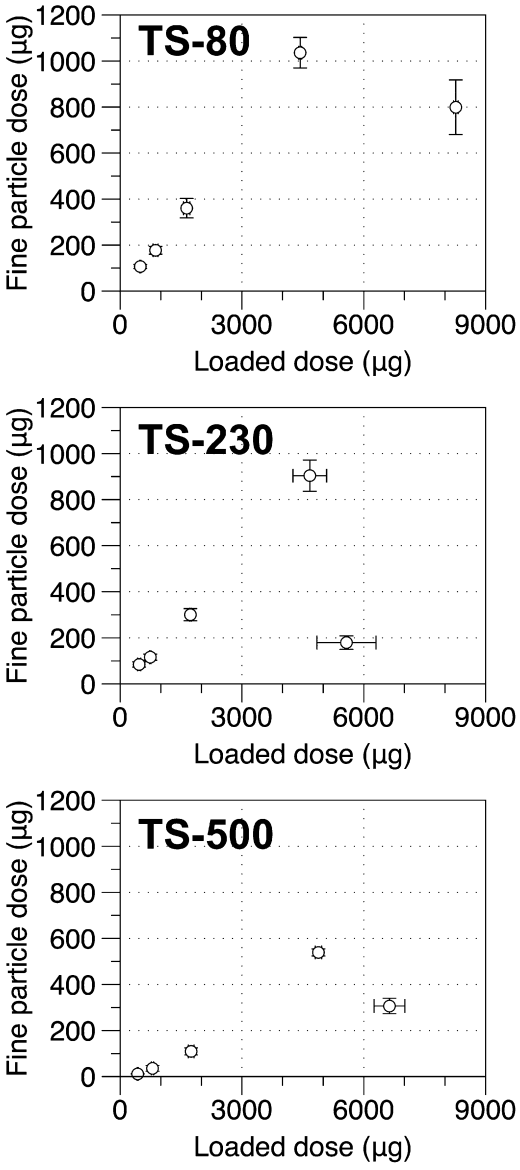

Fig. 6. Plot of fine particle dose vs. loaded dose for each carrier type (error bars indicate standard deviations; $n = 3$).

However, it is important to consider drug–drug adhesion as well as drug carrier adhesion. While previous studies have reported this to be an adhesive system (via observation by SEM (Ooi et al., 2011)), as the carrier:drug ratio is decreased the number of drug particles will approach, and in some cases, exceed monolayer coverage. As the ratios of drug to carrier become large it is envisaged that a transition exists from an ordered mix, via drug agglomeration, to drug carrier segregation. The deviation from linearity at high drug loadings accompanied with the increase in CV, observed in content uniformity measurements (Section 3.2), to some extent, agrees with such a hypothesis.

3.5.3. Influence of loaded dose on fine particle fraction

The FPF may be defined as the overall efficiency of the carrier system at liberating drug during the aerosolisation process. From Section 3.3, it is clear that there is a direct linear relationship between FPD and loaded dose, at low drug loadings. This is reflected in the FPF, where no significant change in aerosolisation perfor-

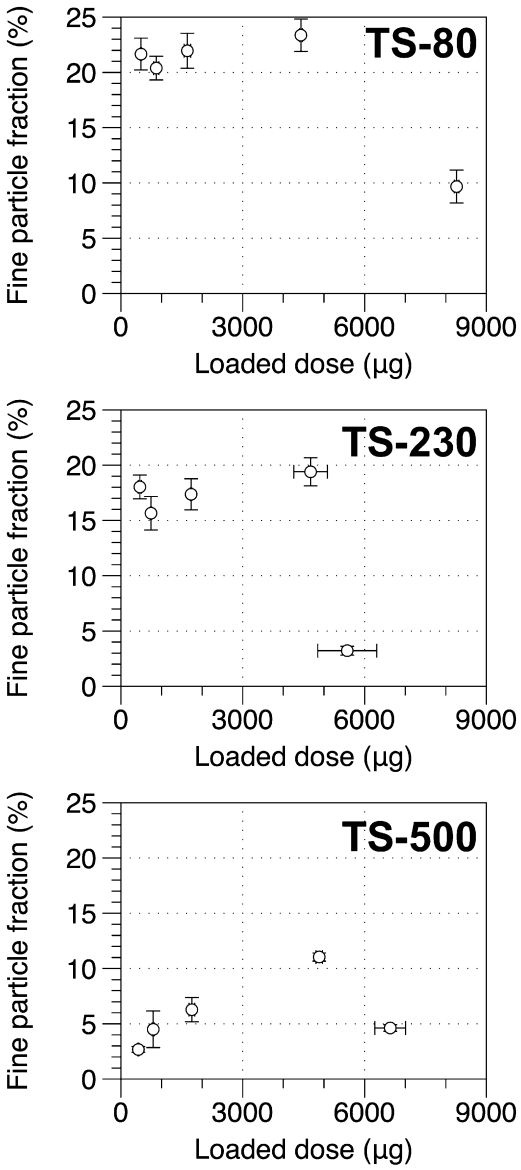

Fig. 7. Plot of fine particle fraction vs. loaded dose for each carrier type (error bars indicate standard deviations; $n = 3$).

mance was observed at high carrier:drug ratios (Type III region), for the TS-80 and TS-230 formulations (Fig. 7A and B, respectively). As the loaded dose was increased, it appears that there is a slight increase in FPF (~10:1 was significant for TS-230) followed by a significant decrease in FPF at ~5:1). Such a dramatic change must be due to a fundamental transformation in the formulation structure. This is most likely a 'drug–carrier-agglomerate-segregation' (Type III–IV–V region) transition. For the TS-500 formulations (Fig. 7C) this was even more apparent at low loaded dose values (i.e. high carrier:drug ratios) where the relative number of particles is likely to be high enough to exceed monolayer coverage at an earlier stage. To understand the potential transition, it is important to consider the theoretical number of drug particles with respect loaded dose and carrier size.

3.6. Theoretical considerations of blend structure and its relationship to aerosol performance and blend structure

The theoretical number of drug particles per carrier and the drug–carrier surface coverage, at different drug:carrier ratios can

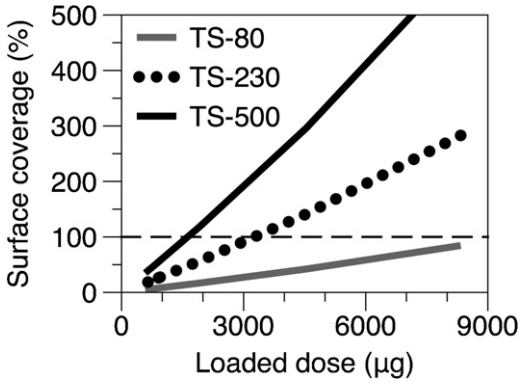

Fig. 8. Theoretical surface coverage of drug on each carrier.

be calculated from the $d_{0.5}$ and densities of each formulation component using Eq. (1):

$$\%\,\text{coverage} = \frac{\pi r^2 n_{\text{drug}}}{4\pi r^2} \times 100 \quad (1)$$

where n_{drug} is the theoretical number of drug particles per carrier calculated from Eq. (2):

$$n_{\text{drug}} = \frac{m_{\text{drug}}/1.33\pi r^3 \rho_{\text{drug}}}{m_{\text{carrier}}/1.33\pi r^3 \rho_{\text{carrier}}} \quad (2)$$

where m represents the mass of either drug or carrier present in the formulation at a given carrier:drug ratio. While only theoretical, this approach allows comparison with the fine particle dose and fractions, reported in Figs. 6 and 7, respectively. The theoretical surface coverage for each carrier type (based on a 50 mg formulation mass) is plotted against loaded dose and is shown in Fig. 8.

For TS-80, the theoretical surface coverage of drug ranges from 5% to 85% across the dose range studied. This equated to ~100–1500 particles per carrier. In comparison, the larger TS-230 carrier had between ~3000 and 60,000 drug particles per carrier across the dose range studied. While the theoretical surface coverage was less than 100% at lower drug loadings, as this increased, the surface coverage exceeded 100% (at ratios ≤10:1 with 280% at a carrier:drug ratio of 5:1). TS-500 exceeded the monolayer threshold at all but two doses studied. Such observations may explain the deviation from linearity at high drug loadings since the formulation will transition from a simple drug coating to a multi-particulate layered system; where the drug agglomerates and, in extreme cases, segregates.

By comparing the theoretical coverage (Fig. 8) to the FPD (Fig. 6) and FPF (Fig. 7) it can be seen that the significant changes in formulation behaviour occurs as the drug coverage approaches or exceeds 100%. To further study this theory, SEM images were taken of each formulation to assess the blend structure. Scanning electron micrographs of each carrier type at the highest (~5:1) and lowest (~85:1) drug loadings are shown in Fig. 9 (images were scaled so that magnification was equivalent). It can be seen that for the lowest drug loading, all formulations contained evenly distributed drug across the surface of the carrier as would be expected of an ordered mix. In this case no independent drug–drug agglomerates were observed. In comparison, the highest drug loading resulted in either large multilayer particulate systems (as can be seen in the TS-500 image) or agglomerates (as in the TS-80 image). These agglomerates maybe preferentially produced as a multilayer, which are subsequently detached during blending. Such agglomerated/multilayer particulate systems are likely to have significantly different aerosol performance than the sub-monolayer ordered

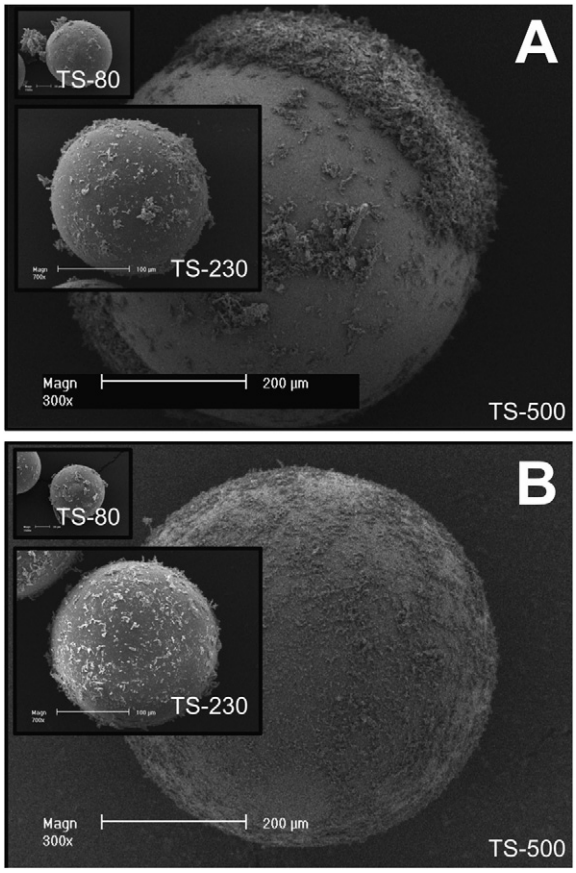

Fig. 9. Scanning electron microscopy images of (A) 5:1 and (B) 85:1 carrier:drug blends. Images sizes adjusted to same scale.

mixes (as observed in the change in aerosol performance and blend uniformity).

4. Conclusions

This study has shown that aerosol performance of drug from ordered mixes is independent of drug loading (i.e. drug:carrier ratio), when the drug to carrier surface coverage is less than a monolayer. As the monolayer is approached, the formulation undergoes a transition to an agglomerated system, where increased performance is observed. At very high drug loadings this agglomerated system transitions to a segregated system with a concurrent catastrophic decrease in performance. It is important to note that this study utilises model particles that contain no fines. In adhesive systems, these fines must be considered along with the drug particles and may influence the monolayer coverage. In addition, preferential binding to fines may result in a more complex mechanism than described here. Furthermore, this model is based on an 'adhesive' drug–carrier system. When the force of cohesion between drug particles becomes greater than that of the drug–carrier adhesion, the model may no longer be suitable. It is speculated that in such cases an agglomerated system is likely to become more dominant. This study has also shown carrier size directly influences performance; with larger carriers resulting in poorer performance. It is speculated that this phenomena may be due to the number of carrier particles present in the formulation and the resulting number of collisions during aerosolisation. Finally it is important to note this study was conducted using a device that relies on the aerosolisation of a powder bed followed through a low-pressure drop device. Future studies should consider devices with addition dispersion mechanisms such as spinning capsules, high-pressure drops and tortuous exit orifices.

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