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Expert Review

The Influence of Fine Excipient Particles on the Performance of Carrier-Based Dry Powder Inhalation Formulations

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Abstract. The inclusion of a small amount of fine particle excipient in a carrier-based dry powder inhalation system is a well researched technique to improve formulation performance and is employed in the pharmaceutical industry. The removal of intrinsic fines from a lactose carrier has been found to decrease formulation performance, whereas adding fines of many different materials into formulations increased performance. Changing the particle size of these fines, the amount added and the technique by which they were prepared also affected formulation behaviour. Despite this body of research, there is disagreement as to the mechanism by which fines improved formulation performance, with two main hypotheses presented in the literature. The first hypothesis suggested that fines prevent the drug from adhering to the strongest binding sites on the carrier, whilst the second proposed that fine particles of drug and excipient form mixed agglomerates that are more easily dispersed and deaggregated during aerosolisation. The evidence in support of each hypothesis is limited and it is clear that future research should aim to produce stronger mechanistic evidence. The investigation of interparticulate interactions using techniques such as atomic force microscopy and inverse gas chromatography may prove useful in achieving this aim.

KEY WORDS: dry powder inhaler; fines; fine particle excipient; ternary interactive mixtures.

INTRODUCTION

Three factors govern the amount of inhalable drug delivered by a dry powder inhaler (DPI)—the patient's inspiratory manoeuvre, the design of the inhaler device and the formulation it contains (1). Carrier-based dry powder formulations can be modified in many different ways in order to optimise drug delivery (1). One such method that has been researched extensively in the last 10–15 years is the inclusion of a small amount of fine particle excipient ("fines") within the powder blend, in addition to the coarse carrier and fine drug particles, to produce what is known as a ternary formulation (as opposed to a binary formulation, which contains only coarse carrier and drug). This review considers this work, comparing and contrasting the findings of the different workers who have investigated various facets of the area.

One of the challenges in reviewing DPI research is the diverse methodology employed by different workers. Different materials, mixing processes, inhaler devices and aerosolisation conditions are all known to have a dramatic effect on formulation performance (2) and no two research groups employ methods in which all such factors are standardised. The details of many of these variables, as used in the cited research, are therefore tabulated, to enable the reader to consider such effects. It is striking, however, that many of the effects of fines are found to be consistent across a variety of research methodologies.

REMOVING INTRINSIC FINE PARTICLES FROM A LACTOSE CARRIER

In order to allow a more accurate quantification of the effects of adding fines to a formulation, a number of studies have incorporated pre-treatment of a coarse lactose carrier to remove any pre-existing ("intrinsic") fine particles, by either air-jet sieving (3–7), air washing lactose held on a sieve (8–10) or wet decantation with lactose saturated ethanol (11,12). In all cases, such treatment was found to decrease the performance of formulations containing a variety of different drugs, which were blended by different techniques and aerosolised from different inhalers. Such results are in accordance with the findings of a number of studies which, when using various grades of carrier material, found that those containing the highest proportion of intrinsic fines gave the greatest performance (6,7,13–15), although one study found this was dependent on the type of inhaler used (14).

The work of Islam *et al.*, examined binary blends of salmeterol xinafoate with various grades of carrier lactose (11,12). As the proportion of lactose particles <5 μm diameter in the carrier material increased, there was a concomitant increase in the fine particle fraction (FPF) of the formulation, to a maximum when the intrinsic fine lactose

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proportion was ~15%; further increases did not produce improved performance (11). Wet decantation was then employed to remove the fines from two grades of carrier, which resulted in a decrease in the FPF (11,12). A significant correlation was established between the FPF of salmeterol xinafoate and the proportion of fine lactose particles in the carrier material. A similar relationship was seen for all the various grades of lactose used and treatments applied to them, suggesting that the proportion of fine lactose in the formulations was the key factor controlling performance and that carrier lactose particle size and surface characteristics are less important (11).

When considering the results of these studies, the possibility that the removal of intrinsic fines might induce other changes in the carrier material should be borne in mind. For example, air-jet sieving or air washing might lead to triboelectric charging of the lactose, which has been shown to decrease DPI performance (16). Although lactose is practically insoluble in ethanol (17), wet decantation might have induced surface changes in the coarse particles, for example the recrystallisation of amorphous regions or micro-scale morphological changes. These possible confounding factors were not investigated or discussed by the original authors. The consistent finding that the removal of fines, by whatever mechanism, results in decreased performance lends credence to the hypothesis that this is caused by reducing the proportion of intrinsic fines, however.

ADDING LACTOSE FINES TO A FORMULATION

The majority of research in this area has focused on the addition of lactose fines to blends of coarse lactose (typically a 63–90 μm size fraction) and drug (3–6,8–12,18–37). The fine lactose used in these investigations typically had a volume median diameter (VMD) of 4–7 μm and the proportion added was typically in the range 1.5 to 10%, but proportions as high as 95% have been investigated (20,25,27,28). Further details of these studies are given in Table I. Although salbutamol sulphate has been the most frequently investigated drug, a number of other drugs have also used: beclomethasone dipropionate (5,29), bovine serum albumin (3,4), budesonide (23,37), formoterol fumarate dihydrate (37), glucagon (33), liposomal amikacin (30), liposomal amphotericin B (31,32), salmeterol xinafoate (11,12,20,26,28,35,36) and a candidate NK1 receptor antagonist (FK888) (27).

Most of this research has made use of *in vitro* measurements of formulation performance and the vast majority of this has found that the addition of lactose fines increases (by varying magnitudes) either the fine particle dose (FPD) or FPF of the drug (3–6,8–12,18,22–33,35,37) (see Table I). The evidence from these *in vitro* studies is supported by data from one *in vivo* study, which found that the inclusion of lactose fines in a salbutamol sulphate carrier-based formulation increased both the urinary excretion of the drug and the post-administration forced expiratory volume in one second (FEV_1) (21). Increases in both of these parameters suggest increased pulmonary delivery of the drug.

Two of these studies should not be mentioned without a caveat relating to the types of lactose used as carrier (Sorbolac 400, Meggle, Germany) and fines (25 μm sieved Pharmatose 325M, DMV International, The Netherlands) (31,32,38). Sorbolac 400 is more usually used as fines and is described by its manufacturer as a fine milled lactose with ≥90% of particles <32 μm diameter (39). Pharmatose 325M, however, is usually used as a coarse carrier and has a typical particle size distribution of $d_{10\%}$ = 5.0 μm, $d_{50\%}$ = 54.3 μm and $d_{90\%}$ = 95.9 μm (25). This suggests, therefore, that even when sieved through a 25 μm sieve, the Pharmatose 325M used as fines in this work (31,32) would have had a similar, if not larger, particle size than the Sorbolac 400 used as carrier. Unfortunately, no particle size data is provided in either study to clarify this issue and so the comparability of these studies with the majority of research in this field is questionable.

NON-LACTOSE FINES

The effect of non-lactose fine excipients on the performance of ternary formulations has also been investigated. Fines of erythritol (37), glucose (24,35,40), mannitol (6,35,37), polyethylene glycol 6000 (4), sorbitol (6,35) and trehalose (37) have all been found to increase either the FPD or FPF of a variety of drugs when added to a binary formulation (see Tables II and III for further details). When directly compared, fines of different materials have produced varying increases in formulation performance compared to each other and to lactose fines, with lactose fines producing poorer, equal and better performance in various studies (see Table II).

One of these studies also examined the deposition of lactose and glucose from formulations containing fines of one of these sugars, salbutamol sulphate and a coarse lactose carrier (24). Unsurprisingly, addition of increasing quantities of lactose fines was found to increase the FPD of lactose and addition of increasing quantities of glucose fines produced an increased glucose FPD. Addition of glucose fines also increased the lactose FPD however, whilst binary blends of micronised salbutamol sulphate and coarse lactose produced a higher lactose FPD than aerosolisation of the coarse lactose carrier alone. The authors attribute these latter unexpected effects to destabilisation of the interaction between coarse and intrinsic fine lactose particles by the addition of fine particles of another material.

Such findings are in accordance with work published by Zeng *et al.* (10), who were unable to detect any lactose with an aerodynamic diameter <6.18 μm upon aerosolisation of a formulation of air washed coarse lactose and salbutamol sulphate, even though 8% of the carrier consisted of particles in this size range. The authors suggested that as the coarse lactose had undergone air washing, the remaining fines would have been strongly adhered to larger particles and thus would not have detached upon aerosolisation. When 1.5% lactose fines (VMD = 5 μm) were included in the formulation however, up to 1.7% of the recovered lactose had an aerodynamic diameter <6.18 μm.

VARYING THE AMOUNT OF FINES ADDED TO A FORMULATION

A number of studies have investigated the effects of varying the concentration of fines added to a formulation. Over the range 1.5 to 10%, the addition of greater proportions of fines was found to increase the FPD or FPF of the drug (3,4,6,8,21,24,25,40). Estimates of the optimum concentration

of fines have varied from 9 or 10% (25,30–33) *via* 16% (40), 20% (28,41) and 37.5% (27) to 50% (40), with concentrations as high as 95% having been investigated (25). Such variation can presumably be attributed to the different materials and methods used in these studies. Work by Stewart *et al.*, with lactose-based salmeterol xinafoate binary formulations (26) and by Islam *et al.*, with similar ternary formulations (11) suggested that the optimum FPF occurs when the ratio of drug particles to fine excipient particles is 1. As the ratio increases, FPF decreases.

FINE LACTOSE PREPARATION TECHNIQUE

In a study published in 2001, Zeng *et al.*, investigated the effect of the method used to produce lactose fines on the performance of ternary formulations (22). Both micronised and recrystallised lactose fines (VMD = 5.0 and 5.9 μm, respectively) were found to increase the FPD of salbutamol sulphate compared to a binary formulation, with recrystallised fines producing a greater increase (51%) than micronised fines (35%).

The authors speculate that this difference could be due to two factors, the presumed presence of amorphous material in the micronised fines (to which drug particles would be expected to bind more strongly) and the needle-like particle shape of the recrystallised fines. Consequently, it was speculated, upon aerosolisation, a greater number of salbutamol sulphate particles might have detached from the recrystallised fines than from the micronised fines and that any drug which did not detach from the recrystallised fines might have penetrated further into the lung, due to the crystal habit of these fines.

These authors also concluded that the effects of lactose fines (particles <10 μm diameter) on formulation performance dominated any influence that coarse carrier particle size or roughness may have had. Similar conclusions have been drawn by Stewart *et al.* (26).

PARTICLE SIZE OF FINE LACTOSE

Zeng *et al.*, investigated the influence of the size of lactose fines on the performance of ternary formulations and found that fines with a VMD of 5.0 μm produced a greater increase in the FPD of salbutamol sulphate than those with a VMD of 15.9 μm (8–10). Similar work by Adi *et al.*, employed fines of four different particle size ranges (<5, 5–10, 10–20 and 20–45 μm) and found that those with a median diameter of 5.5 μm gave the greatest FPF of salmeterol xinafoate (28).

In another study, Adi *et al.*, examined the effects of lactose fines with four different median diameters on the performance of formulations of salmeterol xinafoate (36,41). It was found that fines with a VMD of 7.9 μm gave greater performance than fines with VMDs of 3.0, 17.7 and 33.3 μm. Analysis of scanning electron micrographs (SEMs) of these formulations suggested that 7.9 μm fines gave the greatest degree of drug particle detachment from the carrier, whilst 3.0 μm fines led to the formation of multilayers and agglomerates covering the carrier and the two larger fractions acted as secondary carriers, with drug particles adhered to their surface.

THE EFFECT OF FINES ON DRUG RETENTION IN THE INHALER DEVICE

In addition to their effects FPD or FPF, fines have also been found to both increase (6,9,10,22,42–44), decrease (6) or not effect (3–5,24) the proportion of drug retained in the inhaler after aerosolisation. It is therefore apparent that this effect is dependant upon both the materials and methods used. Where the addition of fines to a formulation has been found to increase the amount of drug retention in the device, the effect has been attributed to either the decreased flowability of powders containing a higher proportion of fine particles (6,44) (such an effect on flowability has been observed by other workers (4)) or to the increased adhesiveness of fine particles, due to their increased true contact area (42). As the increased adhesiveness of fine particles is thought to cause their poor flowability (45), these two explanations can be considered to describe the same phenomenon.

THE EFFECTS OF LACTOSE FINES ON DRUG-CARRIER ADHESION

In 1998, Podczeck described the use of a centrifuge technique to assess the adhesion between salmeterol xinafoate and various lactose carriers produced by blending fine, medium and coarse grades of lactose to give differing particle size distributions (20). An increasing proportion of fines in the carrier was found to produce large increases in the adhesion force. Podczeck concluded that this was related to the large increase in the total surface area of the carrier (and thus contact area between drug and excipient) caused by increasing the proportion of fines. The findings of this work are very different to those of Lord and Staniforth (19), however. Using a different centrifuge technique, these workers found that inclusion of increasing concentrations of lactose fines (VMD = 12.6 μm) in a blend of 0.8% salbutamol sulphate and coarse lactose resulted in decreasing adhesion between the drug and carrier. Clearly more work is required to fully characterise the variables that influence the effect that fine particles have on the adhesion between drug and carrier.

THE MECHANISM BY WHICH FINES IMPROVE FORMULATION PERFORMANCE

There is disagreement in the literature as to the mechanism by which fines improve the performance of carrier-based DPI formulations. Broadly speaking, two different mechanisms have been proposed, each with some supporting empirical evidence, but they remain speculative. In the following two sections, each hypothesis and its supporting evidence, as described by its proponents, are reported.

Hypothesis 1: The Occupation of Areas of High Adhesion by Fine Excipient Particles

Early work in this area (1,8,19,46) explained the effects of fines by reference to the work of Hersey on the interactions between coarse and fine particles in the formation of ordered mixtures (47). It was proposed that fine excipient particles preferentially bind to the areas on the surface of the coarse carrier with the strongest binding

Table I. Details of Investigations into the Effects of Lactose Fines on the Performance of Carrier-Based DPI Formulations

Reference	Drug	Coarse carrier	Fine lactose median diameter (μm)
Zeng *et al.* (1996) (8)	Salbutamol sulphate 1.5%	Lactose 63–90 μm	4.96
Lord & Staniforth (1996) (19)	Salbutamol sulphate 0.8%	Lactose (VMD = 65.6 μm)	12.6
Zeng *et al.* (1996) (8)	Salbutamol sulphate 1.5%	Lactose 63–90 μm	4.96 & 15.93
Lucas *et al.* (1998) (3)	BSA 2.0% or salbutamol sulphate 2.0%	Lactose 63–90 μm	5.4
Zeng *et al.* (1998) (9)	Salbutamol sulphate 1.5%	Lactose 63–90 μm	5.0 & 15.9
Lucas *et al.* (1998) (3)	BSA 2.0%	Lactose 63–90 μm	5.4
Podczeck (1998) (20)	Salmeterol xinafoate 0.2%	Lactose 20–70 μm and/or ≥70 μm	3.1, 6.1 & 2.6
Zeng *et al.* (1999) (10)	Salbutamol sulphate 1.5%	Lactose 63–90 μm	5 & 15.9
Zeng *et al.* (2000) (5)	Beclomethasone dipropionate 1.5%	Lactose 63–90 μm	7
Tee *et al.* (2000) (6)	Salbutamol sulphate 1.5%	Lactose, mannitol or sorbitol 63–90 μm	7.10
Tee *et al.* (2001) (21)	Salbutamol sulphate 1.5%	Lactose	?
Zeng *et al.* (2001) (22)	Salbutamol sulphate 1.5%	Lactose <63 μm & 63–90 μm	5 & 5.9
Harjunen *et al.* (2002) (23)	Budesonide 6.2%	Spray dried lactose (VMD = 122 μm)	?
Louey and Stewart (2002) (24)	Salbutamol sulphate 1–10%	Lactose	4.0
Louey *et al.* (2003) (25)	Salbutamol sulphate 2.5% & 5%	Lactose	4.0
Stewart *et al.* (2003) (26)	Salmeterol xinafoate 2.5%	Lactose	N/A
Nakate *et al.* (2004) (27)	FK888 12.5%	Pharmatose 325M	6.7
Adi *et al.* (2004) (28)	Salmeterol xinafoate 2.5%	Inhalac 120	4 sizes. Best 5.5 μm
Islam *et al.* (2004) (11)	Salmeterol xinafoate 2.5%	Lactose	4.0
Islam *et al.* (2004) (12)	Salmeterol xinafoate 2.5%	Lactose	<5
Gilani *et al.* (2004) (29)	Beclomethasone dipropionate 1.5%	Pharmatose 325M	4.9
Hartmann and Steckel (2004) (34)	Salbutamol sulphate 0.1% & 0.9%	Respitose SV003	?
Shah and Misra (2004) (30)	Liposomal amikacin 17%	63–90 μm Pharmatose 325M	?
Shah and Misra (2004) (31)	Liposomal amphotericin B 14%	Sorbolac 400	25 μm sieved Pharmatose 325M
Shah and Misra (2004) (32)	Liposomal amphotericin B 14%	Sorbolac 400	25 μm sieved Pharmatose 325M
Endo *et al.* (2005) (33)	Glucagon 1:100	Lactose or erythritol	2.5
Adi *et al.* (2005) (35)	Salmeterol xinafoate 2.5%	Glucose, lactose, mannitol or sorbitol 106–180 μm	?
Adi *et al.* (2005) (36)	Salmeterol xinafoate	Inhalac 120	3.0, 7.9, 17.7 & 33.3
Jones *et al.* (2005) (37)	Budesonide 1.5%, formoterol fumarate dihydrate 1.5%, drug A 1.5% or drug B 1.5%	Lactose 63–90 μm	6.2 μm

characteristics, thus forcing drug particles to bind to areas with weaker binding characteristics (see Fig. 1). On inspiration, drug particles are therefore more easily liberated from the surface of carrier particles, increasing the proportion of drug available for inhalation.

Zeng *et al.*, have speculated that their studies of the effect on formulation performance of the order in which carrier, drug and fines are blended provide evidence to support this hypothesis (5,8,10,18). These found that formulations produced by blending the coarse carrier and fines before adding the drug (thus giving the fines the first opportunity to bind to areas of high adhesion on the carrier, see Fig. 2A) gave greater performance than formulations produced by blending the coarse carrier and drug first (thus giving the drug particles the first opportunity to bind to areas of high adhesion on the carrier, see Fig. 2B). The magnitude of this effect ranged between a 60 and 70% increase in FPD, although this was reduced when aerosolisation occurred at higher flow rates (8,10). The other possible blending order (drug and fine excipient particles before addition of coarse carrier) tended to yield an intermediate FPD. An identical interpretation of similar data is also found in the work of Shah and Misra (30,32).

Zeng *et al.*, also examined the effect of blending order on the FPD of lactose produced by ternary formulations (10). The formulation produced by first blending salbutamol sulphate and coarse lactose (where fine lactose might be unable to adhere to the strongest binding sites as they are

Table I. Continued.

Percentage of fine lactose added	Performance assessed by	Inhaler used	Fine lactose median diameter (μm)	Control formulation	Influence of additional fine lactose
6.0	TSI	Rotahaler®	60	Carrier + drug	FPF ↑ by up to 116%
1, 2, 4, 8 & 16	Centrifugal adhesion force	N/A	N/A	Carrier + drug	↓ adhesion force
1.5, 3.0, 6.0 & 9.0	TSI	Rotahaler®	60 & 90	Air-jet treated carrier + drug	FPF ↑ by up to 161%
2.5, 5.0, 7.5 & 10.0	TSI	Diskhaler®	60	AJS carrier + drug	FPD ↑ by up to 101%
1.5%	TSI	Rotahaler®	60	Air-jet treated carrier + drug	FPD ↑ by up to 148%
2.5, 5.0, 7.5 & 10.0	TSI	Diskhaler®	60	AJS carrier + drug	FPD ↑ by up to 60%
10, 20 & 30	Centrifugal adhesion force	N/A	N/A	Carrier + drug	↑ adhesion force
1.5	TSI & ACI	Rotahaler®	60 & 90	Air-jet treated carrier + drug	FPD ↑ by up to 104%
2.5 & 5	TSI	Rotahaler®	60	AJS carrier + drug	FPD ↑ by up to 1781%
1.5 & 4.4	TSI	Rotahaler®	60	AJS carrier & drug	FPD ↑ by up to 150%
4.4	*In vivo*	Cyclohaler®	N/A	Carrier + drug	Urinary salbutamol excretion ↑ 228%. ↑ FEV_1
5	ACI	Rotahaler®	60	Carrier + drug	FPD ↑ by up to 51%
4.8	ACI	Taifun®	28.3	Carrier + drug	FPF ↑ by up to 244%
1, 5 & 10	TSI	Rotahaler®	60	Carrier + drug	FPF ↑ by up to 250%
5–95	TSI	Rotahaler®	60	Carrier + drug	FPF ↑ by up to 92%
N/A	TSI	Rotahaler®	60	N/A	N/A
12.5–62.5%	TSI	Spinhaler®	60	Carrier + drug	FPF ↑ by up to176%
1–20%	TSI	Rotahaler®		Carrier + drug	FPF ↑
To original	TSI	Rotahaler®	60	Carrier minus fines + drug	FPF ↑ to original level
To original	TSI	Rotahaler®	60	Carrier minus fines + drug	FPF ↑ to original level
2.5	TSI	Spinhaler®	60	Carrier + drug	FPF ↑ by 40% (not significant)
2	NGI	FlowCaps®	31	Carrier + drug	FPF ↑ by up to 34%
5, 10 & 15	TSI	Rotahaler®	60	Carrier + drug	FPF ↑ by up to 126%
5, 10 & 15	TSI	Rotahaler®	60	Sorbolac 400 + drug	FPF ↑ by up to 29%
5, 10 & 15	TSI	Rotahaler®	60	Sorbolac 400 + drug	FPF ↑ by up to 48%
9, ~17 & 33	ACI	Jethaler®	28.3	None	–
10	TSI	Rotahaler®	60	Carrier + drug	FPF ↑
Varying	TSI	Rotahaler®	60	?	FPF ↑
10	NGI	Rotahaler®	60	Carrier + drug	FPD ↑ by up to 203%

ACI Andersen cascade impactor, *AJS* air jet sieved, *BSA* bovine serum albumin, *FEV_1* forced expiratory volume in one second, *FPD* fine particle dose, *FPF* fine particle fraction, *N/A* not applicable, *NGI* next generation impactor, *TSI* twin stage impinger

occupied by drug particles, see Fig. 2B) produced double the lactose FPD of the formulation produced by blending coarse and fine lactose first (where fine lactose might be expected to adhere to the strongest binding sites, see Fig. 2A). The authors concluded that this provides further evidence in support of the passivation of strong binding sites hypothesis.

Zeng *et al.*, have also found that addition of a small amount of lactose fines (just enough to produce a complete mono-layer over the coarse carrier material) to a formulation of salbutamol sulphate and coarse lactose produced a larger increase in the FPD of the drug than that produced by the addition of up to six times as many fines as were originally added (9). They therefore speculate that the greatest contribution to the improved performance of ternary dry powder inhalation formulations is from lactose bound to the carrier and thus the dominant mechanism by which improved performance is produced is the passivation of the strongest binding sites.

Zeng *et al.*, note, however, that under this hypothesis, a certain amount of redistribution of fines and drug particles between different binding sites must occur, as whatever blending order is used, formulations containing additional fine excipient particles produce greater FPDs than those without additional fines (5,10). To further illustrate this point, one investigation found that when formulation blending time was increased from 15 to 60 min, the order in which the

Table II. Details of Investigations into the Effects of Non-Lactose Fines on the Performance of Carrier-Based DPI Formulations

Reference	Drug	Coarse carrier	Fine material and median diameter	Percentage fines added
Lucas *et al.* (4)	BSA 2.0%	Lactose 63–90 μm	PEG 6000 4.0 μm	5.0
Endo *et al.* (33)	Glucagon 1:100	Lactose or erythritol	Erythritol 2.5 m	9, ~17 & 33
Tee *et al.* (6)	Salbutamol sulphate 1.5%	Lactose, mannitol or sorbitol 63–90 μm	Mannitol 4.31 μm or sorbitol 6.17 μm	1.5 & 4.4
Arnold *et al.* (40)	Fenoterol 2%	Glucose	Glucose 5 μm	4 & 16
Arnold *et al.* (40)	Ipratropium bromide 0.8%	Glucose	Glucose 8 μm	5, 10, 25 & 50
Adi *et al.* (35)	Salmeterol xinafoate 2.5%	Lactose, glucose, mannitol or sorbitol 106–180 μm	Lactose, glucose, mannitol or sorbitol	10
Louey and Stewart (24)	Salbutamol sulphate 5%	Pharmatose 325M	Glucose 4.4 μm	1, 5 & 10
Jones *et al.* (37)	Budesonide 1.5%, formoterol fumarate dihydrate 1.5%, drug A 1.5% or drug B 1.5%	Lactose 63–90 μm	Erythritol 4.2 μm, mannitol 5.8 μm & trehalose 5.2 μm	10

components were blended had no significant effect on formulation performance, an effect attributed to equilibrium being reached in the redistribution of fine lactose and drug particles between binding sites during the longer mixing time (5). The dependence of the effects of blending order on blending technique (and drug concentration) are further illustrated by the work of Hartmann and Steckel (34), suggesting that the interpretation of the results of such studies is extremely complicated and hence unable to provide any mechanistic evidence beyond pure speculation.

A number of other studies have proposed the passivation of strong binding sites as the mechanism by which fines improve formulation performance (6,9,13,22,31,48). They provided little or no experimental data of their own to support this hypothesis, however, simply citing the studies discussed above and also suggested a number of other, even more speculative, mechanisms to explain this phenomenon. These included the filling in of crevices in the surface of the coarse carrier (from which drug particles would be difficult to aerosolise) by fines (8,9,22), although it is difficult to see how this mechanism differs from the passivation of the strongest binding sites, since surface crevices in the coarse carrier are, presumably, strong binding sites.

It should be noted that a recent study by Young *et al.*, claimed to provide evidence for the existence of areas of high adhesion on the surface of lactose carrier particles, although the formulations used in this work did not include additional fine excipient particles (49). Another study that used atomic force microscopy (AFM) to measure the adhesive force between a 10 μm silica sphere and various sites on the surface of a lactose carrier found a log-normal distribution of forces however, suggesting that that division of a carrier surface into areas of strong and weak adhesion may be too simplistic (50). The relevance of this study is limited, however, by the choice of a silica sphere (i.e., non-drug) probe (51).

Hypothesis 2: The Formation of Agglomerates of Drug and Fine Excipient Particles

Lucas *et al.*, found that the FPD of salbutamol sulphate and bovine serum albumin from ternary blends with coarse and fine lactose was independent of the blending order used to produce the formulation (3,4). They therefore suggested that it was unlikely that the addition of fines improved formulation performance by preventing adhesion of drug particles to the strongest binding sites. Instead, they speculated that during the blending process, drug particles were distributed between the surface of the carrier and multiplets formed by the aggregation of fines and drug particles (see Fig. 3). The experimental evidence to support this was limited to SEMs of the formulations that showed the presence of both drug-coarse carrier adhesion units and fine particle multiplets, although it had been described previously for other ternary powder blends by Soebagyo and Stewart (52). Lucas *et al.*, further speculated that upon aerosolisation, drug particles were more easily liberated from fine particle multiplets than from the surface of coarse carrier particles, as fine lactose was thought to have a smoother surface than coarse lactose, giving a reduced force of adhesion between drug and fines (3,4). They also suggested that certain fine particle multiplets might also be small enough to form part of the FPD without detachment of drug particles (3,4), a premise supported by the work of Srichana *et al.*, whose work on the deposition of salbutamol sulphate and lactose found that these two components can travel together to the lower regions of the lung (48).

In 1999, Zeng *et al.* (10) compared their own work (which had found significant blending order effects) with that of Lucas *et al.*, discussed above. They suggested that the effect of blending order is dependant upon the particle size of the fines, the device from which the formulation is aerosolised and the flow rate used. In particular, they suggested that blending order becomes significant when formulations are tested at low flow rates through low resistance devices. Lucas *et al.*, used a Diskhaler® in their work, whilst Zeng *et al.*, used a Rotahaler®, a device with less than half the resistance of a Diskhaler® (10), causing Zeng *et al.*, to suggest that this was the reason for the lack of a significant effect attributable to blending order in the work of Lucas *et al.*, (3).

Such an explanation cannot be used to explain the results of Louey and Stewart, who used a Rotahaler® at the same flow rate as Zeng *et al.*, and yet did not find any

Table II. Continued.

Performance assessed by	Inhaler used	Flow rate used ($l.min^{-1}$)	Control formulation	Influence of non-lactose fines	Effect compared to lactose fines
TSI	Rotahaler®	60	Carrier + drug	FPD ↑ by 47%	=
ACI	Jethaler®	28.3	–	–	↑ FPF with either carrier
TSI	Rotahaler®	60	Carrier + drug	See Table III	↑ or ↓ depending on carrier
?	?	?	Carrier + drug	FPD ↑ by up to 115%	–
?	?	?	Carrier + drug	FPD ↑ by up to 154%	–
TSI	Rotahaler®	60	Carrier + drug	FPF ↑	Glucose > lactose > mannitol > sorbitol
TSI	Rotahaler®	60	Carrier + drug	FPF ↑ by up to ~75%	↑ FPF
NGI	Rotahaler®	60	Carrier + drug	FPD ↑ by up to 237%	↑ or ↓ depending on fines and drug combination

ACI Andersen cascade impactor, *BSA* bovine serum albumin, *FPD* fine particle dose, *FPF* fine particle fraction, *NGI* Next Generation Impactor, *PEG* polyethylene glycol, *TSI* twin stage impinger

significant effects of blending order (24). Louey and Stewart also found that the addition of salbutamol sulphate to coarse lactose increased the FPD of lactose produced upon aerosolisation, suggesting that salbutamol sulphate particles can displace intrinsic fine lactose particles from their coarse carrier binding sites (24). The authors suggested that this phenomenon could not occur to any great extent if fines improved formulation performance by preventing drug particle adhesion to the strongest binding sites.

Given these observations, Louey and Stewart extended the hypothesis of multilayer and multiplet formation. They speculated that when contained in such structures, drug particles were more easily liberated from the surface of coarse carrier particles during aerosolisation, as such agglomerates have a greater detachment mass (24). Such a theory is supported by the observation of drug-fine excipient multiplets adhered to the surface of coarse carrier particles (4,24) and is also mentioned in the work of Larhrib *et al.* (13). In 2003 and 2004, Stewart *et al.* (26) and Islam *et al.* (11) presented data showing that the optimum salmeterol xinafoate FPF obtained from lactose-based ternary formulations occurred when the ratio of drug particles to fine excipient particles was 1. As the ratio increased, the FPF decreased. These authors considered this to be consistent with the hypothetical multiplet mechanism outlined above. They speculated that at a high ratio (more drug particles than lactose particles), FPF was low, because multiplets were formed mainly from drug particles and were thus held together by strong cohesive interactions. As the ratio decreased and there were relatively more lactose particles in the formulation, it was speculated that the FPF increased because multiplets were formed of both salmeterol xinafoate and fine lactose particles, which weakened the cohesive interactions between drug particles. No explanation was provided as to why the cohesion between drug particles should be stronger than the adhesion between drug and lactose particles, however.

Islam *et al.*, have also published work that showed that the VMD of a lactose carrier did not affect the FPF produced by a binary blend with salmeterol xinafoate (12). They suggested that as a smaller carrier will have a greater surface area, under the passivation of binding sites hypothesis, a smaller carrier should have more areas with strong binding characteristics and therefore a reduction in carrier size should have produced a decrease in formulation performance. The authors pointed out that their results did not show this effect and were not incompatible with the hypothesis of mixed multiplet and multilayer formation. Agglomerate formation was also mentioned by Adi *et al.*, as being important for drug aerosolisation, as it was thought to

Table III. Mean FPD ± Standard Deviation (μg) of Formulations Containing Lactose, Mannitol and Sorbitol Carriers and Fine Particles, as Reported by Tee *et al.* (6)

			Fine material			
		Binary formulation	Lactose	Mannitol	Sorbitol	Percent fines
Carrier material	Lactose	29.7 ± 4.3	33.7 ± 6.9	51.3 ± 6.3	49.6 ± 3.7	1.5
			58.6 ± 16.5	63.0 ± 4.2	63.6 ± 4.1	4.4
	Mannitol	40.9 ± 4.4	57.7 ± 4.6	45.8 ± 5.9	50.0 ± 6.3	1.5
			73.1 ± 9.1	36.1 ± 8.1	61.0 ± 4.8	4.4
	Sorbitol	30.5 ± 3.0	53.8 ± 5.9	43.8 ± 1.5	45.1 ± 3.7	1.5
			76.3 ± 9.3	43.4 ± 2.6	50.0 ± 3.2	4.4

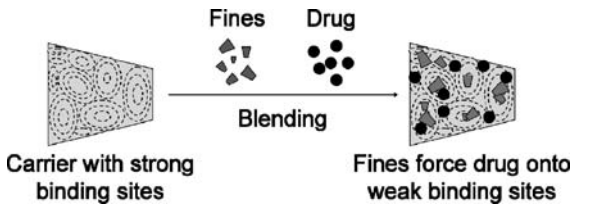

Fig. 1. Under hypothetical mechanism 1, drug particles are more easily liberated from the surface of carrier particles when fines are present, as the fines adhere to the strongest binding sites on the carrier surface, forcing the drug onto weaker binding sites.

lead to the detachment of drug particles from the surface of the carrier (35,36,41).

Comparing the Hypothetical Mechanisms and Future Research

It seems, then, that no definitive conclusion can yet be reached as to the mechanism by which fine excipient particles improve the performance of DPI formulations, especially as the aerosolisation of the only drug investigated more than once (salbutamol sulphate) has been found to be both affected (8,10,18) and unaffected (3,4,24) by its blending order with coarse and fine lactose. In truth, the evidence in support of both mechanisms is limited, being restricted to the presence or absence of an effect of blending order (which, as discussed, is affected by many other variables), images showing the presence of mixed multiplets in unaerosolised formulations and calculations based upon the effects of adding different proportions of fines, which have been used in support of both mechanisms.

Further insights into the mechanism(s) by which fines improve DPI performance are most likely to come from a greater understanding of the interparticulate interactions of the components present in ternary formulations and how these relate to the subsequent deaggregation processes. Although the basic principles of interparticulate interactions have been described (for example, in the work of French *et al.* (53) and Shekunov *et al.* (54)), experimental measurements are often several orders of magnitude greater than theoretical values (55,56). In addition, there is an absence of studies providing a theoretical description of the deaggregation process that occurs during the aerosolisation of complex, three component, ternary formulations.

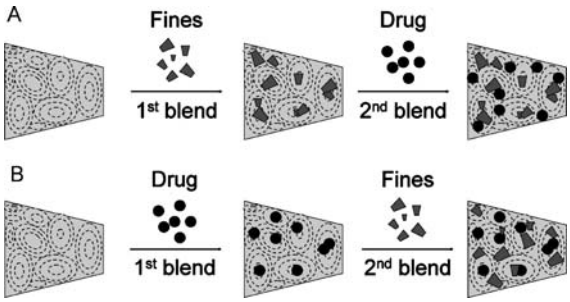

Fig. 2. Speculated effect of blending order on final blend structure. A—when fines are blended with the carrier first, they have the first opportunity to adhere to the strong binding sites, forcing the drug onto weaker binding sites. B—when the drug is blended with the carrier first, it has the first opportunity to adhere to the strong binding sites, forcing the fines onto weaker binding sites.

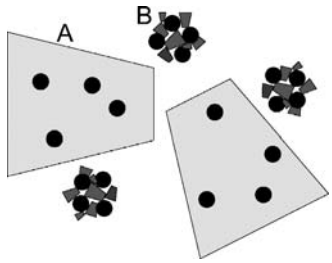

Fig. 3. Representation of the distribution of drug particles between the surface of the coarse carrier (A) and multiplets or agglomerates of drug and fines (B) as proposed by Lucas *et al.* (3,4).

Experimentally, colloid probe AFM and inverse gas chromatography (IGC) have been used to give an experimental insight into the interactions found within binary DPI formulations and to relate this to their performance. Bunker *et al.*, have recently written an excellent review of this AFM work (51), whilst the use of IGC in conjunction with studies of formulation performance is limited to the work of Cline and Dalby (57) and Tong *et al.* (58). To date, however, only one preliminary study has applied such techniques to the study of ternary formulations (37) and although the results appeared interesting, it is too early to say if this approach will prove useful in elucidating the mechanism(s) responsible for the effect of fines on DPI performance. It is clear, however, that future research into the effects of fines should employ techniques such as AFM and IGC in order to attempt to explain this phenomenon.

CONCLUSIONS

The inclusion of fines in carrier-based dry powder inhalation systems is an extensively researched and useful technique for the improvement of formulation performance. Carriers containing greater proportions of intrinsic fines give better performance, which can be decreased by their removal. The addition of fine particles of lactose or one of many other excipients to a formulation increases formulation performance, although this may be at the cost of decreased emission of drug from the device. The optimum median particle size for additional fines appears to be approximately 5–8 μm.

Both the optimum concentration of fines to include in a formulation and the material they should be remains unclear, due to apparently conflicting findings. In all probability, there are not single answers to these questions, the optimum in each case depending on the interplay of the other materials in the formulation, the processing techniques and aerosolisation conditions. The solution to these issues may therefore lie in further research into the vexed question of the mechanism by which fines improve formulation performance, which may be best addressed by theoretical and experimental research addressing the various interparticulate interactions found within a ternary formulation.

As a final note, caution needs to be exercised in the development of these formulations, as the long term implications of the inhalation of fine excipient particles are currently unclear and may produce concern amongst clini-

cians and regulatory authorities (59). Such concerns are given weight by research showing that the aerosolisation of ternary formulations produces a greater FPD of the excipient than the aerosolisation of binary formulations.

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