Coarse Lactose Particles as Dispersion Enhancers During Aerosolization of Dry Powder Formulations

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Summary

A combination of coarse and fine particle size grade excipients is typically used in dry powder inhaler (DPI) formulations to improve the uniformity of drug distribution. In this study, the role of coarse particles as dispersing agents of fine particle agglomerates during powder dispersion was investigated by dry dispersion laser diffraction analysis (LDA). LDA allowed fast and effective investigation of fine particle interactions typical in DPI drug products. Particles with different cohesivity (lactose monohydrate versus soda-lime glass) and morphology were compared with respect to their effectiveness in deagglomerating fine particle agglomerates. The forces controlling these interactions – cohesive forces between particles and dispersion forces acting upon agglomerates – were used to describe the relationship observed between the concentration of added coarse particles and the proportion of fine mass fraction (FMF, defined as particles <6 µm by LDA). In addition, the effect of particle density on FMF was investigated using denser coarse particles. Understanding the balance of these forces allows rational selection of excipients to use in a DPI drug product.

Introduction

Impaction-based assessment of aerodynamic particle size distribution (PSD) is the current industry standard for dry power inhaler (DPI) performance assessment [1]. This, however, is time and resource intensive. LDA, on the other hand, is almost universally used to measure the PSD of APIs and has also been used for DPI assessment. Most LDA methods, however, are wet methods, which involve suspending the test article in a non-solvent. For DPI particle interaction analysis, dry dispersion methods that utilize air as a dispersing medium are preferred. The use of dry dispersion LDA for DPIs reduces testing time and resources, as compared with impaction-based methods.

In this study, we used LDA to delineate particle interactions [2]. The particle interactions and dispersion forces affect the deagglomeration of powders during aerosolization. This impacts the FMF, which is presumed to correlate with inhalable particle fraction. We investigated the effect of coarse and fine particle lactose interactions on the FMF from powder mixtures. In addition, lactose particles were compared to glass particles, with lower cohesivity [3] and higher density (~2.5 g/cm^3 for glass vs. ~1.5 g/cm^3 for lactose [7]).

Experimental Methods

Binary lactose monohydrate systems consisting of Respitose® SV003 (DFE Pharma, Inc.; Goch, Germany) and InhaLac® 400 (Meggle Group Wasserburg; Wasserburg, Germany) – coarse and fine lactose grades, respectively – were manufactured in coarse lactose concentrations of 0, 25, 50, 75, 87.5, 92.5, 95, 97.5, and 100% w/w. These grades of lactose have a manufacturer-reported d(0.9), d(0.5), and d(0.1) of 75-106, 53-66, and 19-43 µm for Respitose® SV033 and 15-35, 4-11, and 0.8-1.6 µm for InhaLac® 400. Each lactose mixture had 30 grams blended for 30 minutes in 60 mL glass bottles using a Turbula® Type T2C blender (Willy A. Bachofen AG, Basel, Switzerland) at 67 rpm. The PSD of the blends were measured by Sympatec HELOS® (Sympatec GmbH; Clausthal-Zellerfeld, Germany) with the R3 lens and a RODOS® dry dispersion unit operated at 2 bar. Samples were placed into glass test tubes, which were then placed into the Aspiros® delivery module.

Lactose mixtures, glass mixtures, and lactose-glass mixtures were also analyzed by placing each component sequentially into the sample tube – coarse particles followed by fine particles (Table 1). The only mixing these samples experienced were during dispersion in the Sympatec equipment. The glass particles were either 1–10 µm or 10–100 µm mean particle diameter (catalogue numbers PS192 and PS313, respectively, Whitehouse Scientific®; Chester, United Kingdom), which represented fine and coarse particles, respectively. Glass mixtures were only sequentially added due to their small sample quantities.

Particle morphology and agglomerations of the mixed lactose blends, neat lactose particles, and neat glass particles were investigated by scanning electron microscopy (SEM) using Phenom™ instrument (FEI Company, Inc.; Hillsboro, Oregon). Samples were fixed on aluminum stubs with double-sided adhesive tabs and sputter-coated with gold film for 3 minutes at a current of 25 mA. SEM micrographs were captured at magnifications between 520x and 4700x.

Table 1 - Sequentially added samples tested by LDA

Sample Number	% Fine Lactose	% Coarse Lactose	% Fine Glass	% Coarse Glass
1	47	53	-	-
2	55	45	-	-
3	60	40	-	-
4	-	-	29	71
5	-	-	51	49
6	-	-	68	32
7	49	-	-	51
8	50	-	-	50
9	52	-	-	48

Results

The fine and coarse grades of both lactose and glass had PSDs in overlapping size ranges (Table 2) and were considered to be similar.-

Table 2 - Particle size distributions by LDA (n=3 for Lactose; n=1 for Glass)

Particle Size	Fine Lactose (InhaLac® 400)	Coarse Lactose (SV003)	Fine Glass	Coarse Glass
d_{10} (µm)	1.16	29.02	2.69	25.59
d_{50} (µm)	7.42	54.73	4.40	46.96
d_{90} (µm)	26.56	73.59	7.29	66.90

The expected proportion of fine particles recovered (FMF) upon LDA testing of any cohesive sample is expected to be different than the total number of fine particles actually present in the sample because (a) most of the fine particles are present in an agglomerated state that needs to be dispersed during analysis by the dispersion forces and (b) the dispersion forces selected for this study were sought to be discriminatory and reproducible, but not extremely high to disperse all fine particles. Therefore, the FMF obtained upon LDA analysis of 100% coarse and 100% fine particles were considered to represent the range of FMF expected from the binary mixtures of the same fine and coarse particles. Connecting these points in Figure 1 leads to the red line illustrated in Figure 1A and Figure 1B for glass and lactose particles, respectively.

When binary mixtures were analyzed, the FMF decreased with increasing proportion of coarse particles for both glass and lactose, as expected. However, the FMF for glass particles decreased linearly with the increasing concentration of coarse particles (Figure 1A), while the binary mixtures of lactose particles showed a non-linear curve (Figure 1B).

To understand the effect of cohesivity and particle density on deagglomeration during aerosolization, sequentially added mixtures of fine lactose particles with coarse lactose particles were compared with mixtures of fine lactose particles with coarse glass particles (also sequentially added to the sample tube). The binary mixtures of fine lactose with coarse glass resulted in higher FMF compared to the mixtures of fine lactose with coarse lactose particles (Figure 2).

Both fine lactose and fine glass particles formed agglomerates prior to LDA dispersion, as seen by SEM (Figure 3). Nonetheless, as expected the morphology was distinctly different between the two materials. Lactose was characterized by a triangular or tomahawk shape for the coarse grade, but became irregular in shape for the fine grade lactose. Glass was spherical for both coarse and fine grades.

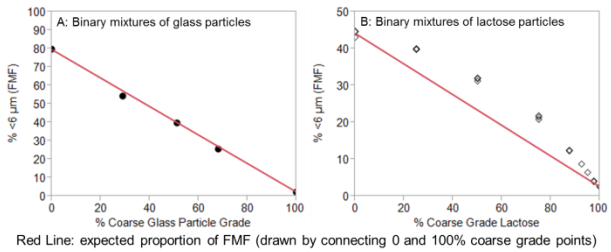

Figure 1 - FMF as a function of the coarse grade material concentration (red line: expected proportion of % <6 µm)

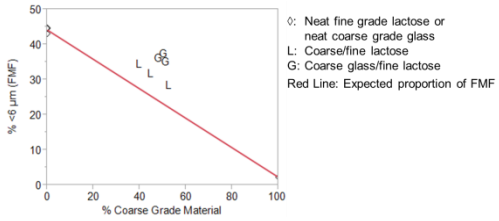

Figure 2 - Comparison of glass and lactose coarse materials with fine lactose added sequentially in Aspiros® tube

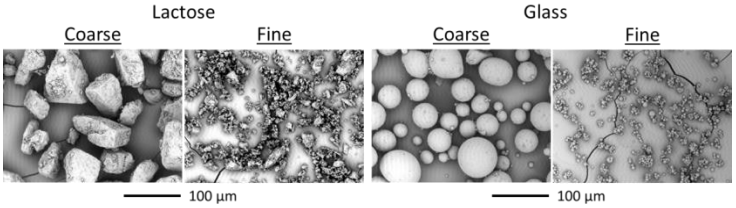

Figure 3 - SEM micrographs of lactose and glass materials

Discussion

To compare the dispersion behaviour of two different types of materials with differences in their inter-particle interactions, glass particles, with lower cohesive strength, were compared with lactose [3][4]. The linear relationship of FMF as a function of added coarse glass particles (Figure 1A) indicated a consistent deagglomeration efficiency during powder dispersion, which was independent of the amount of coarse particles. Thus, FMFs were obtained as expected from the physical mixtures of non-interacting particles.

In contrast, lactose mixtures had higher FMF, as compared to the additive contribution from the two grades of lactose used in the mixture – as represented by the red line in Figure 1. The more cohesive fine lactose particles had lower FMF (than glass particles) in the 100% fine lactose mixture – indicating that many small particles were present in the agglomerated state during LDA testing. The higher FMF with the addition of coarse particles to the fine particle lactose indicated more breakage of fine particle agglomerates in binary lactose mixtures. This was attributed to higher dispersion forces in samples that contained a mixture of fine and coarse particles. The higher particle momentum of the coarser lactose particles colliding with fine lactose particle agglomerates was hypothesized to result in higher FMF in the mixtures of fine and coarse lactose particles. By increasing dispersion forces and decreasing the total powder cohesive strength (lower fine particle concentration), more fine particle agglomerates were dispersed to a size less than 6 µm than an additive contribution from the single components.

These observations point to a balance of cohesion and separation forces during dispersion, as outlined by Pilcer [5]. Previously Guchardi [6] suggested that non-linearity could be a result of light scattering intensity differences between fine and coarse particles. However, the linear behaviour of glass confirms that the non-linearity of lactose is not due to light scattering intensity differences between the coarse and the fine particles.

Both coarse lactose and coarse glass particle size grade materials have a similar amount of inherent FMF, between 2-3% w/w. The inherent FMF of the coarse particle size grade lactose was consistent with previously published work [7]. The presence of fine particles in the coarse grade particles is also seen in Figure 3. These fine particles contribute to the FMF in the 100% coarse particles when tested by LDA and, hence, the red-line of expected FMF does not intercept the x-axis in Figures 1 and 2.

Similarly, the fine particle size grade lactose and glass materials have PSDs that spanned both sides of the FMF designation of 6 µm, as can also be observed in the SEM micrographs in Figure 3. Therefore, when the neat fine grade materials are tested, the FMF is less than 100% (y-intercept in Figures 1 and 2). In addition, the ability of the fine particles to deagglomerate during LDA also affects the FMF. The dispersive pressure of 2 bar was selected to allow reproducible measurements and discrimination between sample mixtures, not necessarily to fully disperse the neat fine grade materials to their fine particle content. This is similar to the situation with DPI use. Hence, deagglomeration is controlled by the balance between the dispersion forces and the cohesive forces [8]. The FMF reflects the balance of the two forces.

Secondly, the hypothesis of particle momentum in the sample contributing to fine particle deagglomeration during dispersion was further tested by using coarse particles of higher density. By adding the coarse glass particles and fine lactose particles into the Aspiros® glass tube sequentially, the effects of mixing prior to dispersion – such as fine lactose particles adhering to larger glass particles or an increase in powder bed permeability – were removed. This allowed for the effect of particle density during dispersion to be more clearly studied. In this study, coarse glass particles increased the FMF of fine lactose particles in binary mixtures, more than coarse lactose particles (Figure 2). This observation was consistent with the hypothesis that higher density of glass (compared to lactose) imparts higher mechanical force on fine particle agglomerates during dispersion, as illustrated in Figure 2.

The LDA observations for glass and lactose powder mixtures can be used to define the balance of inter-particle cohesive interactions and powder dispersion forces. Figures 4A and 4B describe two schemes for the balance of cohesive and dispersion forces, representing the binary mixture of glass particles and lactose particles, respectively. Without coarse particles added, the balance of forces are depicted by the "a" and "b" coordinates on the y-axis. These coordinates, "a" and "b", reflect both the fine material PSD and its ability to deagglomerate. Assuming no particle fracturing during dispersion, similar schematics can be used to describe additional scenarios where the balance of forces alters the FMF – such as a reduction of FMF due to strong cohesion between fine particles and coarse particles.

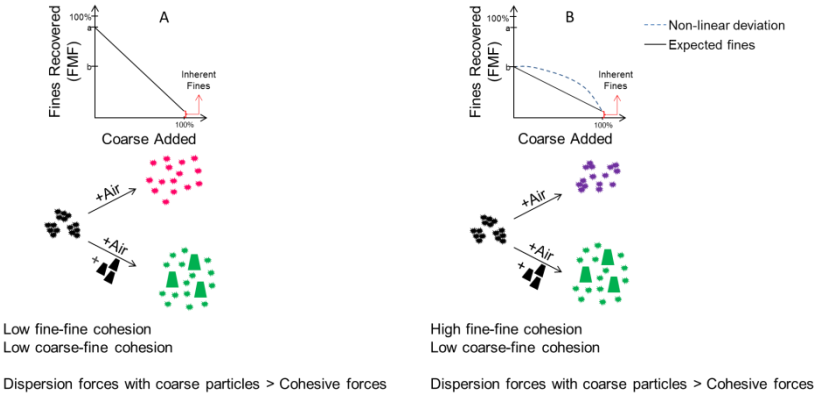

Figure 4 - Schematic of the balance of forces acting upon binary mixtures glass (A) and lactose (B)

Conclusions

Coarse lactose particles were shown by dry dispersion laser diffraction analysis (LDA) to be an effective dispersing agent of fine particle agglomerates during powder aerosolization. The coarse lactose particles modified the balance between inter-particle cohesive and dispersive forces, enabling more fine particle deagglomeration in binary mixtures as compared to the additive contribution of the single component systems. These data indicate that coarse size particles can help create a more robust and effective dry powder inhaler (DPI) drug product.

In addition, LDA was identified as a fast and effective method of comprehending lactose particle interactions typical of DPI drug products. The forces controlling these interactions – cohesive and dispersion forces acting upon agglomerates during aerosolization – were used to describe the relationships between the concentration of added coarse material and the amount of fine mass fraction (FMF, % <6 µm). LDA also demonstrated how particle density of the coarse material changes the balance of these forces in favor of dispersion. Thus, the FMF was higher than expected when denser coarse particles were used in binary mixtures with fine lactose particles. This allows mechanistic understanding of the inter-particle interactions during dispersion and can be used as a routine analytic tool to understand the development and consistency of particle interactions in DPI drug products.

[1] Buttini F, Colombo G, Kwok P, Wui W: *Aerodynamic Assessment for Inhalation Products: Fundamentals and Current Pharmacopoeial Methods*. In: P Colombo, D Traini, and F Buttini, (eds): *Inhalation Drug Delivery*. John Wiley & Sons, Ltd; pp91-119, 2013.

[2] Jaffari S, Forbes B, Collins E, Barlow D, Martin G, Murnane D: *Rapid characterisation of the inherent dispersibility of respirable powders using dry dispersion laser diffraction*, International Journal of Pharmaceutics 2013; **447**(1–2): pp124-131.

[3] Calvert G, Ghadiri M, Dyson M, Kippax P, McNeil-Watson F: *The flowability and aerodynamic dispersion of cohesive powders*, Powder Technology 2013; **240**: pp88-94.

[4] Tuley R, Shrimpton J, Jones M D, Price R, Palmer M, Prime D: *Experimental observations of dry powder inhaler dose fluidisation*, International Journal of Pharmaceutics 2008; **358**(1): pp238-247.

[5] Pilcer G, Wauthoz N, Amighi K: *Lactose characteristics and the generation of the aerosol*, Advanced Drug Delivery Reviews 2012; **64**(3): pp233-256.

[6] Guchardi R, Frei M, John E, Kaerger J S: *Influence of fine lactose and magnesium stearate on low dose dry powder inhaler formulations*, International Journal of Pharmaceutics 2008; **348**(1): pp10-17.

[7] Thalberg K., Berg E, Fransson M: *Modeling dispersion of dry powders for inhalation. The concepts of total fines, cohesive energy and interaction parameters*, International Journal of Pharmaceutics 2012; **427**(2): 224-233.

[8] de Boer A. H., Hagedoorn P, Hoppentocht M, Buttini F, Grasmeijer F, Frijlink H. W.: *Dry powder inhalation: past, present and future,* Expert Opinion on Drug Delivery 2017; **14**(4): 499-512.