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COMMUNICATION

Modification of Electrostatic Charge on Inhaled Carrier Lactose Particles by Addition of Fine Particles

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ABSTRACT

Triboelectrification affects particle adhesion and agglomeration and hence the formulation, manufacture, and use of dry powder inhaler (DPI) devices. Electrostatic charge measurement of two component mixes of spray-dried or crystalline lactose fine particles (<10 μm) 0, 5, 10, 15, 20, and 30% w/w with spray-dried or crystalline lactose 63–90 μm, respectively, has been undertaken using a system incorporating pneumatic transport of the mixed powders to a stainless steel cyclone charging device. The magnitude of charge on the mixes was shown to decrease with increased fine particle content, and there was no significant difference in charge for each concentration between spray-dried and crystalline lactose. Both the variation of charge and powder adhesion to the cyclone surface increased with increase in fine particle content. The proportion of fine particles in carrier systems in DPIs may thus have an important role where triboelectrification is involved.

INTRODUCTION

Dry powder inhaler (DPI) formulations often consist of micronized (<5 μm) drug particles mixed with larger excipient particles (63–90 μm) to form ordered units to provide an inert carrier for the very-low-dose potent drugs, minimize aggregation of the fine drug particles, and increase the flow properties of the mix. Liberation of drug from the excipient carrier after delivery from an inhaler device allows the fine particles to penetrate to the deep lung areas. A small amount (<10% w/w) of lactose fine (<10 μm) particles is often incorporated to

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promote this drug separation in the turbulent airflow from patient inhalation. The mechanism for this is generally not understood. Deep lung deposition from these DPIs is small and variable with typical quoted values for the respirable fraction in the range 5% w/w (1) to 16.4% w/w (2). Electrostatic charge accumulated on the powders during formulation, manufacture, and use of these DPIs is thought to affect the performance of the powders during mixing and device filling, passage of the drug–excipient complexes through the device on inhalation, separation of the complexes, and ultimately deposition in the respiratory tract (3).

During various powder processing operations such as mixing, milling, and device filling, powder contact with various solid surfaces (e.g., metals and polymers) invariably leads to an electrostatic charge on the surface of the materials as a result of triboelectrification (4). This charge has been identified in the mechanisms of adhesion and cohesion (4,5) and is often derived from a complex bipolar system (5). Many factors have been shown to affect the sign and magnitude of charge on a powder sample, including particle shape and size distribution (4,5), nature and work function of the contacting materials (6), contact area and frequency (7), surface roughness and purity (8), and atmospheric conditions (9).

Evidence suggests (10) that electrostatic charge accumulation on powders may influence the performance of DPIs, and there is a clear need to investigate charge generation in DPI powder formulations. The objective of this work was to investigate the effects of adding lactose fine particles on the electrostatic charging of lactose carrier particles. The proportion of fine particles in carrier systems may have an important role in DPI manufacture and use where triboelectrification is involved.

MATERIALS AND METHODS

Materials

The following materials were used: spray-dried lactose, Zeparox (Borculo Whey, UK) and crystalline lactose, medium (Borculo Whey).

The 63- to 90- and <10-μm size fractions were prepared by sieving using BS test sieves agitated on a screening machine (Allgaier ATS600/1) followed by air-jet sieving (Alpine 100MZR for crystalline lactose and Alpine Turboplex ATP50 for spray-dried lactose).

Methods

Powder Characterization

Particle sizing was undertaken using laser diffraction (Malvern Mastersizer) in which riffled (Glen Creston) samples were dispersed in butan-1-ol and sonicated for 5 and 10 sec for spray-dried and crystalline lactose, respectively, before measurement.

Mixing

Two-component lactose systems (10 g) consisting of 63–90 and <10 μm (5–30% w/w) were mixed in a stainless steel cylindrical vessel (0.1 liter) on a Turbula mixer (Glen Creston TC2) at 30 rpm for mixing times in the range 5–90 min. Tumbling mixers have been shown to be an adequate method of providing homogeneity when mixing small amounts of such coarse and fine particulate systems (11). Five random (~300 mg) samples were taken from each mix and analyzed for fine particle content to optimize the mixing conditions using the method outlined below.

Analysis of Mix

The two-component mixes were analyzed using a novel method (12) in which samples were dispersed in butan-1-ol, sonicated, and the mean particle size determined using laser diffraction (Malvern Mastersizer). Mean particle size (μm) was found to be linearly related to fine particle content (% w/w) using the calibration data shown in Table 1.

Electrostatic Charge Measurement of Two-Component Lactose Mixes

The effect of increasing percent fine particle content (0–30% w/w) in a two-component mix with the 63- to 90-μm size fraction on electrostatic charge was investigated using the percent concentrations and mixing times shown in Table 3.

Electrostatic charge measurement was undertaken using the apparatus shown in Fig. 1 (5,8), which incorporated pneumatic powder feed, triboelectric charging via a stainless steel cyclone separator, and charge and mass measurement using a modified Faraday well. Samples of 1.0 g of mix were fed into the stainless steel horizontal pipe and conveyed at <10% relative humidity and 8 m/sec using dry compressed air (Jun-Air 2000). A polonium-210 radioactive charge neutralizer (13) was used to establish a baseline charge on the powder before entry into the cyclone separator via a tangential input pipe. The powder was separated from the carrier gas after triboelectric charging and deposited in the Faraday well connected to an electrometer (Keithley 610) and force compensation load cell (Precisa 400M) for real-time measurement of charge and mass, respectively.

Table 1

Calibration Data for Two-Component Crystalline and Spray-Dried Lactose Mixes

Fine Particle Content (% w/w)	Mean Particle Size (μm) of Crystalline Lactose Mix		Mean Particle Size (μm) of Spray-Dried Lactose Mix	
0	77.4	(0.7)	64.1	(2.3)
5	67.7	(0.7)	60.4	(1.7)
10	62.9	(0.5)	54.8	(2.8)
15	55.3	(1.9)	51.1	(1.4)
20	47.7	(2.9)	45.0	(2.1)
30	39.4	(3.2)	30.7	(4.0)
Gradient	1.28		1.10	
Y intercept	−52.5		−44.5	
Correlation coefficient	0.9924		− 0.9916	

Mean particle size (μm) (%CV) of mix versus % w/w fine particle content.

RESULTS AND DISCUSSION

Powder Characterization

Table 2 shows size analysis and surface area values for crystalline and spray-dried lactose samples. These sieve fractions (63–90 and <10 μm) will be used to consider the charge values from the two types of lactose; however, it is important to consider the actual size distributions when attempting to elucidate charging and adhesion behavior of powders. In general, similar size distributions were obtained for the two types of lactose and the <10-μm size; however, a wider distribution for the 63- to 90-μm fraction was obtained for the crystalline lactose, perhaps a result of particle shape effects during sieving. Surface area determination gave mean ($n = 3$) values of 0.13 and 0.23 m^2/g for the crystalline and spray-dried 63- to 90-μm fraction, respectively, suggesting the more irregular surface and/or porous nature of the spray-dried particle.

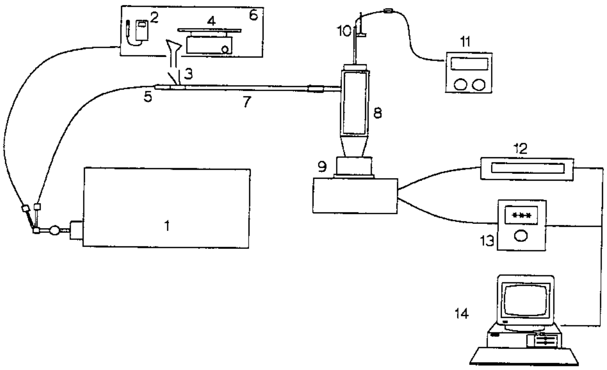

Figure 1. Apparatus for charge measurement. 1, Compressor; 2, relative humidity probe; 3, Venturi funnel; 4, vibratory feeder; 5, ionization nozzle; 6, sealed chamber; 7, feed pipe; 8, cyclone; 9, Faraday well/balance; 10, Pitot tube; 11, flow meter; 12, balance electronics; 13, electrometer; 14, computer.

Optimization of Mixing

The optimum mixing times for fine particle content in the range 5–30% w/w are shown in Table 3. The mix was considered adequate when the % w/w fine particle content was ±0.5% of the expected value and the coefficient of variation (CV) for the five samples was <5%.

Values in Table 3 show an optimum mixing time of 60 min for crystalline lactose mixes up to 20% w/w and 90 min for 30% w/w fine particle content. In contrast, lower mixing times were needed for spray-dried lactose, which increased from 10 min at 5% w/w to 60 min at 30% w/w fine particle content. Lower mixing times were perhaps a result of shape effects; however, this needs to be further investigated.

Electrostatic Charge Measurement of Mixes

The mean (% CV) ($n = 5$) specific charge values (nC/g) for crystalline and spray-dried lactose two-component mixes are shown in Table 4. Generally, as the % w/w fine particle content increases, the mean specific electronegative charge decreases for both crystalline and spray-dried lactose. In addition, the mass of powder deposited in the Faraday well for both types of lactose decreases with increased % w/w fine particle content (Table

Table 2

Characterization of Lactose Sieve Fractions Sizing by Laser Diffraction; Surface Area by Nitrogen Adsorption (Flowsorb II 2300, Micromeritics)

Lactose Sample	Sieve Fraction (μm)	Mean (μm)	Median (μm)	Range (10–90%) (μm)	Surface Area (m^2/g)
Crystalline	63–90	84.0	78.0	42.4–129.6	0.13
Spray-dried	63–90	64.1	62.1	40.2–90.2	0.23
Crystalline	<10	7.3	6.5	2.7–13.1	1.58
Spray-dried	<10	6.7	6.0	2.5–12.0	1.56

Table 3

Optimum Mixing Times for Crystalline and Spray-Dried Lactose 63–90 μm and <10 μm (5–30% w/w)

Theoretical Fine Particle Content (% w/w)	Optimum Mixing Time (min) Crystalline Lactose	Fine Particle Content (% w/w) Crystalline Lactose	Optimum Mixing Time (min) Spray-Dried Lactose	Fine Particle Content (% w/w) Spray-Dried Lactose
5	60	5.0	10	5.0
10	60	9.6	10	9.9
15	60	14.9	20	14.7
20	60	19.9	20	20.0
30	90	30.4	60	29.4

Table 4

Mean Specific Charge (nC/g) for Two-Component Crystalline and Spray-Dried Lactose 63–90 μm and <10 μm (5–30% w/w)

Fine Particle Content (% w/w)	Mean Specific Charge (nC/g) (% CV) for Crystalline Lactose Mix	Mean Specific Charge (nC/g) (% CV) for Spray-Dried Lactose Mix
0	−70.7 (9.2)	−77.3 (12.6)
5	−27.1 (16.2)	−30.9 (30.5)
10	−18.7 (24.9)	−15.3 (22.2)
15	−17.9 (28.1)	−6.6 (21.9)
20	−7.2 (35.1)	−6.9 (70.6)
30	−8.5 (52.2)	0.0 (600.0)

5), suggesting an associated increased powder adhesion to the inner surfaces of the charging apparatus.

Both crystalline and spray-dried lactose are shown to acquire an electronegative charge in contact with the stainless steel surface. Stainless steel is found near the electropositive end of the triboelectric series (14) and hence will theoretically readily donate electrons to semiconductors such as lactose. The magnitude of charge at each % w/w fine particle content was similar for crystalline and spray-dried lactose with the exception of 15%

Table 5

Mean Amount (% w/w) of Sample Deposited in Faraday Well

Fine Particle Content (% w/w)	% w/w Deposited Crystalline Lactose Mix	% w/w Deposited Spray-Dried Lactose
0	59.5	70.6
5	72.7	65.5
10	66.9	69.9
15	53.7	66.8
20	50.7	54.7
30	43.5	46.1

w/w and 30% w/w, where the differences in charge between the two types of lactose were significantly different ($p < 0.05$). Addition of fine particles from 0% w/w to 5% w/w gave the greatest significant ($p < 0.05$) decrease in net charge.

In this work, adhesion occurred to the inner surfaces of the charging apparatus that was extensive but not significantly different ($p < 0.05$) for each type of lactose. A degree of caution must be adopted with the interpretation of the charging results due to this adhesion because little information is gained from the charge acquired from the adhering particle. In addition, very little information is available on the contact area involved with the charge accumulation/transfer process. It is thought that this adhesion may arise because of high particle charge: mass ratios, surface asperities, contact surface roughness, and particle deformation on substrate contact. Adhered material may reduce the frequency of particle–steel interactions and lead to increased particle–particle interactions, which may be responsible for producing a complex bipolar system and hence affect the final net charge. CV values for charge for both spray-dried and crystalline lactose increase with increased fine particle content, suggesting particle–particle interactions are taking place. Micrographs from scanning electron microscopy revealed the adhering powder to contain a larger proportion of the fine particle fraction than the 63- to 90-μm fraction. Recent work in these laboratories has involved detaching adhered particles from the inside surface of the cyclone using a gentle airstream and has revealed a higher net charge-to-mass ratio for adhered powder than powder initially deposited in the Faraday well.

We have therefore shown the proportion of fine particles in a two-component mix with spray-dried or crystalline lactose 63–90 μm will affect the electrostatic properties of the mix and is most likely due to increased particle–particle interactions.

CONCLUSIONS

Electrostatic charge measurement of two-component mixes of spray-dried or crystalline lactose fine particles (<10 μm) 0–30% w/w with spray-dried or crystalline lactose 63–90 μm, respectively, has been undertaken using a novel method (5,8). The magnitude of charge on the mixes was shown to decrease with increased fine particle content, whereas the variation of charge and powder adhesion to the cyclone surface increased with increase in fine particle content. It was postulated that complex particulate interactions may be responsible for the alteration in charge properties, and hence the proportion of fine particles in carrier systems in DPIs may thus have an important role where triboelectrification is involved.

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