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Research Paper

Investigation of Electrostatic Behavior of a Lactose Carrier for Dry Powder Inhalers

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Purpose. This study aims to elucidate the electrostatic behavior of a model lactose carrier used in dry powder inhaler formulations by examining the effects of ambient relative humidity (RH), aerosolization air flow rate, repeated inhaler use, gelatin capsule and tapping on the specific charge (nC/g) of bulk and aerosolized lactose.

Materials and Methods. Static and dynamic electrostatic charge measurements were performed using a Faraday cage connected to an electrometer. Experiments were conducted inside a walk-in environmental chamber at 25°C and RHs of 20% to 80%. Aerosolization was achieved using air flow rates of 30, 45, 60 and 75 L/min.

Results. The initial charges of the bulk and capsulated lactose were a magnitude lower than the charges of tapped or aerosolized lactose. Dynamic charge increased linearly with aerosolization air flow rate and RH. Greater frictional forces at higher air flow rate induced higher electrostatic charges. Increased RH enhanced charge generation. Repeated inhaler use significantly influenced electrostatic charge due to repeated usage.

Conclusions. This study demonstrated the significance of interacting influences by variables commonly encountered in the use DPI such as variation in patient's inspiratory flow rate, ambient RH and repeated inhaler use on the electrostatic behavior of a lactose DPI carrier.

KEY WORDS: aerosol; charge; dry powder inhaler; electrostatic; triboelectrification.

INTRODUCTION

Pulmonary drug delivery by therapeutic aerosols generated from nebulizers, metered dose inhalers (MDI) and dry powder inhalers (DPI) has been a vital facet of asthma and chronic obstructive pulmonary diseases management. Powder aerosols are shown to be an effective means for delivery of antimicrobials and biomolecules such as vaccines, genes and insulin for local treatment of lung diseases as well as for systemic drug delivery. Owing to the inconvenience associated with the use of nebulizers and the prohibition of CFC propellants in MDI, the DPI has gained increased interest as the preferred formulation for inhaled drug delivery (1,2).

Generation and accumulation of electrostatic charges on any semiconductor or insulator materials such as many pharmaceutical powders upon handling is a well known phenomenon (3). More importantly, the effect of static electrification on the efficiency of various processes from powder production and formulation up to its end usage is often significant (4). Triboelectrification of aerosol particles in DPI and MDI has recently emerged as an important subject in the pulmonary drug delivery research because this phenomenon has been shown to influence the efficiency of pulmonary drug delivery by its effect on powder adhesion or retention on inhalers, deaggregation of drug from carrier particles and lung deposition of the active drug particles (5,6). Electrostatic deposition on inhalers could significantly limit the emitted dose. Numerical simulations had demonstrated much easier deaggregation of charged, dry powder particles in the oropharyngeal cavities as compared to uncharged particles because electrostatic repulsion in the former rendered the aggregates less tightly bound (7). However, oppositely charged particles might give rise to strong agglomeration. Electrostatic charge was shown by computational models to enhance drug particle deposition at the upper airways due to space charge and in deep lung due to image charge, that is, an attractive, opposite charge induced on the airway walls (8,9).

A number of studies had examined the static electrification and charge relaxation behaviors of pharmaceutical powders associated with pharmaceutical processes such as powder mixing, coating, spray drying, melt agglomeration, powder transport and formulation of interactive mixtures for DPI in the attempt to understand the associated effects on these

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processes and improve quality of the eventual formulations (10–18). In order to mimic the powder processing conditions, a controlled triboelectrification step was often performed using turbula mixers, cyclone chargers or corona chargers to induce a considerable degree of static electrification on the powder particles. The generated charge and consequential charge decay characteristics were then quantified. However, to investigate the electrostatic property of aerosol particles during the *in use* condition of a DPI, instead of imparting charges to the particles through such triboelectrification processes, direct measurement of the inherent charge of aerosol particles upon aerosolization would undoubtedly serve as a more direct indicator for DPI performance.

Despite its significant influence on pulmonary drug delivery, aerosol electrostatics remained relatively unexplored (2,19). Among the limited studies investigating aerosol electrostatics pertaining to inhaled drug delivery, the most commonly employed method for particle charge measurement was the Faraday cage. The cage was connected in line with the air flow system (20) or a cyclone separator (21) to directly measure the charge of lactose carriers and to a two-stage aerosol sampling apparatus for charge measurement of the fine particle fractions of various DPIs (5) and MDIs (22). The air stream Faraday cage had been used to measure electrostatic charges associated with drug–carrier interactive mixture (23,24). An alternative method for aerosol charge measurement utilized an electrostatic grid-probe (6). The commercially available electrical low-pressure impactor (ELPI) (25–28) and electrical single particle aerodynamic relaxation time (E-SPART) analyzer (29,30) allowed simultaneous determination of aerosol particle charges and particle size distributions. Determination of charge distribution had also been achieved using electron force microscopy on the nanometer scale on single particles and by fluorescent latex spheres imaging technique on the macroscopic powder layers consisting of micron-sized powders (31).

Static electrification of particles could be affected by several factors relating to the particle properties and contact surfaces such as particle size, shape, surface roughness, purity, fine particle content on coarse lactose carrier, contaminants, contact area, contact frequency, as well as the inherent electrical and mechanical properties of the contacting materials (4,10,15,21). Environmental factors with significant influences in static electrification are relative humidity and temperature. Induction of electrostatic charges on aerosol particles upon aerosolization is well recognized (5,32). While air velocity was a commonly examined variable for particle triboelectrification in cyclone chargers (4,33) and fluidized beds (32,34), reported studies on inhalation aerosol electrostatics usually employed a single air flow rate, typically 30, 45 or 60 L/min to achieve powder aerosolization (5,20,22,25–28,35). Consequently, the air velocity or flow rate factor was not addressed. As most of the marketed DPIs are passive devices dependent on patient's inspiratory effort, it was essential to perform electrostatic charge measurement on the powder aerosols at a wide range of air flow rates in order to account for the difference in the inhalation flow rates generated by different individuals. An air flow rate of 60 or 65 L/min was cited as optimal for DPI particle deaggregation (7,36). Thus, it was reasonable that the range of air flow rate employed in this study encompasses these values.

Relative humidity (RH) is another important factor known to affect electrostatic charge of powder particles, hence studies on aerosol electrostatics were performed at a single standardized ambient RH, typically within the 30 to 60% range (5,20,22,24,26,35). However, the electrostatic charge of DPI formulations could be subjected to variation of ambient RH during its storage and use. Exposure of the DPI formulations to drastic change in RH upon inhalation is inevitable as the powder aerosol is discharged from the inhaler into the highly humid environment of the oral cavities and airways. Therefore, it is essential to investigate the effect of varying ambient RH conditions on the electrostatic charge of powder aerosols. The effect of different powder storage RH on aerosol electrostatics and DPI performance had recently been reported (35). The effect of aerosolization humidity, that is, the ambient RH, and its importance on powder aerosol electrostatics as well as DPI performance was clearly acknowledged by Young *et al.* (35). To date, there is only one reported study addressing the influence of ambient RH on DPI electrostatics of two commercially available drug-only DPIs, Pulmicort® and Bricanyl® Turbohalers® (28). Despite the known dependence of powder particle charges on air flow rate and ambient RH, systematic investigation focusing on effects of both of these factors on aerosol electrostatics for inhaled drug delivery has not been carried out before.

While the effect of different inhaler types on the observed difference in electrostatic charges of the resulting powder aerosol is well established (5,37), little attention had been dedicated into exploring the implication of repeated inhaler use on the electrostatic charge behavior of the inhaled powders. As repeated uses are inevitable for most inhalers, the current study attempts to address this concern by employing two identical inhalers of different use histories for the electrostatic charge measurements.

The main objective of this study is to investigate the electrostatic charge behavior of aerosolized lactose particles over a range of air flow rate (30 to 75 L/min) and RH (20% to 80%). It is of direct practical relevance to employ a wider range of air flow rate and RH than the commonly reported range. We also aim to examine the effect of repeated inhaler use on the electrostatic charge behavior of the aerosolized lactose particles. To establish the initial electrostatic charge behavior of the lactose samples before their aerosolization, the effects of powder storage in different RH, gelatin capsules and routine powder handling were investigated in this study. The findings of this study will help to provide some insights into the relatively unexplored realm of aerosol electrostatics for DPI applications.

MATERIALS AND METHODS

Materials

InhaLac® 230 (Meggle, Wasserburg, Bavaria, Germany) was used as model lactose carrier in the electrostatic charge measurement. Hard gelatin capsules size no. 3 was obtained from Capsugel (Greenwood, SC, USA). Analytical grade propan-2-ol was purchased from Fischer Scientific (Pittsburgh, PA, USA). Ultrapure water was supplied by the Millipore water purification system (Millipore, Billerica, MA, USA).

Particle Size Determination

Particle size distribution of lactose was determined by the laser diffraction technique using the small volume module of the Malvern Mastersizer 2000 (Malvern Instruments, Malvern, Worcestershire, UK). The lactose was dispersed in propan-2-ol and a suitable amount of the suspension was added drop wise into the liquid sample cell. The average particle size was measured from three replicates. The volume-weighted particle size distribution of the lactose was found as follows: $d(0.1)=60.8$ μm, $d(0.5)=97.2$ μm, $d(0.9)=153.4$ μm.

Dynamic Vapor Sorption Experiment

Effect of RH on the moisture sorption of lactose was determined at 25±0.1°C by dynamic moisture sorption experiment using the DVS apparatus (Surface Measurement Systems, London, UK). Approximately 50 mg of lactose sample was dried for 20 h under a nitrogen stream at 0% RH. This was followed by RH ramping from 0% to 90% with 10% stepwise increment and equilibrium moisture content determined by $dm/dt<0.002\%$/min.

Electrostatic Charge Measurement

All experiments involving charge measurement were carried out at 25±1°C inside a walk-in environmental chamber equipped with temperature and RH control systems. Lactose powders were laid out as thin layers on earthed aluminium foils and equilibrated overnight at predetermined RH prior to all charge measurements. A Faraday cage connected to an electrometer (Keithley 6517, Keithley Instruments, Cleveland, OH, USA) was used to measure electrostatic charges of the lactose. The electrometer was connected to a computer *via* the GPIB interface for data acquisition. The specific charge of lactose (nC/g) was obtained by dividing the net charge obtained by the mass of lactose used in each measurement. The average specific charge values of at least four replicate samples were reported for each measurement condition employed.

It should be noted that the operator was not electrically insulated when conducting the experiments. Care was taken to avoid any direct physical contact with the powder since electrostatic charging of the powders could be affected. Physical contact was limited to the barrel of the plastic inhaler which was not conductive. It was observed from preliminary studies that operator with and without rubber gloves did not result in significant difference in electrostatic charge values than its inherent variability.

Static Charge

Static charge refers to the electrostatic charge on bulk lactose powder. It was measured using the Faraday cage positioned vertically without involving aerosolization of the powder. Accurately weighed lactose sample (approximately 25 mg) was transferred into the inner metal container of the Faraday cage. The electrometer, originally adjusted to zero would register the inherent charge present on the sample. A charge profile was plotted from the data acquired during each measurement to aid in the determination of the net charge of the powders. The net charge was obtained by subtracting the final, stable charge value after powder loading into the Faraday cage from the baseline charge value (approximating zero) before powder loading. The initial charges of free bulk lactose samples were measured at four different ambient RH conditions, 20, 35, 50 and 80±3%.

The effect of gelatin capsule and routine handling operations on electrostatic charge of lactose was investigated at 35% RH. Approximately 25 mg of lactose was filled into hard gelatin capsules. Charge measurement was performed by emptying the capsule content into the Faraday cage after the samples were subjected to the following treatments: (a) about 10 min after filling into the capsules, (b) overnight storage in capsules, and (c) tapping for 10, 40, 100 or 200 taps on a tapping machine.

Charge dissipation of lactose was investigated at 20% RH. Approximately 0.5 g of lactose was transferred into an aluminium container (35 mm diameter×40 mm height). The powder was then subjected to 30 min of mixing in the T2F Turbula mixer (Retsch, Haan, North Rhine-Westphalia, Germany) in order to induce triboelectrification. Static charge was measured by pouring the powder into the Faraday cage immediately after cessation of powder mixing and at different holding times of 5, 10, 20, 30 and 60 min. Static charge of the bulk lactose powder employed in this study was measured prior to mixing to establish its initial charge. Aluminium container was selected from a preliminary study employing a range of containers made of different types of materials such as plastic, glass and metal (stainless steel). Aluminium was found to be best for providing consistent and reproducible electrostatic charge readings with lactose.

Dynamic Charge

Dynamic charge refers to the electrostatic charge imparted on bulk lactose powder upon its aerosolization from the model dry powder inhaler, Rotahaler® (Glaxo SmithKline, Ware, Hertfordshire, UK). The experimental setup (Fig. 1) consisted of an acrylate flow tube of 100 cm length×25 mm inner diameter fitted with a mouthpiece adaptor at one end and a vacuum pump adaptor at another end. These adaptors were custom made using polytetrafluoroethylene (PTFE) to tightly fit the mouthpiece of the inhaler and the vacuum pump tubing. Air flow rate was controlled by an air flow meter. The Faraday cage was positioned horizontally surrounding the dry powder inhaler for charge measurement. The inhaler was deemed to be adequately shielded from external electrostatic fields by the body of the Faraday cage consisting of thick, stainless metal.

Prior to its use in experiments, the inhaler was cleaned using a standard procedure. Particulate contaminant was removed by rinsing with water. This was followed by rinsing with pure ethanol and finally ultrapure water. The two halves of the inhaler were exposed overnight for drying and to be equilibrate to the same ambient conditions for the charge measurement inside the walk-in environmental chamber.

A whole, empty capsule was inserted into the square hole located at the barrel of the Rotahaler®. For the other half of the inhaler which was mounted onto the mouthpiece adaptor, accurately weighed lactose sample (approximately 10 mg) was loaded into the air chamber, that is the inner surface

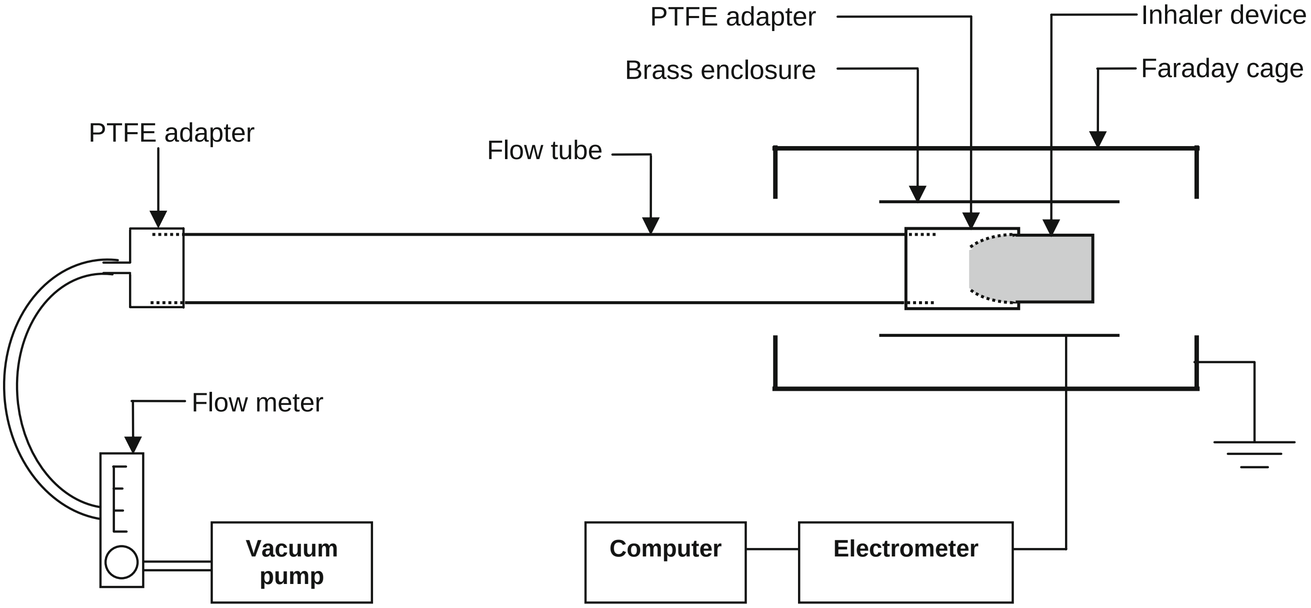

Fig. 1. Schematic diagram of experimental setup for dynamic charge measurement.

away from the mouthpiece and the grill. The inhaler was reassembled and the electrometer was adjusted and stabilized at zero. Data acquisition by the electrometer was initiated followed by application of air flow to aerosolize and draw the lactose samples out from the DPI. Air flow rates of 30, 45, 60 and 75 L/min and RH conditions of 20%, 35%, 50% and 80% were employed for the dynamic charge measurements. Two different Rotahaler® inhalers, designated as Inhaler no. 1 and Inhaler no. 2, both identical except that Inhaler no. 1 had been repeatedly used for a large number of previous experiments whereas Inhaler no. 2 was relatively new, were used for the measurement at each air flow rate and RH. A charge profile was plotted from the data acquired during each measurement to aid in the net charge determination. The net charge of lactose particles was obtained by subtracting the final, stable charge value after aerosolization from the baseline charge value (approximating zero) before aerosolization. The use of the Rotahaler® was modified in this study in that the lactose powder was not filled into the capsule and the inhaler barrel was not turned to open the two halves of the capsule as per its normal usage. The rationale of the modified usage will be discussed below.

Statistical Analysis

Electrostatic charge results obtained from static charge measurement were evaluated statistically using either independent sample *t* test or one-way ANOVA where appropriate. For dynamic charge measurement, the electrostatic charge results obtained were evaluated statistically using three-way ANOVA whereby aerosolization air flow rate, RH and inhaler were defined as the independent variables (factors). The ANOVA tests were conducted at an alpha level of 0.05 and post-hoc statistical analyses of the means of individual groups were performed using Tukey's test. For all statistical analyses, $p<0.05$ denoted significance.

RESULTS

Effect of Relative Humidity on the Initial Electrostatic Charge of Lactose

The electrostatic charge measurements on the bulk undisturbed lactose powders which were conditioned overnight at pre-determined RH were defined as the initial charges of lactose at a particular RH. Fig. 2a shows a typical charge profile obtained from the static charge measurement of a sample. All the lactose samples tested demonstrated net negative static charges. A trend of decreasing initial charge was observed as RH was increased (Table I). However, the initial charges observed were largely insignificant ($p>0.05$, one-way ANOVA) except for the initial charge at 80% RH which was significantly lower ($p<0.05$) than those at 20% and 35% RH.

Effect of Handling on the Electrostatic Charge of Lactose

The effect of routine handling of lactose on specific charge was investigated. It was found that lactose storage in gelatin capsules resulted in significantly higher specific charges on the powders ($p<0.05$, independent sample *t* test) as compared to the free, undisturbed powders. Each of the respective lactose samples was compared separately with the free, undisturbed powder using independent sample *t* test (Table II). The effect of tapping of lactose filled in gelatin capsules was also investigated. Significant increase in lactose charges ($p<0.05$, one-way ANOVA) was apparent from 100 taps onwards (Table II).

Charge Dissipation Behavior of Lactose

Triboelectrification of lactose was significant upon tumbling in the Turbula mixer as the lactose became charged after

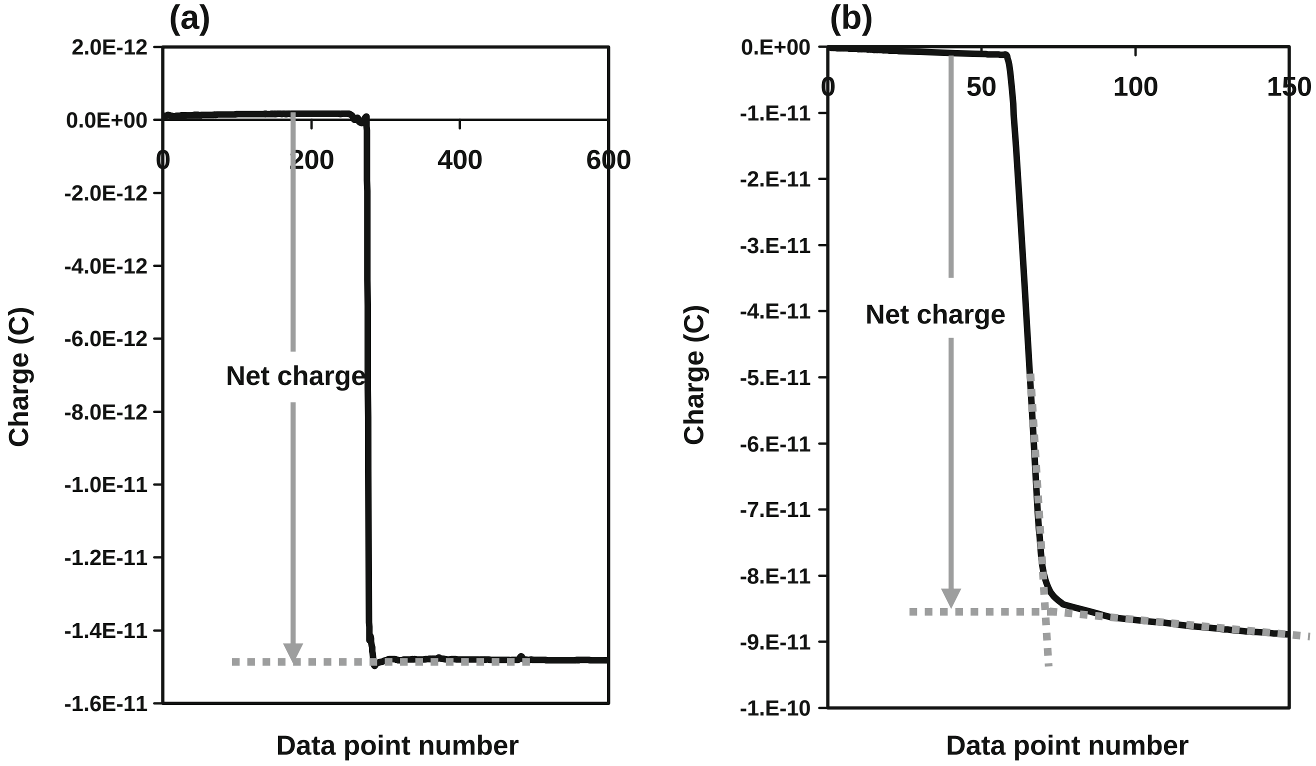

Fig. 2. Charge profile for bulk lactose powder (**a**) and lactose upon aerosolization at an air flow rate of 60 L/min (**b**) at 20% relative humidity.

tumbling (Table III) at least seven folds higher than the initial charge of the bulk lactose (−0.304±0.227 nC/g). There was no marked change in specific charge values for the lactose measured immediately after tumbling (time zero) up to 30 min of holding time ($p>0.05$, one-way ANOVA). This indicated slow charge dissipation or high propensity of charge retention on the lactose at 20% RH.

Effect of Air Flow Rate, Relative Humidity and Inhaler on the Electrostatic Charge of Lactose

In this study, the effect of air flow rate (30, 45, 60 and 75 L/min), ambient RH (20%, 35%, 50% and 80%) and repeated inhaler use on dynamic charge of lactose were investigated. Fig. 2b shows a typical charge profile for a lactose sample upon aerosolization and Fig. 3 shows the trend of dynamic charge with respect to air flow rate and ambient RH. Aerosolization was found to induce marked electrostatic charge on the lactose since the dynamic charge values of the aerosolized lactose particles was at least one order of a magnitude higher than its initial charge (Tables I and IV). Unlike static charge, the dynamic charge on lactose demonstrated positive polarity. A three-way ANOVA analysis was performed to determine the effect of air flow rate, ambient RH and different inhaler (Inhaler no. 1 and no. 2) on dynamic charge of lactose. Both the air flow rate and ambient RH were found to significantly influence the magnitude of dynamic charges on lactose particles. The effect of air flow rate and RH on lactose charges was independent as indicated by the absence of significant interaction ($p>0.05$). However, significant interaction was observed between RH and the inhaler. In general, an increase in air flow rate and ambient RH resulted in an increase in magnitude of dynamic charge on lactose particles (Table IV). From post-hoc comparisons, the dynamic charges were not significantly different at 20%

Table I. Effect of Relative Humidity on Electrostatic Charge of Lactose (n=8–16)

Relative humidity (%)	Specific charge (nC/g)
20	−0.340±0.124
35	−0.210±0.084
50	−0.141±0.039
80	−0.078±0.033^{a,b}

^{a,b} $p<0.05$ from ^{a}20% and ^{b}50% RH

Table II. Effect of Powder Handling on Electrostatic Charge of Lactose at 35% Relative Humidity

Description	Specific charge (nC/g)
Free undisturbed powder, equilibrated overnight	−0.210±0.084
Powder in gelatin capsule (n=6–14)	
10 min after capsule filling	−0.601±0.254^{a}
Stored overnight	−0.779±0.276^{a}
Powder subjected to tapping (n=2–6)	
No. of taps	
0	−0.779±0.276
10	−1.817±0.380
40	−1.822±1.188
100	−3.049±1.257^{b}
200	−6.009±0.962^{b,c,d,e}

$^{a–e}$ $p<0.05$ from the free undisturbed powder, equilibrated ^{a} overnight, and $p<0.05$ from ^{b}0, ^{c}10, ^{d}40, and ^{e}100 times of tap; one-way ANOVA, Tukey's test for post-hoc statistical analyses

Table III. Effect of Different Holding Time on Electrostatic Charge of Lactose at 20% Relative Humidity (n=3–6)

Time (min)	Charge/mass ratio[a] (nC/g)
0	−2.448±0.809
5	−2.094±0.109
10	−1.999±0.493
20	−2.647±0.214
30	−2.381±0.838
60	−3.042±0.387

[a] p>0.05 for all sampling time points; one-way ANOVA, Tukey's test for post-hoc statistical analyses

and 35% RH while the dynamic charges at 50% and 80% RH were significantly higher than those at lower RHs. Thus, the effect of RH on dynamic charge of lactose could be summarized as follows: 20%=35%<50%<80% RH. However, it should be noted from Table IV that specific charge values for Inhaler no. 1 were obviously higher at 35% RH as compared to 20% RH, while there is no consistent trend demonstrated by Inhaler no. 2 at the corresponding RHs. These conflicting trends could be attributed to the dependence of aerosol electrostatic behavior on the inhaler employed as well as the significant RH–inhaler interaction. The influence of inhalers on the observed aerosol electrostatic behavior will be further elaborated in subsequent sections. As for the effect of air flow rate, statistically significant difference in dynamic charge was not detected at consecutive air flow rates, that is, 30=45 L/min and 45=60 L/min. However, the higher air flow rates of 60 or 75 L/min imparted significantly higher dynamic charges, in the order, 30<60<75 L/min and 45<75 L/min.

The relationships between dynamic charge of lactose particles and air flow rate at any particular RH or dynamic charge and RH at any particular air flow rate were found to be linear. The linear regression correlation coefficients, r for the dynamic charge–flow rate relationships ranged from 0.9195 to 0.9998, and r for the dynamic charge–RH relationships ranged from 0.9180 to 0.9961.

The type of inhaler employed in electrostatic charge measurement was known to influence charge values of DPI powders (5,25). It was a common assumption that the use of two identical inhalers would yield consistent electrostatic charging behaviors and resultant charge values when identical samples and experimental conditions were used, thus minimizing data variation due to the inhalers. To verify this assumption, the inhaler employed was included as one of the independent variables in the ANOVA test. Significant difference was detected for the dynamic charge of lactose when a different inhaler was used. Post-hoc test could not be applied as a part of the ANOVA as only two inhalers were compared. Thus, to identify the particular air flow rate and RH whereby the inhalers exerted significant effect on dynamic charge, two-sample independent *t* tests were performed and the results are shown in Table V. From Table V, the effect of different inhalers on dynamic charge of lactose was significant at lower air flow rates and lower RHs. At the maximum air flow rate and RH employed in this study (75 L/min and 80%, respectively), dynamic charge was independent of inhaler regardless of air flow rate and RH.

Vapor Sorption Behavior of Lactose

There was a gradual increase in moisture sorption on the lactose powder when RH was increased from 0% to 90% (Fig. 4). Moisture sorption was slow at low RH but started to increase more quickly above 70% RH. The total sorbed moisture at 20% and 80% RH was 0.01% and 0.025%, respectively.

DISCUSSION

Origin of Electrostatic Charge

Electrostatic charges present on powder or polymer surfaces are known to originate from contact charging and triboelectrification. Contact charging occurs when two dissimilar materials are brought into contact, allowing transfer of electrical charge, either as electrons or ionic species. The contact of a particle with another surface sets up an electrical double layer and thus a contact electric field due to the differences in work function between the adjacent surfaces. The work function is defined as the minimum energy needed to remove an electron from a solid to a point immediately outside the solid surface. Electron transfer would take place from the material with lower work function to that of higher work function until the establishment of a balance in electron energy or Fermi levels between the materials in contact. Subsequent separation of these materials resulted in accumulation of a net charge on each material surface having opposite polarity but same charge magnitude. When material contact is accompanied by frictional effects such as surface rubbing, sliding, rolling or impaction, the term triboelectrification is used (3,33,38). Although the theoretical concept of work function could not be directly applied to charge transfers between insulators as for most pharmaceutical powders, electron or ion transfers could still occur through surface contaminants and defects on these materials (33,38).

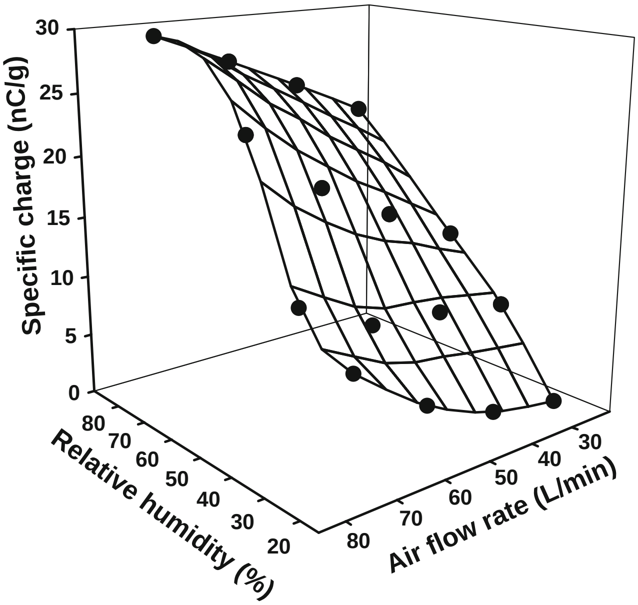

Fig. 3. Effect of aerosolization air flow rate and relative humidity on dynamic charge of lactose.

Table IV. Effect of Relative Humidity (RH) and Aerosolization Air Flow Rate on Dynamic Charge of Lactose (n=4–14)

	Specific charge (nC/g)							
	Air flow rate (L/min)							
RH (%)	30	CV (%)	45	CV (%)	60	CV (%)	75	CV (%)
Inhaler no. 1								
20	1.539 ± 0.264	17.1	2.587 ± 0.404	15.6	5.062 ± 1.101^{b}	21.8	9.344 ± 2.138^{b}	22.9
35	7.979 ± 1.202^{a}	15.1	8.859 ± 2.522^{a}	28.5	$9.408\pm3.707^{a,b}$	39.4	$12.357\pm2.689^{a,b}$	21.8
50	12.612 ± 1.624^{a}	12.9	15.490 ± 2.704^{a}	17.5	$18.720\pm4.831^{a,b}$	25.8	$23.676\pm9.523^{a,b}$	40.2
80	21.461 ± 5.145^{a}	24.0	24.269 ± 10.013^{a}	41.3	$26.919\pm7.736^{a,b}$	28.7	$29.506\pm8.255^{a,b}$	28.0
Inhaler no. 2								
20	3.559 ± 0.709	19.9	5.741 ± 0.575	10.0	9.025 ± 1.742^{b}	19.3	11.534 ± 2.945^{b}	25.5
35	3.133 ± 0.752^{a}	24.0	5.630 ± 1.941^{a}	34.5	$5.404\pm1.825^{a,b}$	33.8	$9.751\pm4.463^{a,b}$	45.8
50	6.689 ± 2.799^{a}	41.8	11.406 ± 2.478^{a}	21.7	$14.426\pm5.405^{a,b}$	37.5	$20.526\pm9.547^{a,b}$	46.5
80	18.055 ± 4.466^{a}	24.7	19.709 ± 4.822^{a}	24.5	$26.286\pm8.288^{a,b}$	31.5	$31.373\pm8.369^{a,b}$	26.7

$^{a–b}$ $p<0.05$ for the effect of ^{a} RH and aerosolization air ^{b} flow rate on dynamic charge; three-way ANOVA, Tukey's test for post-hoc statistical analyses

Rationale for Lactose Selection

In contrast to many studies that measured electrostatic charge and the subsequent charge decay in pharmaceutical powders subjected to a controlled triboelectrification process, the current study attempts to quantify the inherent charge of bulk lactose at rest and the dynamic charge of aerosolized lactose particles pertaining to its use in DPI. Lactose was employed in the investigation of electrostatic phenomenon in this study because it is the only major excipient used in DPIs (39). Although the drug component of the drug–lactose interactive mixtures for DPI was often found to possess significant specific charge after aerosolization (27,35), lactose constitutes the largest proportion of the formulation which could make up more than 99% of the product by weight (39). Thus, lactose particles could contribute significantly, even wholely, to the total electrostatic charges generated on DPI formulations. However, the electrostatic behavior of lactose aerosol particles was seldom the main focus of reported studies on aerosol electrostatics for DPI application. It is worthwhile to explore the electrostatic property of the lactose carrier as the first step towards a better understanding on the electrostatic property of the more complex DPI formulations comprising the drug–lactose interactive mixtures.

The InhaLac® 230 sieved crystalline lactose was employed as the model lactose in this study as it is one of the recently used lactose carrier in DPI formulations (40,41) having a particle size distribution suitable as coarse carrier particles. In this study, particle aggregation and adhesion of fine particle to the inhaler surface after aerosolization was not apparent as this lactose was considered to have good flowability, with a Hausner ratio of 1.16 (42). This was advantageous in minimizing error in charge measurement and bipolar charging due to particle adhesion on inhaler surface.

Table V. Effect of Inhaler in Producing a Statistical Difference in Dynamic Charge of Lactose at a Particular Air Flow rate and Relative Humidity

	Air flow rate (L/min)			
Relative humidity (%)	30	45	60	75
20	*	*	*	**
50	*	*	**	**
35	*	*	**	**
80	**	**	**	**

Two-sample independent t test
$*p<0.05$, $**p>0.05$

Data Analysis

The high variability and unpredictability of electrostatic charge measured in most inhaler systems as well as in other applications is well known (43) and generally acceptable to a certain extent. Such variability often precludes the application

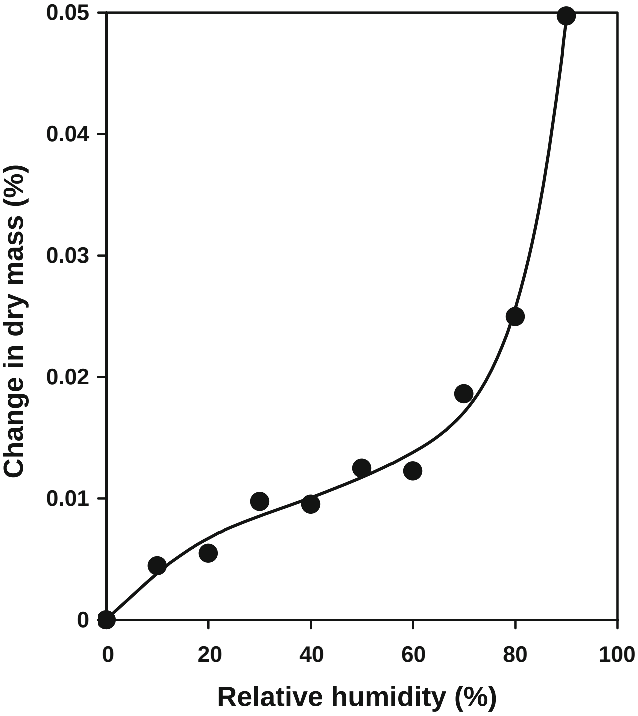

Fig. 4. Moisture sorption isotherm of lactose at 25°C.

of comprehensive statistical analysis for data interpretation. In this current study, the use of three-way ANOVA to confirm the observed effect of air flow rate, RH and inhaler on dynamic charge of lactose was an added advantage as the reliability of the trends observed could be verified and the empirical uncertainty often associated with electrostatic charge data interpretation could be minimized. This is because the two/three-way ANOVA is well regarded as a powerful tool for hypothesis testing as these statistical tests include the element of factorial experimental design.

Static Charge

Effect of Ambient RH on Static Charge

In this study, the initial charges of the lactose particles were found to be relatively low from the static charge measurement. Although statistically significant difference was not detected for initial charges from 35% to 50% RH, there was a gradual decrease in charge values as RH values were increased. The population variations for the initial charge was stable ($p>0.05$, Levene's test for equal variance), with coefficients of variation (CV) ranging from 28% to 42%. The inability to demonstrate significant difference in the initial charge values could be attributed to the fairly high variability as commonly perceived for electrostatic charge measurements. Thus, a greater change in RH was necessary before significant difference could be detected. An increase in ambient moisture level was reported to result in formation of a water film around the powder particles, facilitating relaxation or dissipation of static charge accumulated on particle surfaces (44–46). This could account for the lower initial charge of lactose at higher RH.

Effect of Gelatin Capsule and Handling on Static Charge

In DPI, the drug/carrier dispersion was usually inhaled from a gelatin capsule (47). It was important to investigate whether significant electrostratic charge would be induced on lactose particles from their contacts with the gelatin capsule surface. It is acknowledged that the action of powder transfer and capsule filling itself could potentially introduce significant amount of electrostatic charge. Therefore, caution was taken to carry out these actions in a controlled and reproducible manner. Although lactose particle contacts with the gelatin capsule surface had induced significantly higher static charge to the powder as compared to its initial charge, the charge magnitude created was still relatively low as compared to the dynamic charge induced by aerosolization. The tumbling or vibration effects during transport or handling of the DPI formulations were simulated by subjecting the capsulated lactose powders to tapping. This process was shown to result in substantial triboelectrification arising from the repeated impacts and friction of lactose particles with the capsule surface as well as between the lactose particles (11). In accordance to the triboelectrification behaviors of most powder materials, the specific charge of lactose was expected to increase with further increase in tapping frequency until a saturation charge value was attained (10). This phenomenon will be deemed to occur when sufficient amount of tapping were to be applied to the lactose powder.

Dynamic Charge

For dynamic charge measurement, the Faraday cage was mounted surrounding the dry powder inhaler, thus the charge value registered on the electrometer was essentially the net charge borne by the inhaler immediately after content aerosolization. The aerosolization process brought about triboelectrification of lactose particles and the resultant charges imparted on the lactose particles were equivalent in magnitudes but opposite in polarity to the charges measured on the inhaler. The charge polarity registered by the electrometer upon lactose aerosolization was negative, thus the charge polarity of the aerosolized lactose particles would be positive. The different polarity observed for static (negative) and dynamic (positive) charges could be attributed to exposure of the lactose to different types of contacting surfaces (27,33), that is, metal and plastic surfaces before measurement of the static and dynamic charge, respectively. The negative charge polarity measured on the inhaler indicated the presence of electron donor sites on the lactose particles and electron acceptor sites on the inhaler (33). Measurement of the electrostatic charge imparted on the inhaler instead of the aerosolized lactose particles offered an obvious advantage. This approach ensured that the charge values obtained represented the electrostatic charge of lactose induced solely by two factors relevant to the use of DPI, that is, inhaler material and air flow for aerosolization of the lactose. Once discharged from the inhaler into the flow tube, the charged lactose particles would be subjected to additional influence from the surface of the flow tube. Such influence would render in erroneous results if charge measurement were carried out directly on the aerosolized lactose particles.

It should be noted that the use of Rotahaler® in this study was not strictly in accordance to its standard use instruction. The lactose sample was not initially filled into a capsule but loaded directly into the air chamber of the inhaler. Thus, the barrel needed not to be turned to break open the capsule. In the normal usage of the Rotahaler®, one half of the opened capsule would rattle within the air chamber upon application of air flow. If normal inhaler usage is fully simulated, apart from the aerosolization air flow rate, RH and inhaler type, the net electrostatic charge measured would be dependent on the extent of triboelectification of lactose powder loaded into the capsule, consistency of capsule insertion, turning of the barrel, powder adhesion on capsule surface, and the speed and intensity of rattling which in turn would be dependent on the air flow rate. These added variables would certainly mask the effects of the fundamental factors affecting electrostatic charge under investigation in this study, that is the air flow rate, ambient RH and inhaler type. Therefore, the use of Rotahaler® was modified in this study in order to reduce the complexity of the charge measurement and direct powder loading into the inhaler chamber was deemed to be a less encumbered approach and could provide less confounded results with better measurement reproducibility.

Effect of Aerosolization Air Flow Rate on Dynamic Charge

Aerosolization has been shown to induce significant electrostatic charge on lactose particles by triboelectrification. Specific charges in the range of +2.3 to +30.3 nC/g were measured using the range of air flow rates (30 to 75 L/min) and RHs (20% to 80%) employed in this study. The observed increase in the extent of lactose particle triboelectrification with an increase in air flow rate is not unexpected as higher air flow rate would result in higher frictional forces on the particles upon aerosolization. In addition, the frequency and intensity of particles–inhaler wall/grid and particle–particle collisions were also increased. It was noted in a fluidized bed that particle–particle interactions usually resulted in almost equal number of positively and negatively charged particles while particle–wall interactions resulted in unipolar particle charges (32). Unlike the fluidization process in a fluid bed where intense particle–particle collisions occurred due to the opposing flows of particles, the overall mass powder flow during aerosolization was largely unidirectional in the direction of air flow. Air flow turbulence and eddies were expected to occur mainly at the grid but of relatively low intensity since Rotahaler® is among the commercial DPI inhalers showing the lowest air flow resistance (48,49). Thus, the resultant particle–particle collisions were deemed to be of much lower order and a major fraction of the charge generated was a result of particle–inhaler wall/grid interactions. This rendered in minimal bipolar charging as observed from the charge profiles (Fig. 2) of the lactose studied. It should be noted that since the Faraday cage employed in this study measured only the net charge, occurrence of bipolarity at any particular instant in time would not be registered on the resultant charge profiles. The trend of increased charge with increased air flow rate was also demonstrated in studies involving controlled triboelectrification of lactose using controlled gas velocities supplied to a cyclone charger lined with steel or plastic surfaces (33,50). The magnitude of specific charge on lactose was shown to increase linearly with increased gas velocities. In a fluidized bed, increased gas velocity was found to increase the induced charge on polyethylene particles due to enhanced particle–probe collisions (34).

Effect of Ambient RH on Dynamic Charge

While RH was shown to have important influence on electrostatic charge generation and dissipation on powder and polymer particles, the effect of RH on different systems has been largely unpredictable (12,51). Increased ambient RH was often found to result in decrease in magnitude of electrostatic charge on the surfaces of various particles (10,11,13,18,34,46,52,53). Increased powder storage RH was also found to decrease the electrostatic charge of the powder upon aerosolization at an ambient RH of 45% (35). When RH was increased, an adsorbed moisture layer, in the form of water vapor as well as hydrated ions, was formed on particle surfaces. These could serve as charge carriers that enhanced surface conductivity, thus facilitating charge relaxation or dissipation from particle surfaces into the free space. However, it was interesting to note a significant increase of dynamic charge of lactose when ambient RH was increased beyond 35% in this study. A number of studies had reported increased particle electrostatic charge upon RH increase (2,12,28,38,54–56). Rowley and Mackin (12) observed an increased triboelectrification of α-lactose monohydrate on polyvinyl chloride surface from 0% to 20% RH and attributed this to moisture sorption phenomenon. An increased charge to mass ratio was reported for sodium cromolyn powder when RH was increased and this was attributed to higher air permittivity at higher RH (2). According to the Pauthenier limit, the maximum charge limit on a particle surface is given by $Q_{\max}=4\pi\varepsilon_0 r^2 pE$, where $p=3\varepsilon_r/(\varepsilon_r+2)$, r= particle radius, E=electric field in which the particle is subjected to, ε_r=particle relative permittivity, and ε_0=air permittivity (53). Thus, particles would acquire larger magnitude of $Q_{\max}$ at higher RH. Although the increase in ε_0 with RH could be negligible under ambient temperature and pressure (28), the possibility of this effect on the microenvironment of the system under study could not be negated. The magnitudes of electrostatic charge on polystyrene and polyethylene particles were found to increase slightly from 10% to 65% RH but increased markedly from 65% to 90% RH (38). Kwok and Chan observed increased electrostatic charge on aerosolized budesonide from Pulmicort® Turbohaler® above 65% RH (28). An increase in tendency for agglomeration was expected for budesonide at high RH. Upon air flow application, successfully deaggregated agglomerates were deemed to consist of budesonide particles possessing higher electrostatic charges and coupled with slow charge dissipation of the insulating budesonide, thus high charge values were measured after powder aerosolization. However, the observed dynamic charge increase with RH for the InhaLac® lactose in this study was likely to follow a different mechanism than the aforementioned. This is because the agglomeration tendency of the InhaLac® powder was low in view of its much larger particle size, $d(0.5)=97.2$ μm as compared to budesonide in Pulmicort® Turbohaler® (<6 μm). At ambient conditions, the contacting surfaces were known to be interposed by adsorbed water layers which facilitated charge transfer between them. The thickness of this water layer increased with RH, resulting in larger area of contact and higher contact electric field, thus higher extent of charge transfer leading to greater amount of charges imparted on the contacting particles. The phenomenon of increased charge transfer leading to higher electrostatic charge accumulation when the contact area was increased had been demonstrated in polyethylene terephthalate polymer films in contact with metal surfaces (57). An increased contact electric field at RH>65% was likely to render in ionic dissociation of adsorbed water molecules as given by $H_2O \leftrightarrow H^+ + OH^-$ (38). The ionic charge densities of the particles were increased due to preferential attachment of ions of one polarity. Parallel to this proposition, hydrated ion clusters, $(H_2O)_nH^+$ and $(H_2O)_nOH^-$ originated from water molecules had been reported to affect surface conductivity and particle charge (52). Formation of hydrated ions provided additional charge sites on the particles (56).

It was apparent that adsorbed moisture on particle surfaces could exert opposing effects on static electrification and the net particle charge would be governed by the interplay among several different mechanisms (56). The moisture-mediated increase in surface conductivity had promoted greater charge transfer between the surfaces in contact, thus increased particle triboelectrification. However, the concurrent increase in charge dissipation or neutralization could reduce the net particle charges. The lactose powder used in this study was relatively non-hygroscopic in view of the low amount of moisture adsorbed (0.05% of dry weight) at 90% RH. However, it still demonstrated a gradual increase in moisture sorption when RH was increased from 0% to 90% (Fig. 4). This is consistent with previous reports on moisture sorption of lactose (35,58,59). The gradual increase in moisture sorption with RH would increase the area of particle surface coverage by the moisture layer, hence subjecting the triboelectification behavior of the particles to the influence of RH. It was envisaged that the mechanisms that promoted electrostatic charge generation on lactose particles, namely attachment of higher number of hydrated ions on particle surfaces and increased lactose–inhaler charge transfer predominated over charge dissipation. Thus, an increased specific charge of aerosolized lactose was observed at increased RH. The charge dissipation process was particularly insignificant for non-hygroscopic materials (28) and in non-equilibrium conditions during the dynamic charge measurement in this study. Charge transfer from lactose to the inhaler surface was apparent from the change of lactose charge polarity from negative (static charge) to positive charge upon aerosolization (dynamic charge). Unlike metal surfaces which are good conductors, it was conceivable that significant dissipation of charge induced on the inhaler and lactose particles by the aerosolization process would not be apparent as these materials are known to be insulators. For insulators, as exemplified by most pharmaceutical powders and polymers, the high resistivity exceeding 10^{13} mΩ (13,19) resulted in prominent retention of transferred charge and highly protracted charge dissipation (3,17,33,38). High propensity of charge retention on lactose particles charged by tumbling in a Turbula mixer was demonstrated in this study. Significant charge dissipation was not observed on charged lactose particles even after 30 min of holding time (Table III). Increased RH was reported to predominantly increase the rate of charge dissipation but not the charge generation on acrylate polymer (53) and polyethylene (34) particles. Considering such corroboration for this current study whereby charge dissipation process was deemed to be insignificant, the increase in RH would not bring about a decrease in the charge magnitude of the aerosolized lactose particles.

RH had demonstrated opposing effects on the static and dynamic charges of lactose measured in this study. While an increase in RH to 80% resulted in a decrease in static charge, similar RH increase resulted in a significant increase in dynamic charge. In the static charge measurement for bulk lactose, the particle surface was allowed to attain its equilibrium charge state *via* charge dissipation during the overnight storage. Increased extent of charge dissipation occurred at higher RH resulting in a lower magnitude of static charge. However, given the speed and dynamics of the dynamic charge measurement, there was insufficient time to facilitate dissipation of charges induced on lactose particles upon contact with the inhaler surface and aerosolization.

Effect of Repeated Inhaler Usage on Dynamic Charge

While many studies focused on the electrostatic property of DPI formulations in different types of inhaler devices (5,37), little effort had been expended into discriminating possible differences in the electrostatic behavior of powder aerosols in the same type of inhaler but subjected to different durations of use. This is an important practical issue for DPI application especially for Rotahaler® as this inhaler could be used repeatedly by the patient for an extended period of time. Although both the Rotahaler® inhalers employed in this study were physically identical and were subjected to the same pre-treatment, i.e. washing and conditioning prior to experiments, significant difference in lactose dynamic charges was observed between these inhalers at lower air flow rate and RH ranges. One of the possible reasons behind the observed difference in the inhalers was the extent of repeated use. Inhaler no. 1 had been used for a great number of measurements whereas Inhaler no. 2 was a relatively new device. Thus, Inhaler no. 1 would be subjected to a greater extent of surface stress and surface defects, thus affecting triboelectrification behavior of the inhaler and the powder particles. The manner in which moisture was adsorbed and distributed on these inhaler surfaces could be different especially at low RH since moisture adsorption was expected to be low. This could account for the statistical interaction observed between RH and inhaler. However, at higher air flow rates and/or RHs, triboelectrification of lactose particles was more intense and this process was dominated by the influence air flow rate and RH such that the effect of inhaler age became insignificant. Thus, statistically significant change in dynamic charges was not observed for the different inhalers at high air flow rate and/or RH conditions.

Practical Considerations on Drug Incorporated Carrier

This study has reported the electrostatic properties of a coarse lactose carrier which represented the main component of most DPI preparations. However, the incorporation of a drug for therapeutic application of DPI will likely to alter the electrostatic properties of each component in the drug–lactose interactive mixture. Thus, a discussion on the drug–lactose carrier electrostatic properties is presented, mainly in the context of the inherent material properties of the drug and lactose carrier in order to provide some practical insights for DPI application. The magnitude and polarity of electrostatic charge on a material is dependent on its position on the triboelectric series which ranks materials based on their work functions. A triboelectric series was proposed by Byron *et al.* based on fine particle dose charge of pure materials aerosolized from the Dryhaler® as follows: budesonide> lactose>albuterol sulfate>terbutaline sulfate≥albuterol base≥beclomethasone, in the order of increasing work function or electronegativity (5). This series indicated the propensity for drugs situated on the right hand side of lactose to acquire negative charges upon deaggregation from the interactive mixtures. Likewise, the lactose carrier will acquire positive charge. The observation of Young *et al.* of negative fine particle dose charge for albuterol sulfate aerosolized from the Cyclohaler® was coherent with the proposed triboelectric series (35). However, both positive and negative polarities had been reported for lactose carriers and/or drugs such as albuterol sulfate, terbutaline sulfate and budesonide depending on the formulation, drug and lactose particle sizes, lactose grade, capsule material and the type of inhaler used (20,21,27,37). In the drug incorporated lactose carriers, apart from the effects arising from the drug–lactose interaction, the mechanism of charge transfer with the inhaler surface and to a smaller extent, the interaction with external factors such as

RH and air flow rate could be different from the pure compounds. Thus, the electrostatic properties of the drug incorporated lactose carriers will not be easily predictable since it is highly system dependent.

CONCLUSIONS

The electrostatic property of a model lactose carrier for DPI, InhaLac® 230 had been investigated. As opposed to most reported studies on aerosol electrostatics focusing primarily on method development and exploring the influence of different types of inhalers, formulations and particle morphologies on electrostatic properties of inhaled particles, this study focused on investigation of the effects of aerosolization air flow rate, ambient RH and repeated inhaler use on aerosol electrostatic behavior associated with DPI applications. These factors are important as they bear direct practical relevance during the routine use of DPIs by patients.

Static charge of bulk lactose was significantly lowered when ambient RH was increased to 80%. Gelatin capsule and mechanical vibration such as tapping was found to induce significant static charge on lactose. However, the static charges of both free and capsulated lactose powders were much lower than the dynamic charges through the range of RH (20% to 80%) studied.

The dynamic charge of lactose demonstrated a linear increase with aerosolization air flow rate and RH. Increased particle triboelectrification with air flow rate was attributed primarily to increased frictional forces and collisions between particles and inhaler wall/grid. At higher RH, mechanisms leading to increased charge generation on lactose particle surfaces such as increased particle–inhaler charge transfer and presence of a greater amount of hydrated ions on particle surfaces were deemed to predominate over the increased propensity of surface charge dissipation. The insulating property of lactose and inhaler which tended to retain surface charges delayed surface charge dissipation at high RH.

Different extent of repeated inhaler use was found to have significant influence on particle charge due to inhaler surface modification arising from wear and tear. Thus, the implication of prolonged same inhaler device usage on aerosol electrostatics should be borne in mind when conducting experiments or using DPI in the clinical setting.

Although the factors affecting DPI electrostatics such as air flow rate and RH examined in this study have also been common topics of investigation in other reported studies, the significance and unique angles of the current study can be highlighted by three salient points. Firstly, this is the first study investigating the influence of repeated inhaler use on the electrostatic behavior of aerosolized powder from a DPI. The significant influence of prolonged, repeated inhaler usage on DPI electrostatics demonstrated in this study constitutes a new finding that addresses one of the most important but often neglected practical issues pertaining to multi-dose DPI device usage. Secondly, the influence of a series of air flow rate on the dynamic charge of aerosolized powders, albeit following an expected trend as implied by previous studies conducted on many pharmaceutical powders, was not objectively demonstrated in the DPI setting before. Thirdly, the findings of the effect of ambient RH on dynamic charge of the InhaLac® lactose carrier serve as a useful complement to findings afforded by Kwok and Chan on the pure drug powders in DPI systems (28). These are the only two studies to date that reported systematic investigations on the effect of a wide range of practically and clinically relevant ambient RH on electrostatic properties of aerosolized powders from DPIs. It was also remarkable to note from these studies that the ambient RH dependent triboelectrification of aerosolized powders of the pure drug *versus* coarse lactose carrier was governed by different dominant mechanisms, that is, moisture induced agglomeration *versus* charge transfer, respectively.

In conclusion, this study has highlighted the important roles of variables commonly encountered in the use DPI such as variation in patient's inspiratory flow rate, RH conditions and repeated inhaler device usage on the electrostatic property of lactose carrier particles. In view of the possible influence of electrostatic property on drug delivery from a DPI, aerosol electrostatics and factors affecting it should be given due consideration in formulating and evaluating DPI performance and clinical efficacy.

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