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The Effect of Relative Humidity on Electrostatic Charge Decay of Drugs and Excipient Used in Dry Powder Inhaler Formulation

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Electrostatic forces arising from charge accumulation on drug and excipient powders cause agglomeration and adhesion of particles to solid surfaces and problems during the manufacture and use of many pharmaceutical dosage forms, including dry powder inhalers (DPIs). The ability of materials to dissipate the acquired charge is therefore important and the aim of this work was to investigate the charge decay of salbutamol sulfate, ipratropium bromide monohydrate and α-lactose monohydrate. Differences in tri-phasic charge decay rates of the three materials in the order ipratropium bromide > lactose > salbutamol sulfate were demonstrated after corona charging and all materials showed an increased decay rate as the relative humidity was increased up to 86%. Preformulation knowledge of charge accumulation and decay in such materials will contribute to formulation, manufacture and performance of pharmaceutical dosage forms in general, and in particular DPIs.

Keywords dry powder inhaler; charge decay; corona charging; relative humidity

INTRODUCTION

Powders accumulate electrostatic charge from interparticulate collisions and contact with various solid surfaces that may lead to adhesion and agglomeration and hence problems during powder processing, especially in the case of dry powder inhaler (DPI) formulations (Rowley, 2001). The charge accumulation process may be explained by electron transfer and hence will depend on the work function of the contacting materials (Bailey, 1993) which is sensitive to the surface states (Lowell & Rose-Innes, 1980). Surface resistivity (Paasi et al., 2001) of contacting materials, contact surface roughness and contamination (Eilbeck et al., 1999; Elajnaf et al., 2006) have all been shown to influence powder charge acquisition. Relative humidity (RH) has a strong influence on charge generation in powders with most authors reporting a decrease in charge as rh is increased (Rowley & Mackin, 2003).

An important consideration is the timescale for electrostatic charge dissipation, for example when charge decay occurs rapidly, there will be a lower likelyhood of significant charge build-up on the material. Sharma et al. (2001) showed the surface resistivity of polymer powders can be lowered by orders of magnitude following adsorption of moisture on the powder surface, resulting in a corresponding lowering of acquired charge due to an increased charge decay rate. Charge decay is complex and has been measured by different techniques with each representing a different view of the subject (Paasi et al., 2001), however, measurements using corona charging have been found to correlate with charging due to triboelectrification (Chubb, 2002). Since decay curves are often characterized by a series of exponential decay phases and hence difficult to interpret, Malave-Lopez and Pelag (1985) suggested linearization of the curves in order to compare decay behaviour and this approach has been used in this work. Previous investigations of salbutamol sulfate, ipratropium bromide monohydrate and α-lactose monohydrate (Elajnaf et al., 2006) during triboelectrification with polymers used in inhaler device fabrication, e.g. polypropylene and acetal, showed charge accumulation and sign to be dependent on the nature of the powder and polymer used as a contact surface. The aim of this study was to investigate the charge decay characteristics of salbutamol sulfate, ipratropium bromide monohydrate and α-lactose monohydrate under different humidity conditions (0–86% RH). In order to investigate the effect of RH, it was necessary to design and construct an apparatus incorporating a corona charging unit and Faraday well measurement system which was based on a previous system (Carter et al., 1998). It is envisaged that such preformulation knowledge of charge accumulation and decay in pharmaceutical drugs and excipients will contribute to improved formulation, manufacture and performance of dosage forms, and in this case DPIs.

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MATERIALS AND METHODS

Materials

Micronized salbutamol sulfate and ipratropium bromide monohydrate were supplied by GlaxoSmithKline (Ware, UK) and Boehringer Ingelheim (Ingelheim, Germany), respectively. Regular lactose (Lactochem, α-lactose monohydrate) was obtained from Borculo Whey (Chester, UK). A 63–90 μm size fraction of lactose was obtained by vibratory sieving of the regular lactose through 90 μm and 63 μm test sieves (Endecotts, London) for 20 min. The powder fraction retained on the 63 μm sieve was then air jet sieved (Alpine, Augsburg, Germany) for 10 min on a 45 μm sieve. Particle size distribution of the micronized drugs and lactose (63–90 μm) size fraction was determined by laser diffraction in the dry state (Helos, Sympatec GmbH, Clausthal-Zellerfeld, Germany) fitted with a Rodos (Sympatec GmbH, Clausthal-Zellerfeld, Germany) powder dispenser operated at 2 bar.

Charge Decay Apparatus

The charging unit consisted of a corona charging needle connected to high voltage power supply (Carter et al., 1998). The corona charging needle was fitted above an earthed stainless steel plate fitted to a metallurgical microscope (Met-87, Buehler, Coventry) stage, on which the samples were placed for charging. The charging unit was enclosed in a humidity cabinet and accurate height adjustment was achieved by extending the microscope graduated ring to the outside of the humidity cabinet using Hardy-Spicer couplers. An earthed stainless steel plate was used to rest the analytical sample between measurement intervals and a Faraday well connected to an electrometer measured the charge on the samples. A monocular microscope was used to confirm the distance (300 μm) between the corona needle and the sample to be charged. The humidity control unit consisted of an air compressor (Jun-Air model 2000, Bromsgrove) that supplied dry air to two lines using a 'T' bar connector. One line was connected to a valve (Norgren Martonair, Staffs) and the other passed through a Dreschel bottle filled with water to produce saturated (100% RH) air and subsequently connected to another valve. The two lines were then recombined using a 'T' bar connector and the two valves were used to control the flow rates of the dry and humid air to produce air with 23, 55, and 86% RH. For 0% RH, one dry air line from the compressor passed through a Dreschel bottle filled with crystal silica gel. Figure 1 illustrates the % RH generated by the humidity system versus time to reach equilibrium, measured using a humidity-temperature probe (Testoterm 601, Testo Ltd., Hampshire) with the calibration (±1%) checked using saturated salt solutions (23, 55 and 86% RH).

Preparation of Samples for Charge Decay

Corona charging of powdered samples presents considerable practical difficulties, therefore in order to facilitate handling and charging of the samples, the powders were compacted. Unlubricated samples (approximately 35 mg) of the micronized salbutamol sulfate, ipratropium bromide, lactose (63–90 μm) size fraction were compressed by manual operation of F1 single punch tablet machine (Manesty, Liverpool) keeping the upper and lower punch settings constant to produce circular flat-faced compacts of 4.8 mm diameter. Each compact was brushed under optical microscopy to remove unwanted fine adhered particles, weighed and stored until required for characterization and charging experiments.

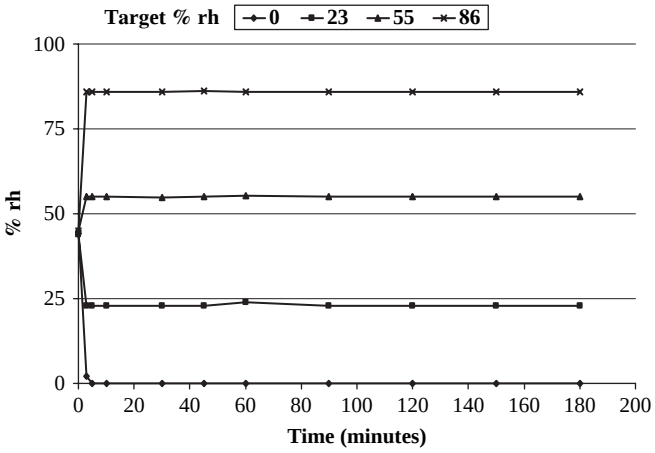

FIGURE 1. Percent RH versus time for humidifying apparatus.

Characterization of Sample Compacts

The surface of the compacts was assessed by scanning electron microscopy (Cambridge S100, Cambridge Instruments) to characterize the morphology and ensure that unwanted fine particles were not present.

The specific surface area ($m^2\ g^{-1}$) of each compact was obtained by single point nitrogen adsorption (Flowsorb II 2300, Micromeritics, Norcross).

Thermal analysis of the powders and compacts was undertaken using differential scanning calorimetry (DSC Q1000, TA Instruments, Crawley). Samples were measured in sealed aluminium pans at a heating rate of 10°C min^{-1} in a temperature range from 40 to 250°C under nitrogen.

Moisture isotherms for the compacts were determined using a dynamic vapour sorption apparatus (DVS 1000, Surface Measurement Systems Ltd., London) at 25°C. Compacts were weighed in the sample cell and equilibrated at 0% RH until a constant mass obtained. Each sample was subjected to incremental increase in RH in steps of 15% from 0 to 90%.

Charge Decay Measurement

The weighed compacts were stored for 4 weeks in Pyrex desiccators containing silica gel or saturated salt solutions of potassium acetate, magnesium nitrate and potassium chloride in order to generate atmospheres of constant relative humidities

(0, 23, 55, and 86% RH) measured with a humidity probe (Testoterm 601). After storage, the compacts were transferred using an earthed instrument to the earthed metal plate inside the charging apparatus which was equilibrated to the same RH as that of the storage RH. The compacts were then exposed to the corona charging needle (–3.0 kV) for 3 min at a separation of 300 μm (Carter et al., 1998). The magnitude/sign of the charge was determined immediately and then at selected time intervals by transferring the compact using an earthed instrument to the Faraday well connected to an electrometer (Keithley 610, Keithley Instruments Inc., USA). This measurement method has been used previously (Carter et al., 1998) and the charge accumulation (nC g^{-1}) and decay were determined for 15 compacts of each drug and lactose.

RESULTS AND DISCUSSION

Characterization of Sample Compacts

Surface rugosity, specific surface area and moisture uptake for the compacts were investigated in order to facilitate the explanation of the effects of moisture on charge acquisition and decay.

Figures 2–4 show differences in the compact surface features for the materials with the ipratropium bromide and lactose displaying the smoothest surfaces and the salbutamol sulfate compacts showing irregular and porous morphology. DSC thermograms confirmed that compaction of the powders of each material did not alter thermal behavior.

The mean specific surface areas (n = 3) for the lactose, salbutamol sulfate and ipratropium bromide compacts were 0.136, 1.063, and 0.060 m^2 g^{-1} respectively, whereas median particle size for the powders was 92.2, 1.7, and 1.7 μm respectively. From the median particle size values, it would be anticipated

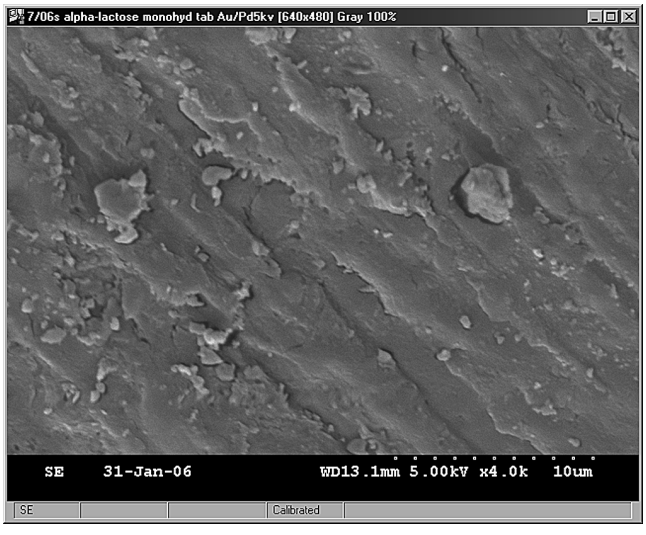

FIGURE 2. Scanning electron micrograph of surface of lactose compact (×4000).

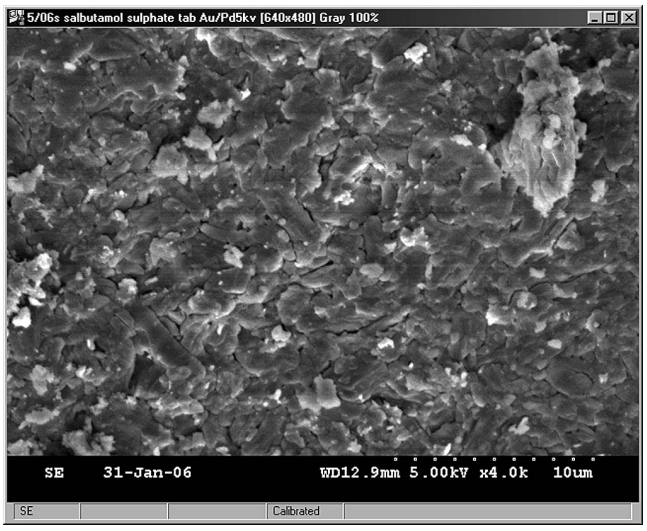

FIGURE 3. Scanning electron micrograph of surface of salbutamol sulfate compact (×4000).

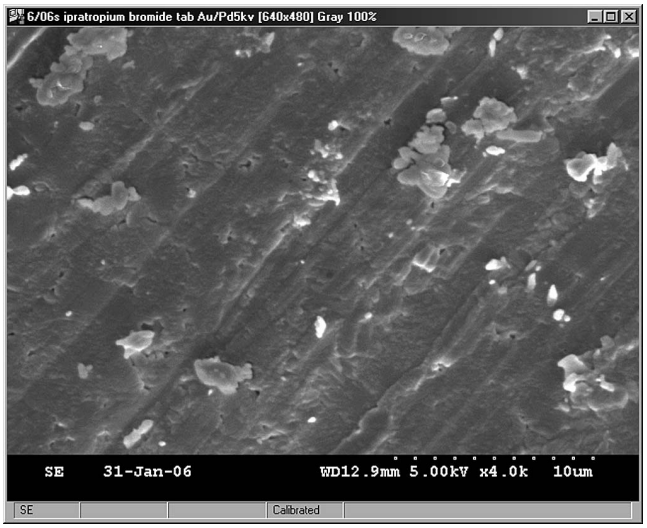

FIGURE 4. Scanning electron micrograph of surface of ipratropium bromide compact (×4000).

that the compacts of the drugs would have similar specific surface areas and of greater value than that for the lactose compacts. Assuming apparent particle densities of 1.54, 1.37, and 1.34 g cm^{-3} for the lactose (Kibbe, 2000), salbutamol sulfate (Moffat et al., 1986) and ipratropium bromide (by calculation of the mass of a determined volume of powder (Multi-pycnometer, MVP-1, Quantachrome, New York)), the porosity of the ipratropium bromide compacts was calculated to be lower (6%) than both the lactose (12%) and salbutamol sulfate (15%) compacts. The lower porosity of the ipratropium bromide compacts, along with the more irregular and porous surface of the salbutamol sulfate compact (Figures 3 and 4) provide evidence to explain the large difference in specific surface area of the

compacted drugs. For comparison, calculation of the mean external surface area of the compacts assuming each to be a regular solid cylinder gave similar values of 1.64, 1.75, and 1.69×10^{-3} m^2 g^{-1} for lactose, salbutamol sulfate and ipratropium bromide respectively, illustrating the vast increase in surface area for each compact as a result of surface irregularities and porosity.

Table 1 gives mean moisture sorption values (n = 2) at selected RHs for the compacts obtained from the vapor sorption studies. The lactose and ipratropium bromide compacts showed similar moisture uptake profiles (sorption) with mean values of 0.1742% w/w and 0.1725% w/w for lactose and ipratropium bromide respectively at 90% RH, although uptake by ipratropium bromide was lower at all other RH values between 15 and 75%. The salbutamol sulfate compacts showed higher uptake than the lactose and ipratropium bromide compacts with a mean value of 0.3905% w/w at 90% RH. Generally, all compacts are relatively non-hygroscopic and each showed a continuous sorption (moisture uptake) and desorption when the RH was increased up to 90% and then adjusted down to zero, with no events that would indicate change in crystal structure. A small hysteresis for each compact suggested small differences in adsorption-desorption kinetics.

Measurement of Electrostatic Charge Decay of Lactose, Salbutamol Sulfate and Ipratropium Bromide

Table 2 shows the mean specific charge for each compact stored and measured under different humidities and these results establish considerable differences in charge decay properties as a result of the compact material type and experimental RH conditions. The mean charge on all the compacts was zero immediately before corona exposure. A relationship between charge accumulation following corona exposure and material type has not been established, nor has a relationship between initial charge and RH. Co-efficient of variation values for the initial charge after corona varied between 8.9 and 18.7% and therefore the reproducibility of these results was considered acceptable. At 0% RH, salbutamol sulfate displayed the longest time for the charge to decay, conversely ipratropium bromide gave the shortest decay times. For all three materials, a reduction in decay time is a clear effect after increasing RH from 0 to 23%, and salbutamol suphate showed a further decrease in decay time from 23 to 55% RH, whereas lactose and ipratropium bromide did not acquire any charge at 55% RH. Although the DVS studies showed that salbutamol sulfate had a higher moisture uptake than lactose and ipratropium bromide, it was not apparent whether this moisture was adsorbed on the surface or absorbed in the bulk of the compacted sample. The photomicrograph of the salbutamol sulfate compact surface (Figure 3) shows an irregular and cracked surface which gave a higher surface area than the other material compacts. Moisture uptake at a specific RH may therefore be distributed into the compact pore structure as well as at the surface and further support for this is given by the compact porosity values, which showed the salbutamol sulfate compacts to be more porous than the lactose and ipratropium compacts.

TABLE 1
Mean Moisture Sorption (n = 2) from DVS

	% w/w Moisture Sorption		
RH	Lactose (63–90 μm)	Salbutamol Sulfate	Ipratropium Bromide
0	0.0000	0.0003	0.0000
15	0.0244	0.0548	0.0188
30	0.0470	0.1151	0.0304
45	0.0734	0.1665	0.0472
60	0.1018	0.2279	0.0766
75	0.1317	0.3679	0.1181
90	0.1742	0.3905	0.1725

Assuming a cross-sectional area of a water molecule is 0.106 nm^2 (Wang et al., 2003) and using the data for mean specific surface area and water sorption data (Table 1) for lactose and the drug compacts, simple calculations suggest moisture contents well in excess of a monolayer coverage for lactose and ipratropium bromide at 15% RH (approximately 10 fold), whereas salbutamol sulfate compacts had a lower calculated moisture content approximately two fold greater than that required for a monolayer at that rh. At 55% RH, lactose and ipratropium bromide compacts had moisture contents approximately 25 and 40 fold greater than that required for monolayer coverage, whereas salbutamol sulfate compacts again gave lower moisture contents, approximately five fold greater than required for a monolayer. The salbutamol sulfate compacts were the only ones that acquired a charge at 55% RH and this may be due to lower amounts of moisture at the surface of the compact. Podczeck et al. (1997) suggested that moisture condensed at 55% RH is enough to cause dissolution in parts of the surface of α-lactose monohydrate particles but the effect of this on charge acquisition and decay is unknown. Both drugs used in this work have aqueous solubility values greater than for lactose, however the effects of surface dissolution at elevated RHs with these drugs has not been studied in this research.

The charge decay characteristics of a material are very dependent on its electrical resistivity and in the case of compacted material, surface charge decay will be more significant than volume charge decay, hence surface resistivity will be a controlling factor for decay rate (Sharma et al., 2001). Paasi et al. (2001) showed that surface resistivity decreases with increasing RH and therefore it is proposed that moisture adsorption will make the compacts more conductive due to the formation of moisture layers over the surface which increases the rate of charge dissipation. Literature values for volume resistivities for lactose and salbutamol sulfate are 1.3×10^7

TABLE 2
Mean Charge Values (n = 15) for Compacts Stored and Measured at Different RH (20 ± 3°C).
Percent Coefficient of Variation (% CV) in Parentheses

	Lactose		Salbutamol Sulfate			Ipratropium Bromide	
% rh	0	23	0	23	55	0	23
Mean compact mass (mg)	35.0	34.9	35.0	35.1	35.2	35.0	34.9
Mean (−ve) charge (nC g^{-1}) (% CV) immediately:							
Before charging	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
After charging	11.5	14.2	10.5	7.2	16.5	15.6	8.3
	(13.8)	(11.3)	(11.5)	(10.2)	(14.3)	(14.2)	(18.7)
After: 5 min	8.5	1.3	7.8	5.5	7.9	9.1	0.0
	(11.3)	(80.0)	(20.3)	(14.8)	(18.5)	(12.3)	(0.0)
15 min	7.1	0.5	6.9	4.9	5.2	6.6	
	(10.5)	(106.5)	(20.1)	(14.7)	(24.4)	(17.5)	
30 min	5.4	0.0	6.0	3.8	2.9	4.0	
	(13.2)	(0.0)	(23.0)	(20.9)	(37.7)	(16.2)	
60 min	3.2		4.6	2.7	0.9	1.0	
	(16.7)		(26.8)	(20.6)	(67.4)	(73.7)	
90 min	1.9		3.9	2.0	0.0	0.0	
	(23.9)		(31.6)	(19.6)	(0.0)	(0.0)	
120 min	1.5		3.3	1.3			
	(24.9)		(32.7)	(38.4)			
180 min	0.0		2.6	0.0			
	(0.0)		(35.5)	(0.0)			
240 min			2.2				
			(40.4)				
600 min			1.2				
			(55.6)				
900 min			0.0				
			(0.0)				

(Suggett, 1996) and 10^{10}–10^{11} Ω m (Bennett, 1998) respectively, but values for ipratropium bromide are not available. Although these are not surface resistivity values, they suggest that salbutamol sulfate would take longer than lactose for charge dissipation as illustrated in Table 2. In experiments without controlling RH (Carter et al., 1998), the decay rate of salbutamol sulfate compacts was found to be considerably lower than for lactose compacts.

Plots of the mean charge versus time (data presented in Table 2) provided typical concave downward curves (Malave-Lopez & Pelag, 1985) that decay to their lowest detectable or residual charge, which is zero in these cases, and as a typical example, Figure 5 shows decay curves for each drug and lactose at 0% RH.

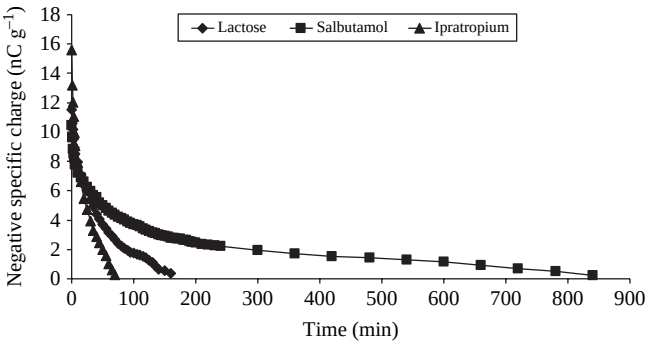

FIGURE 5. Decay curves at 0% RH.

Charge decay should follow an exponential route provided the decay is by conduction and the material is ohmic (Coelho, 1985). The pharmaceutical materials used in this work are unlikely to be ohmic, however ln charge versus time plots have been constructed and are shown in Figures 6–9. These plots show that the decay curves may be characterized by a series of three exponential decay phases, with correlation coefficients (r^2) quoted to show linearity and clearly demonstrate

differences in decay properties as a result of material type and RH. Each plot generally shows a rapid charge decay occurring within approximately the first five min followed by a lower decay rate for most of the charge decay cycle. The decay rate increases towards the end of the cycle in all cases except for the salbutamol sulfate compacts at 0% RH (Figure 7) where the decay finishes with the lowest rate. Figures 6 and 8 show that increasing the RH from 0 to 23% results in an increased charge decay rate for both lactose and ipratropium bromide compacts, the ipratropium bromide decaying more rapidly at each RH. For example, the charge decay rate constants (min^{-1}) have been calculated from the gradients of the linear phases and show at 0% RH, initial rates of 0.06 and 0.1 min^{-1} for lactose and ipratropium bromide respectively, falling to 0.02 and 0.04 min^{-1} for the longer second phase of decay. At 23% RH, lactose and ipratropim bromide gave decay rate constants of 0.47 and 1.27 min^{-1} respectively for the initial decay phase followed by 0.09 and 0.64 min^{-1} respectively for the second phase.

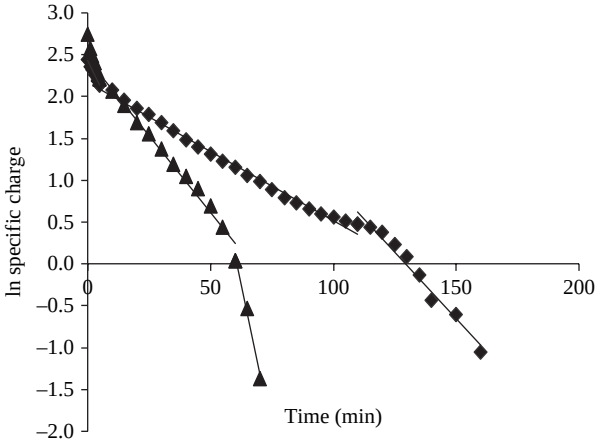

FIGURE 6. Plot of ln specific charge versus time for lactose and ipratropium bromide at 0% RH. r^2 for lactose (◆): 0.9939 (0–5 min), 0.9927 (5–110 min), 0.9709 (110–160 min). r^2 for ipratropium bromide (▲): 0.9875 (0–5 min), 0.9853 (5–60 min), 0.9872 (60 –70 min).

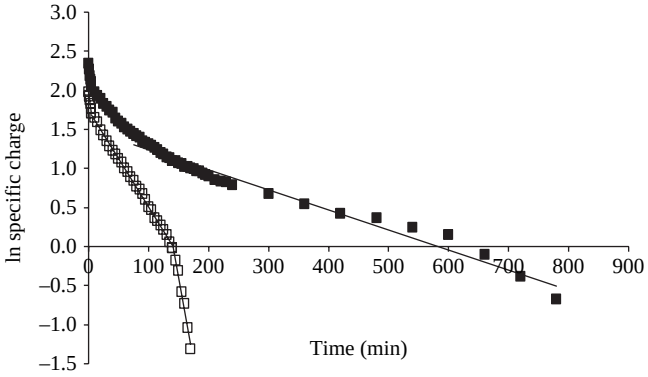

FIGURE 7. Plot of ln specific charge versus time for salbutamol sulphate. r^2 for 0% RH (■): 0.9711 (0–5 min), 0.9915 (5–75 min), 0.9709 (75–780 min). r^2 for 23% rh (□): 0.9967 (0–5 min), 0.9983 (5–140 min), 0.9842 (140 –170 min).

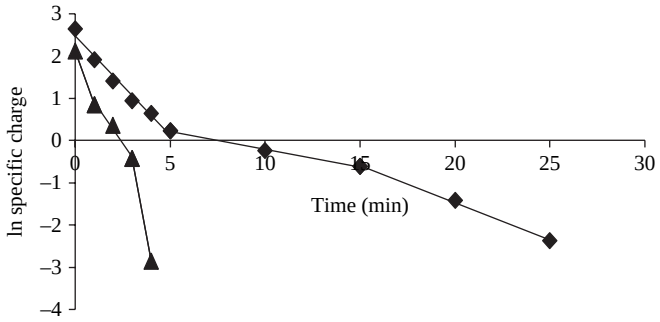

FIGURE 8. Plot of ln specific charge versus time for lactose and ipratropium bromide at 23% RH. r^2 for lactose (◆): 0.9789 (0–5 min), 0.9975 (5–15 min), 0.9979 (15–25 min). r^2 for ipratropium bromide (▲): 1.0000 (0–1 min), 0.9817 (1–3 min), 1.0000 (3–4 min).

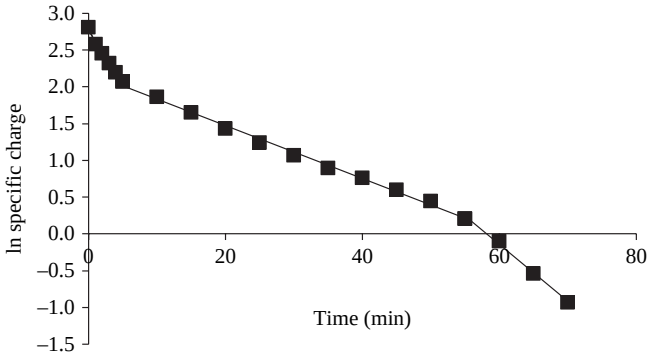

FIGURE 9. Plot of ln specific charge versus time for salbutamol sulphate at 55% RH. r^2: 0.9880 (0–5 min), 0.9957 (5–55 min), 0.9953 (55– 70 min).

Figures 7 and 9 show the charge decay of salbutamol sulfate compacts at 0, 23 and 55% RH and demonstrate increased decay rates at increased RH and show a lower decay rate at 0 and 23% RH when compared with lactose and ipratropium bromide. For example, for the initial phase of decay, rate constants of 0.05, 0.05, and 0.14 min^{-1} were obtained at 0, 23, and 55% RH, respectively, decreasing to 0.009, 0.012, and 0.036 min^{-1}, respectively for the second decay phase. Although separation of the decay curves into a series of exponential phases is a useful way of comparing the decay behaviour, it is evident that the decay curves are governed by more than a single time characteristic and a simple model to describe the multi-phase charge decay is needed.

Linearization of electrostatic charge decay curves as a method of comparing decay behavior can be achieved using Eq. 1 (Malave-Lopez & Pelag, 1985):

$$\frac{Q_0 t}{Q_0 - Q(t)} = k'_1 + k'_2 \mathrm{t} \qquad (1)$$

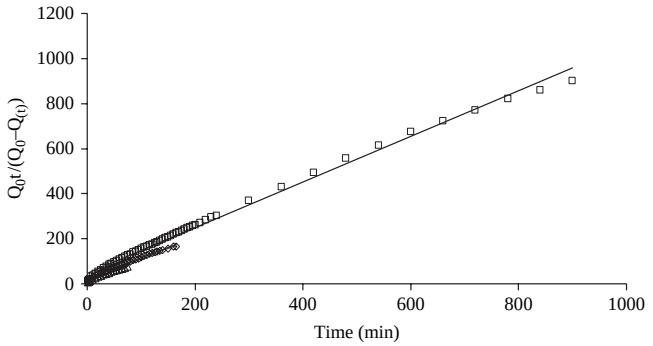

FIGURE 10. Linearisation plot of charge decay at 0% RH for lactose (◇) (r^2 = 0.9880), salbutamol sulphate (■) (r^2= 0.9939) and ipratropium bromide (△) (r^2 = 0.9878).

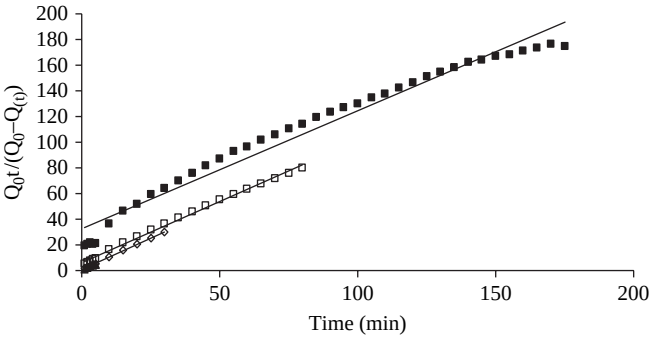

FIGURE 11. Linearisation plot of charge decay at 23% RH for lactose (◇) (r^2 = 0.9999), salbutamol sulphate (■) (r^2= 0.9715) and ipratropium bromide (▲) (r^2 = 0.9978) and salbutamol sulphate at 55% RH (□) (r^2 = 0.9965).

TABLE 3
Initial Charge Decay Rate ($1/k'_1$)(min^{-1}) for Compacts at Selected RH

% RH	Lactose	Salbutamol Sulfate	Ipratropium Bromide
0	0.043	0.021	0.104
23	1.243	0.030	1.751
55		0.159	

where, Q_0 is initial charge, $Q(t)$ the charge after time t, and k'_1, and k'_2 are constants. $1/k'_1$ and $1/k'_2$ are the initial rate constant (time units) and asymptotic or equilibrium charge ratio (dimensionless) respectively. Figures 10 and 11 show the fit of this equation to the charge data presented in Table 2 and along with r^2 values, demonstrate linearity in all cases, thus providing further comparison of the decay of the lactose, salbutamol sulfate and ipratropium bromide at different RHs. Table 3 illustrates the initial charge decay rate ($1/k'_1$) (min^{-1}) obtained from Figures 10 and 11. Furthermore, calculated values of ≥ 1 for $1/k'_2$ were achieved by all materials, indicating complete charge dissipation, except for salbutamol sulfate at 0% RH ($1/k'_2$ = 0.989). The initial charge decay rates ($1/k'_1$) for lactose, salbutamol sulfate and ipratropium bromide were 0.043, 0.021, and 0.104 min^{-1} respectively, at 0% RH confirming the highest decay rate for ipratropium bromide and the lowest for salbutamol sulfate. These values increased to 1.243, 0.030, and 1.751 min^{-1}, respectively, at 23% RH and further increased to 0.159 min^{-1} for salbutamol sulfate at 55% RH, showing that increasing RH reduces the timescale for charge dissipation.

For comparison, Malave-Lopez and Pelag (1985) showed the initial dissipation rate for a herbicide powder was 0.28 day^{-1} at 52% RH (r = 0.9927) which increased to 0.79 hr^{-1} at 92% RH (r = 0.9964). Exposure at 92% RH resulted in almost complete charge dissipation ($1/k'_2$ was approximately 1), whereas at 52% RH only about 60% of the charge was dissipated ($1/k'_2$ = 0.63). The values for $1/k'_1$and $1/k'_2$ for salbutamol sulfate, ipratropium bromide and lactose in this work may therefore be used to provide a method for characterizing the complex charge decay curves.

CONCLUSION

The electrostatic charge decay of α-lactose monohydrate, salbutamol sulfate and ipratropium bromide has been studied under selected humidity conditions using an apparatus designed and constructed for this work incorporating a corona charging unit and Faraday well measurement system. Differences in decay behavior of the three materials have been demonstrated with ipratropium bromide showing the highest decay rates and salbutamol sulfate the lowest. All materials showed an increased decay rate as the relative humidity was increased from 0% up to 86% and it was proposed that adsorbed moisture led to increased charge dissipation and differences in moisture uptake could in part explain the differences in decay rates. The decay curves for the materials were characterized by a series of three exponential decay phases and although this provided useful information, difficulties and limitations with this analysis were experienced and hence the curves were linearized using Eq. 1. This process highlighted the differences between salbutamol sulfate and ipratropium bromide and enabled comparison of the whole decay curves that were governed by more than a single time characteristic.

This work provides preformulation knowledge of importance to formulation, processing and manufacture of pharmaceutical dosage forms where problems arise due to electrostatic charge accumulation. How rapidly a charge distributes over the surface of solid drug/excipient and down to earth is of fundamental importance and careful selection of RH conditions and formulation components may lead to a decrease in the timescale for charge dissipation. It is clear from this research that the two selected drugs, both used in inhaler formulations, have very different charge and charge decay characteristics and this knowledge may be useful during processing into DPI formulations with lactose.

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