Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 282 (2004) 107–114
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Effect of particle morphology on the triboelectrification in dry powder inhalers

Matti Murtomaa [a,*], Velipekka Mellin [a], Päivi Harjunen [b], Tapio Lankinen [c], Ensio Laine [a], Vesa-Pekka Lehto [a]

[a] *Department of Physics, University of Turku, FIN-20014 Turku, Finland*
[b] *Department of Pharmaceutics, University of Kuopio, FIN-70211 Kuopio, Finland*
[c] *Focus Inhalation, P.O. Box 980, FIN-20101 Turku, Finland*

Received 21 January 2004; received in revised form 1 June 2004; accepted 3 June 2004

Available online 30 July 2004

Abstract

Electrostatic charge of lactoses of different particle morphology and amorphous contents were measured during actuation from two different dry powder inhalers (DPIs). Triboelectric studies may give important information when new inhaler devices, materials and formulations are designed in order to improve the drug deposition. Two inhalers, Taifun™ (Focus Inhalation Oy, Finland) and Clickhaler™ (Innovata Biomed Ltd., UK) were filled with lactose powders which were spray dried from different solutions or suspensions of lactose, ethanol and water. Differences in the amorphous contents were determined with isothermal microcalorimetry (IMC) and X-ray diffraction (XRD) and the particle morphology was examined with laser diffraction and electron microscopy (SEM). Samples were actuated from the inhalers at given intervals into the Faraday pail and the generated charges were recorded. Increase in the water concentration of the feed suspension had negligible effect on the charging until it exceeded 70%. Reproducibility of the measurement was found to be better with samples of homogenous particles and higher crystallinity while more amorphous samples with different morphology and wide particle size distribution showed change in the sign of the charge in addition to higher variations of the magnitude. In this study we show that different inhalers, as well as the morphology of the lactose powder, has noticeable effects on the generated charge which has previously been shown to affect the deposition of the drug and the function of an inhaler.

Keywords: Dry powder inhaler; Aerosol; Electrostatic charge; Spray dried lactose

1. Introduction

Electrostatic charges are generated when two different materials are brought into contact and then separated (Harper, 1967). Charges on the pharmaceutical materials often arise due to high surface resistivity of the materials which prevents the charge transferred in contact from leaking back. Charge retention can be reduced by lowering the resistivity by adding moisture (Grosvenor et al., 1991) or some antistatic additive but often it is not advisable when pharmaceutical materials are concerned due to, e.g. stability.

In the pharmaceutical industry the charging of powders is usually a nuisance which may obstruct the

* Corresponding author. Tel.: +358-2-3335735; fax: +358-2-3335993.
E-mail address: matti.murtomaa@utu.fi (M. Murtomaa).

0378-5173/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2004.06.002

manufacturing of the product, effect the powder flow and packing behavior, and reduce fill and dose uniformity (Staniforth, 1994). However, when dry powder inhalers are used, static electricity may improve the deposition of a drug particle, as demonstrated by computer simulations (Balachandran et al., 1997; Bailey et al., 1998; Bailey, 1997). It has been shown that the deposition of inhaled drug aerosol in the respiratory system is governed by inertial impaction, gravitational sedimentation, Brownian diffusion, interception and electrostatic forces (Gonda, 1992). Electrostatic forces have been shown to dominate the deposition particularly in the alveolar region, and these forces can be divided into two different categories: space charge and image charge. Space charge seems to have more effect at the upper region of the respiratory tract, especially when the aerosol cloud is dense, while the image charge forces are dominant in the alveolar region. Similar results have also been reported with nebulisers with enhanced charge and these studies suggested that the deposition could be significantly improved (Hashish and Bailey, 1987, 1991). In addition to computer simulations, clinical studies have also been carried out and they have given evidence about the profits of electric charge on aerosols (Hashish et al., 1998; Fleming et al., 1996, 1997).

In addition to the improved deposition, static charge can also be utilized in targeting the aerosol to the desired location of the respiratory tract (Balachandran et al., 1997).

Powders which are used in DPIs are usually mixtures of small drug particles ($<5\,\mu m$) and larger additive particles (63–90 μm). When a powder has more than one component, electrostatic charging becomes more difficult to understand. In addition to contacts with the inhaler surface, different particles also contact other particles and this may lead to very complicated bipolar charging process. Drug and additive particles will charge with opposite polarity when they contact each other, and this may lead to reduced particle separation and weak performace. Also, small particles tend to adhere to the inhaler surface more than the larger ones which leads to increasing number of contacts between adhered powder and the mixture (Murtomaa and Laine, 2000; Murtomaa et al., 2002a). When a surface has been contaminated with a certain powder, following contacts by the same material usually show reduced charge, because similar materials do not exchange charge to a high degree (Eilbeck et al., 2000; Bennett et al., 1999).

Materials which are used in DPIs as well as the size fraction of the powder have an effect on the triboelectrification process (Eilbeck et al., 1999; Carter et al., 1998). Different plastics have different charging properties, and these are influenced by colorants and other additives. Also the preparation and the amorphicity of the spray dried lactose could have a significant effect (Cassidy et al., 2000; Murtomaa et al., 2002b) and in this paper this effect is taken into consideration in addition to DPI's structure.

As stated above, there are many reasons why the static electrification which takes place in DPIs is a very important factor, and more information is needed about the mechanisms and measurement techniques concerning this issue. The main goal in these studies is to improve the use of therapeutic aerosols, which will be used extensively in the future (Sciarra and Cutie, 1990).

In this study, emphasis has been on the effect of crystallinity, particle morphology and DPI structure on the triboelectrification process. The deposition of the aerosol has not been under study in the present work.

2. Materials and methods

Lactoses of various degrees of amorphicity were prepared by spray drying 15% (w/w) lactose suspension or solution with a Büchi Mini-Spray Drier 190 (Büchi Laboratorium-Technic AG, Switzerland) under the following conditions; air flow rate 15 (dial setting), atomizer air flow rate 700 l/h, heating rate 7 (dial setting), inlet temperature 108 °C, outlet temperature 75–80 °C and feed rate 5 ml/min. The only exception as that lactose was spray dried from pure distilled water (0% ethanol) at inlet temperature of 160 °C and at an outlet temperature of 105 °C. The heating rate was 12 (dial setting). The diameter of the nozzle was 0.7 mm. Each type of lactose was packed into tightly closed plastic bottles and stored in a desiccator (with silica gel at room temperature) prior to the studies. Lactose used was α-lactose monohydrate (Pharmatose 325 M, DMV, The Netherlands).

When the ethanol concentration in the feed solution was changed, samples with crystallinity between 5 and 100% were obtained. In addition to untreated lactose,

six different solutions/suspensions were chosen for the study for which the ratio of ethanol to water in the feed solutions was 0:100, 20:80, 30:70, 50:50, 80:20 and 100:0.

Amorphicity in the lactose samples was determined at least in duplicate with an isothermal heat-conduction microcalorimeter TAM 2277 (Thermometric AB, Sweden) at 25 °C. The sample mass varied between 8 and 100 mg depending on the amorphous content. The miniature humidity chamber technique (Anberg et al., 1992a,b) was employed to detect the thermal response for the recrystallization of amorphous lactose. The extent of the heat evolution was assumed to be directly related to the degree of amorphicity (Sebhatu et al., 1994; Buckton and Darcy, 1999). A lactose sample which was previously spray dried from solution in pure water and for which X-ray diffraction (XRD, Philips PW 1820, The Netherlands) studies showed only diffuse scattering with no characteristic reflections in the diffractogram was regarded as a reference sample for the totally amorphous lactose. The corresponding heat (52.2 J/g) for recrystallization obtained from the IMC measurements was regarded as the reference value. For the samples spray dried from the feed suspension of which the ethanol concentration exceeded 80%, XRD was also used to verify the crystallinity since no exothermic recrystallization peak could be detected in the microcalorimetric studies.

The BET surface areas were measured with an TriStar 3000 (Micromeritics, USA) instrument using five different partial pressures of nitrogen between 0.06 and 0.20 p/p_0. The particle size distribution was measured in ethanol with laser diffraction (Malvern System 2600, Malvern Instruments Ltd., UK). Samples were sonicated for approximately 2 min prior to measurement and the solution was stirred with a magnetic stirrer in order to break up the agglomerates.

Two dry powder inhalers were selected for the study: Clickhaler™ (Innovata Biomed Ltd., UK) and Taifun™ (Focus Inhalation Oy, Finland). In Taifun™ DPI the inhaled air goes through a cyclone chamber made of polypropylene, in which the powder is lifted into the airstream. This setup causes the powder to go through multiple contacts with the chamber surface. Clickhaler™ DPI, on the other hand, is constructed in a manner which allows the powder to flow with less contacts with device surfaces during actuation (Parry-Billings et al., 1999). Powder samples were stored approximately 1 week in silica gel after preparation and then the DPIs were loaded (two devices for each type of lactose) by Focus Inhalation Oy, Finland.

The Faraday pail used in the measurements consisted of an open-end Faraday pail, an electrometer (Keithley 6514, Keithley Instruments Inc., USA) and a personal computer. The device was connected to an airflow system which allowed the flow rate to be measured and controlled. A glass fiber filter, which was replaced after every 10 actuations, was placed in the Faraday pail to collect the inhaled powder. The electrometer was used to measure the charge in the pail and real time charge data was collected from the analog output of the electrometer to the PC via a Pico ADC-100 AD converter (Pico Technology Ltd., UK). The pail was shielded to prevent outside electric field from interfering with the measurements.

After loading the DPIs were stored and actuations taken in relative humidity of 32 ± 2% and at the temperature of 21 ± 1 °C. Two days after loading 20 actuations were taken from each device, which were then left untouched for 7 days. This procedure was made to coat the DPI surfaces with the powder to rule out the adhesion effects which could have had an effect on the first actual measurements. Also in practice, Taifun™ is primed after preparation before leaving the factory. Static charges of the lactose powders were measured from 10 actuations taken from each DPI at 1 min intervals. The measurements were repeated after 6 days of storage. To examine the effect of storing and recrystallization on the amorphous content, measurements were repeated also after 6 months of storage in the same environment. The DPIs were weighed before and after each set of 10 actuations and specific charges of the powders were calculated using the measured mean weight loss.

During the measurement procedure a dose was metered, the DPI's mouthpiece was inserted in the Faraday pail, an actuation was taken at the airflow rate of 30 l/min, the inhaler was removed and the Faraday pail was grounded to remove the charge. Real time data of the process was recorded and an example is shown in Fig. 1. The quantity of the inhaled charge was determined from the curve after the removal of the DPI. Fig. 1 shows also that the measured charge could be obtained directly after the actuation (265 pC) or after the DPI is removed (262 pC). In other words, in these

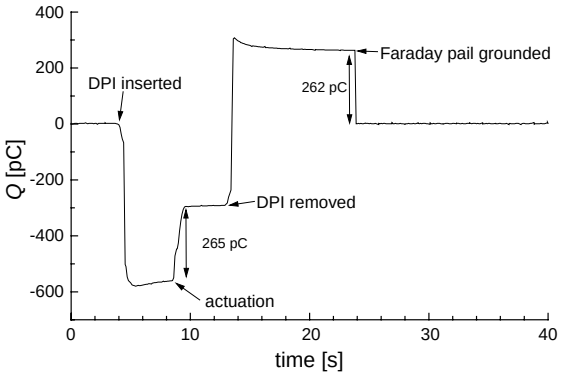

Fig. 1. An example of recorded real-time data of charge measurements.

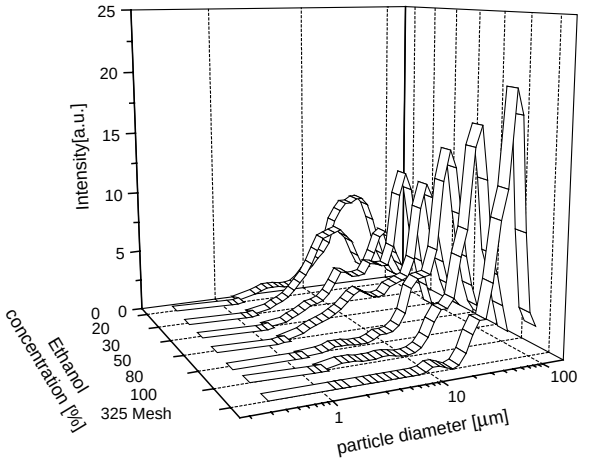

Fig. 2. Size distributions of the lactose samples (325 mesh denotes the untreated lactose).

measurements, the charging of the DPI itself did not disturb the measurements significantly. Fig. 1 shows that in this example the DPI was initially negatively charged, the signal dropped to −600 pC when the DPI was inserted and a corresponding shift upwards was recorded when the DPI was removed.

3. Results

The degrees of amorphicity and BET surface areas of the samples are presented in Table 1. Particle size distributions are presented in Fig. 2, which implies that when the water concentration in the feed solution was increased more lactose was diluted in the solution and the following spray drying yielded small (≈10 μm) spherical amorphous particles. Increase in the water concentration gave rise to small particle content of the lactose powder compared to original 55 μm particles and hence the powder morphology was different. When the spray drying solution consisted only of water and lactose, the produced amorphous lactose particles were strongly agglomerated and could not be separated in the laser diffraction determinations. The effect can be seen in the Fig. 2 and it was also verified with SEM, (XL 30 ESEM TMP, FEI Company, The Czech Republic). SEM-image shows a large (≈200 μm) agglomerate and a great number of small particles (Fig. 3A). Laser diffraction showed the particle size distribution to be wide with mean value at 27 μm. For the sake of comparison, SEM-images of samples which were spray dried from solutions containing 30% ethanol and 100% ethanol are also presented together with untreated lactose (Fig. 3B–D).

Table 1
Values of the amorphicities and surface areas for the lactose samples

Ethanol % (w/w)	Amorphicity (%)	BET surface area (m^2/g)
0	95 ($n = 3$, S.D. = 3)	1.06 ($n = 4$, S.D. = 0.06)
20	26 ($n = 2$, S.D. = 2)	1.00 ($n = 3$, S.D. = 0.04)
30	7 ($n = 2$, S.D. = 0.3)	0.40 ($n = 3$, S.D. = 0.02)
50	5 ($n = 2$, S.D. = 0.4)	0.47 ($n = 3$, S.D. = 0.01)
80	∼0[a]	0.37 ($n = 2$, S.D. = 0.01)
100	0[a]	0.33 ($n = 2$, S.D. = 0.02)
325 mesh	0[a]	0.24 ($n = 2$, S.D. = 0.01)

Numbers of measurements (n) and standard deviations are in parentheses.
[a] Verified with XRD.

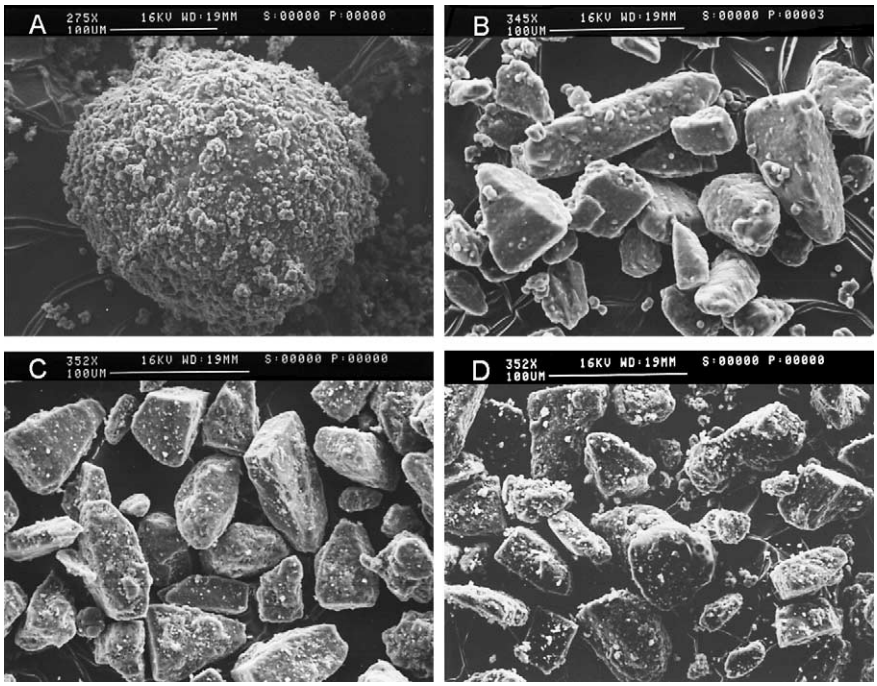

Fig. 3. SEM-images taken from a lactose sample which was spray dried from (A) water solution (0% ethanol), (B) 30% ethanol, (C) 100% ethanol, and (D) untreated lactose 325 mesh

Fig. 4 presents the specific charges of different lactose powders actuated from Taifun™ and Clickhaler™ DPIs 7 days after loading (■) and after 6 days (●) and 6 months (▲) storage time. In both graphs, the presented specific charges are mean values of 10 actuations taken from 2 separate DPIs. Figures show that the standard deviation of the specific charge was large when the water concentration in the feed solution was high and this was believed to be due to the large deviation in the emitted mass of the powder and also to heterogeneous particle morphology.

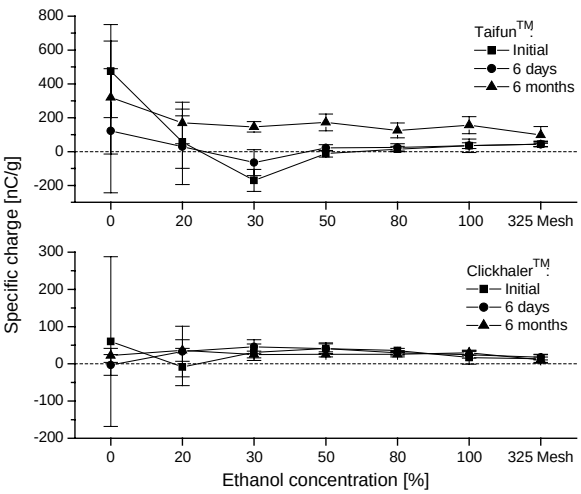

Fig. 4. Mean values (10 actuations from 2 DPIs) of specific charge of different lactoses actuated from Taifun™ and Clickhaler™ DPIs as a function of ethanol concentration in the feed solution.

Effect of storage in the relative humidity of $32 \pm 2\%$ and at the temperature of $21 \pm 1\,^{\circ}C$ was more significant with Taifun™ than with Clickhaler™. This result indicates that the properties of the lactose powder changed during the storage in Clickhaler™ but not as clearly as in Taifun™. With the powder in Taifun™ there is also a desiccant capsule that protects the powder against variations in external humidity conditions. Therefore, it is suggested that the amorphous surface of the lactose powder had already recrystallized in Clickhaler™ prior to first measurements which resulted in unchanged specific charges. In Taifun™ the desiccant slowed down the recrystallization process and a change in the specific charge could be observed. This theory was verified with IMC-measurements by emptying the DPIs after 6 months of storage and mea-

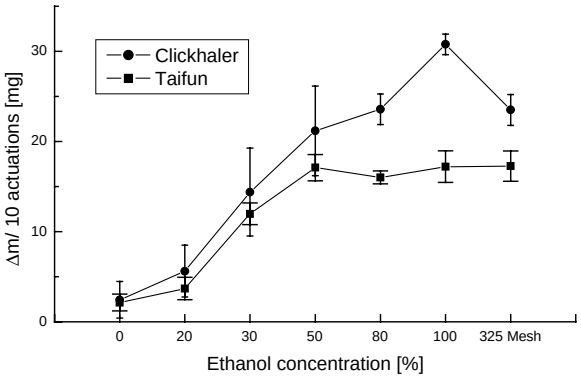

Fig. 5. The mean weight loss of DPI during 10 actuations as a function of ethanol concentration in the feed solution.

suring the amorphicities. Heat flow signals typical for crystallization could be observed from samples which were originally most amorphous (95%) from Taifun^{TM} but not from Clickhaler^{TM}. Remained amorphicity was found to be 54%. From Fig. 4 it can also be seen that the specific charge of the sample prepared from ethanol suspension also changed during the storage. This could be due to the presence of amorphicity produced by the milling effect on the suspended lactose particles in the atomizer (Chidavaenzi et al., 1997). The generated degree of the amorphicity was presumably so low that it could not be detected with IMC or X-ray diffraction. Also, original untreated lactose (325 mesh) seemed to charge slightly more after 6 months of storage but these values were within error limits.

The lactoses with high degree of crystallinity and similar particle size showed fairly constant specific charges as well as emitted dose. The lactoses prepared from low ethanol concentration exhibited less predictable specific charges and even variation in the sign of the generated charge. Although the lactose particles were smaller according to SEM micrographs and laser diffraction, the particles were highly agglomerated. This resulted in low bulk density of the powder and thereby poor performance of the DPIs. This resulted also in larger deviation of emitted dose during measurements. Fig. 5 represents the mass of 10 doses actuated from both DPIs as a function of ethanol concentration in the feed solution. It can be noticed that nearly ten times more crystalline lactose was emitted compared to amorphous.

4. Discussion

Results showed that the preparation of the samples had an effect on the generated specific charge. Good reproducibility was obtained especially with samples of high crystallinity and homogenous particle morphology. It was noticed that the amorphous content of the lactose powder which was loaded into Clickhaler^{TM} had recrystallized before the first measurements. In Taifun^{TM}, on the other hand, the recrystallization process continued during the 6 months of storage. The desiccant inside the drug reservoir of Taifun^{TM} seems to prevent effectively recrystallization of amorphous lactose. As commonly believed, such recrystallization in any of the components may cause agglomeration of the formulation, followed by poor physical stability of the product. All samples showed quite constant specific charge when recrystallization did not take place any more. This can be seen in Fig. 4 where storage time had no effect on the charge of the powder actuated from Clickhaler^{TM} and also in the measurements made with Taifun^{TM} where the generated charges shifted only slightly between the first measurements and measurements made after 6 days of storage. As expected, the charge shifted towards the results obtained after 6 months of storage.

To compare the effect of the structure of the inhaler on the generated charge, untreated lactose (325 mesh) has to be taken into closer study in order to rule out the recrystallization effects. Generated specific charge of such lactose actuated from Clickhaler^{TM} was 14 and 62 nC/g from Taifun^{TM}. Specific charges were found to be 3–5 times higher also with spray dried lactoses actuated from Taifun^{TM} DPIs after 6 months storage compared to Clickhaler^{TM}. The cyclone chamber of Taifun^{TM} increases the number of contacts between the particles and the inhaler wall and therefore causes higher tribocharging. Measured values of charges are of the same order than the values reported earlier for fine lactose particles actuated from Dryhaler^{TM} (Byron et al., 1997).

For lactoses with higher amorphous content (crystallinity $< 93\%$) and heterogeneous particle size distribution the calculated specific charge varied from -300 to $+700$ nC/g for Taifun^{TM} and from -200 to $+250$ nC/g for Clickhaler^{TM}. These great differences in the amount of the charge were most likely associated with the fact that the emitted dose was assumed to

vary in size between actuations, and the performance of the DPI was significantly reduced. Also, particles of different sizes may have different residence times in the cyclone chamber, and therefore, different extents of tribocharge. As shown in Table 1, the specific surface areas were different for each sample, so that the amorphous samples had the largest surface area. Since the charging is a surface phenomenon, the larger contact area of the amorphous samples might explain the higher subsequent charge. Change in the sign of the generated charge, on the other hand, could be due to different particle morphology. Charge was found to be always positive for samples with homogenous particle size distribution. It is possible that the powder which was loaded into the metering slot varied not only in size but also in morphology in some actuations. It has been noticed that same material may carry opposite charge when the particle size is different. Presented method does not give information about the bipolar charging which might be present, especially when the emitted aerosol consists of different particles.

As the control of the triboelectric charging by DPIs plays an important role in the performance of the inhalers, the monitoring of the aerosol charge by the introduced method gives essential information for the design and the formulation of the inhaler structures and materials.

References

Anberg, M., Nyström, C., Castensson, S., 1992a. Evaluation of isothermal heat-conduction microcalorimetry in pharmaceutical stability studies. V. A new approach for continuous measurements in abundant water vapor. Int. J. Pharm. 81, 153–167.

Anberg, M., Nyström, C., Castensson, S., 1992b. Evaluation of isothermal heat-conduction microcalorimetry in pharmaceutical stability studies. VI. Continuous monitoring of the interaction of water vapor with powders and powder mixtures at various relative humidities. Int. J. Pharm. 83, 11–23.

Bailey, A.G., 1997. The inhalation and deposition of charged particles within the human lung. J. Electrostat. 42, 25–32.

Bailey, A.G., Hashish, A.H., Williams, T.J., 1998. Drug delivery by inhalation of charged particles. J. Electrostat. 44, 3–10.

Balachandran, W., Machowski, W., Gaura, E., Hudson, C., 1997. Control of drug aerosol in human airways using electrostatic forces. J. Electrostat. 40–41, 579–584.

Bennett, F.S., Carter, P.A., Rowley, G., Daniker, Y., 1999. Modification of electrostatic charge on inhaled carrier lactose particles by addition of fine particles. Drug. Dev. Ind. Pharm. 25, 99–103.

Buckton, G., Darcy, P., 1999. Assessment of disorder in crystalline powders—a review of analytical techniques and their application. Int. J. Pharm. 179, 141–158.

Byron, P.R., Peart, J., Staniforth, J.N., 1997. Aerosol electrostatics I: properties of fine powders before and after aerosolization by dry powder inhalers. Pharm. Res. 14, 698–705.

Carter, P.A., Cassidy, O.E., Rowley, G., Merrifield, D.R., 1998. Triboelectrification of fractionated crystalline and spray-dried lactose. Pharm. Pharmacol. Commun. 4, 111–115.

Cassidy, O.E., Carter, P.A., Rowley, G., Merrifield, D.R., 2000. Triboelectrification of spray-dried lactose prepared from different feedstock concentrations. J. Pharm. Pharmacol. 52, 13–17.

Chidavaenzi, O.C., Buckton, G., Koosha, F., Pathak, R., 1997. The use of thermal techniques to assess the impact of feed concentration on the amorphous content and polymorphic forms present in spray dried lactose. Int. J. Pharm. 159, 67–74.

Eilbeck, J., Rowley, G., Carter, P.A., Fletcher, E.J., 1999. Effect of materials of construction of pharmaceutical processing equipment and drug delivery devices on the triboelectrification of size-fractionated lactose. Pharm. Pharmacol. Commun. 5, 429–433.

Eilbeck, J., Rowley, G., Carter, P.A., Fletcher, E.J., 2000. Effect of contamination of pharmaceutical equipment on powder triboelectrification. Int. J. Pharm. 195, 7–11.

Fleming, J.S., Hashish, A.H., Conway, J.H., Hartley-Davies, R., Nassim, M.A., Guy, M.J., Coupe, J., Holgate, S.T., Moore, E., Bailey, A.G., Martonen, T.B., 1997. A technique for simulating radionuclide images from the aerosol deposition pattern in the airway tree. J. Aerosol Med. 10, 199–212.

Fleming, J.S., Hashish, A.H., Conway, J.H., Nassim, M.A., Holgate, S.T., Halson, P., Moore, E., Bailey, A.G., Martonen, T.B., 1996. Assessment of deposition on inhaled aerosol in the respiratory tract of man using three-dimensional multimodality imaging and mathematical modeling. J. Aerosol Med. 9, 317–327.

Gonda, I., 1992. Physico-chemical principles in aerosol delivery. In: Crommelin, D.J.A., Midha, K.K. (Eds.), Topics in Pharmaceutical Sciences 1991. Medpharm GmbH Scientific Publisher, Stuttgart, Germany, pp. 95–115.

Grosvenor, M.P., Staniforth, J.N., Jordan, D., Flanders, P., 1991. The effect of varying the electrical resistivity of powder compacts on their voltage decay properties. In: Institute of Physics Conference. Series no. 118, Section 4, pp. 235–239.

Harper, W.R., 1967. Contact and Frictional Electrification. Oxford University Press, London, UK.

Hashish, A.H., Bailey, A.G., 1987. Administration of drugs using nebulisers: effect of electrostatic charge on aerosols. In: Institute of Physics Conference. Series no. 85, Section 1, pp. 81–86.

Hashish, A.H., Bailey, A.G., 1991. Electrostatic enhancement of particle deposition in the lung when using jet and ultrasonic nebulisers. In: Institute of Physics Conference. Series no. 118, Section 1, pp. 45–50.

Hashish, A.H., Fleming, J.S., Conway, J., Halson, P., Moore, E., Williams, T.J., Bailey, A.G., Nassim, M., Holgate, S.T.,

1998. Lung deposition of particles by airway generation in healthy subjects: three-dimensional radionuclide imaging and numerical model prediction. J. Aerosol Sci. 29, 205–215.

Murtomaa, M., Laine, E., 2000. Electrostatic measurements on lactose–glucose mixtures. J. Electrostat. 48, 155–162.

Murtomaa, M., Harjunen, P., Mellin, V., Lehto, V.-P., Laine, E., 2002b. Effect of amorphicity on the triboelectrification of lactose powder. J. Electrostat. 56, 103–110.

Murtomaa, M., Ojanen, K., Laine, E., 2002a. Effect of surface coverage of a glass pipe by small particles on the triboelectrification of glucose powder. J. Electrostat. 54, 311–320.

Parry-Billings, M., Boyes, R.N., Clisby, L.M., Braithwaite, P., Williams, S., Harper, A.E., 1999. Design, development, and performance of a novel multidose dry-powder inhaler. Med. Device Technol. 10, 24–34.

Sciarra, J.J., Cutie, A.J., 1990. Pharmaceutical aerosols. In: Banker, G.S., Rhodes, C.T. (Eds.), Modern Pharmaceutics. Marcel Dekker, New York, pp. 605–634.

Sebhatu, T., Angberg, M., Ahlneck, C., 1994. Assessment of the degree of disorder in crystalline solids by isothermal microcalorimetry. Int. J. Pharm. 104, 135–144.

Staniforth, J.N., 1994. The importance of electrostatic measurements in aerosol formulation and preformulation. Resp. Drug Delivery IV, 303–311.