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Author: Waseem Kaialy

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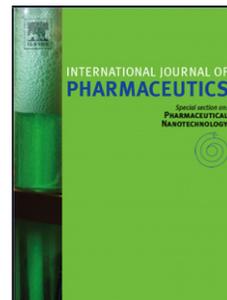
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A review of factors affecting electrostatic charging of pharmaceuticals and adhesive mixtures for inhalation

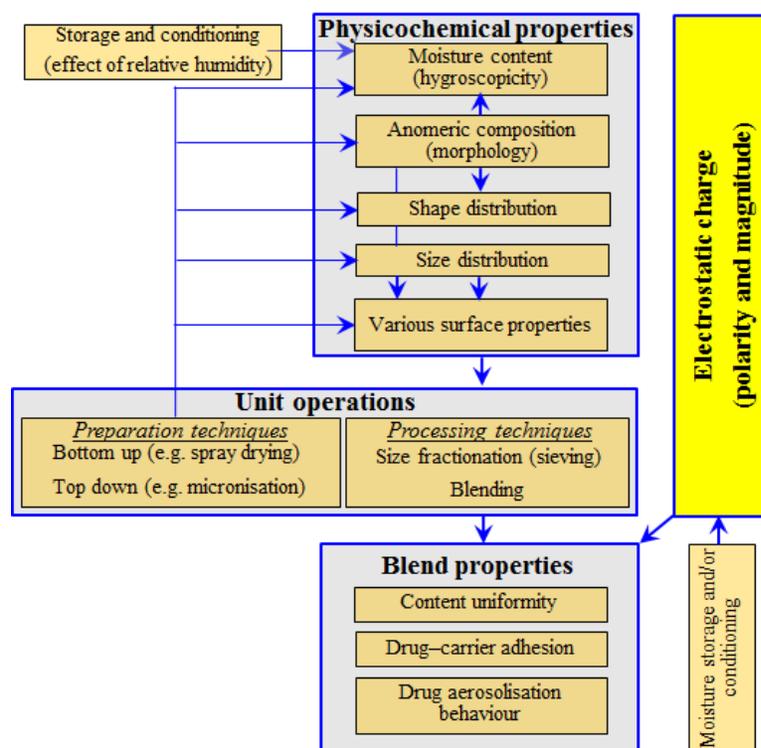
Waseem Kaialy

School of Pharmacy, Faculty of Science and Engineering, University of Wolverhampton,
Wolverhampton, WV1 1LY, UK

Waseem Kaialy, Tel: +441902 321139

E-mail: w.kaialy@wlv.ac.uk

Graphical abstract



Highlights

- Charging of pharmaceutical inhalation powders depends on a combination of many interrelated factors.
- Controlling the charge of inhalation powders is crucial in the development of dry powder inhaler products.
- More controlled studies are justified to increase our understanding in charging.
- Efforts to optimize the charge of drug and carrier particles to maximize DPI performance are warranted.

Abstract

Pharmaceutical powders are typically insulators consisting of relatively small particles and thus they usually exhibit significant **electrostatic** charging behaviours. In the inhalation field, the measurement of **electrostatic** charge is an imperative stage during pharmaceutical formulation development. The electrostatic charge is affected by the interplay of many factors. This article reviews the factors affecting **the electrostatic charging** of pharmaceutical powders with a focus on dry powder inhalations. The influences of particle resistivity, size distribution, shape distribution, surface roughness, polymorphic form and hygroscopicity, as well as the effects of moisture uptake, environmental conditions, pharmaceutical processing (i.e., milling, sieving, spray drying and blending), and storage on the **electrostatic** charge behaviours of **pharmaceuticals, with focus on** inhalation powders, were reviewed. The influence of electrostatic charge on the performance of dry powder inhaler formulations in terms of drug content homogeneity, **the passage of drug through the inhaler device**, drug-carrier adhesion/detachment, and **drug deposition on the respiratory airways** were discussed. The understanding gained is crucial to improving the safety, quality, and efficiency of the pharmaceutical inhalation products.

Abbreviations

AFM, atomic force microscopy; BCMS, bipolar charge measurement system; BET, Brunauer, Emmett and Teller; BOLAR, bipolar charge analyser; CM, commercial mannitol; CMR, charge-to-mass ratio; **CSR, charge-to-surface ratio**; $d_{50\%}$, median diameter; DPIs, dry powder inhalers; ELPI, electrostatic low-pressure impactor; Eq, Equation; E-SPART, electrical-single particle aerodynamic relaxation time equipment; FPF, fine particle fraction; LDV, laser doppler velocimeter; MDIs, metered dose inhalers; nC/g, nano-coulomb/gram; RH, relative humidity; SDM, spray dried mannitol; SS, salbutamol sulphate.

Keywords: Aerosolisation; Dry powder inhalers; Electrostatic charge; Pharmaceutical processing; Physicochemical properties.

1. Overview of electrostatic charge

1.1. Charging mechanisms

Electrostatic effects on solids have been recognised for a long time, yet our understanding remains limited due to its complexity. Several authors explained the fundamentals of electrification phenomenon and charging mechanisms (Chiou et al., 2003; Crofts, 1988; Gonsalves, 1953; Matsusaka, 2011; Matsusaka et al., 2010; Vick, 1953; Yatsuzuka et al., 1996). Although it is still indefinite whether charge-transfer takes place through electron, ion or material transfer, or a combination of these, charge-transfer has been mostly described based on electrons as the charge carriers (Cross, 1987; Harper, 1943; Lowell and Rose-Innes, 1980). In general, contact electrification or contact charging is the main mechanism of charge-transfer for solid particles. Contact charging is a phenomenon by which an electric charge transfers from one surface to another when two electrically-isolated surfaces are brought into contact and then separated (Taylor and Secker, 1994). Materials may subsequently gain a positive or negative netcharge that is usually a complex bipolar system (Bailey, 1993, 1984). Triboelectric charging or tribocharging within powders develops when the contact is accompanied with frictional forces such as sliding, rubbing, rolling or impaction in an unionised environment (Greason, 1992; Lowell and Rose-Innes, 1980; Trigwell et al., 2008). In pharmaceutical

processes **tribocharging** ('**frictional electrification**') refers to a method of particle electrification that occurs during unit operations (Matsusaka et al., 2010). *Corona charging* is a process by which a neutral particle is charged by exposing it to a single polarity of an ion or a charged particle that could be discharged in a bi-ionised field. Corona charging is **usually favoured in many applications because of its reliability and high charge values. It is** regularly used when there is a need to charge a surface in a defined way (Cross, 1987).

2. Charging of powders in industrial handling

Pharmaceutical solids are usually insulators and thus they are likely to carry an electrostatic charge during powder handling processes (Askal, 1997; El-Sadek et al., 1993; Khaled, 2008). In industrial handling processes with bulk solids, the materials are very likely to be charged and consequently the concept of an electrically neutral particle is scarcely true (Glor, 1988). Any handling of powders (regardless of their formulation and **the** types of the materials used for storage and processing) results in collisions **among** the individual particles with **one another** and with the walls of the process equipment. This, in turn, results in the accumulation of charge on the surfaces of these particles (Glover and Chan, 2004), **as will be explained in chapter 3.1**. In general, bulk powders could be triboelectrically charged by several ways, such as vibrating devices (Dascalescu et al., 2005), high-shear blenders (Eliassen et al., 1999), low-shear blenders (Engers et al., 2006), fluidised beds (Calin et al., 2007), rotary drums (Inculet et al., 1998), drying, and transport (Saleem et al., 2008). In contrast, several approaches have been applied to reduce the electrostatic charging, such as grounding of all parts of powder charge equipment (Kassebaum and Kocken, 1997), placing a ground probe in the processing equipment (Blythe and Reddish, 1979), the use of the radioactive ionization device (Kassebaum and Kocken, 1997), the use of a superimposed electric field (Ebadat et al., 1990), working under high environmental relative humidities (Cartwright et al., 1985), and the use of antistatic agents (Kassebaum and Kocken, 1997).

3. Factors that affect electrostatic charging of pharmaceuticals

The electrostatic charge could be found in powders having similar or dissimilar chemical composition(s). It has been acknowledged that the static electrification generated during powder handling operations is incompetently understood and hard to predict because of its inherent

multivariate nature (Rowley, 2001). In general, different powders might develop different polarities and **levels** of charge according to their inherent ‘intrinsic’ electrical properties (Chakrabarty et al., 2008; Valverde et al., 2008) and types/**properties (e.g., surface area)** of the surfaces they contact during different processing steps (Lachiver et al., 2006; Rowley, 2001). The generation and decay of electrostatic charge on the surface of charged particles **also** depend on their physicochemical properties, such as surface resistivity (Lachiver et al., 2006; Sharma et al., 2001b), surface roughness (Eilbeck et al., 1999), surface impurities, size distribution, shape distribution (Carter et al., 1998), and molecular structure (Duke and Paton, 1981). The electrostatic charge is **furthermore influenced by** environmental conditions (e.g., the relative humidity (RH) and atmospheric pressure) (Rowley and Mackin, 2003), particle motions and binary collisions (Liao et al., 2011), and magnitude of the frictional forces (Pavey, 1998). The influence of some factors on the **electrostatic charging** of pharmaceuticals is discussed below (Figure 1).

3.1. Work function

Electron-transfer results from the contact of two contact points having different work functions. The work function is an intrinsic surface property defined as the minimum energy required to move the weakest bound electron from the surface of a solid to the vacuum energy level (Gallo and Lama, 1976). The direction of electron-transfer is expected to go from the material with a lower work function to that with a higher work function. The electron-transfer process continues until the *Fermi level*, which is the level where the probability of occupancy of states with electrons in the allowed energy state is, of two materials reaches equilibrium (Davies, 1969). The following separation of these materials leads to the accumulation of charge on the surface of each material, such that they have an equal level of charge but opposite signs (Gallo and Lama, 1976).

When two charged particles are brought into contact, they will experience attraction or repulsion depending on their electrical charge signs. *Coulombic forces* govern the magnitude of the electrostatic attraction/repulsion forces (F_{ei}) between particles, as defined by Coulomb’s law (**Eq. 1**) (in the simplest case of two-point charges) (Seville et al., 1997).

$$F_{el} = \frac{q_1 q_2}{4\pi\epsilon\epsilon_0 d^2} \quad (1)$$

where q_1 and q_2 are the electrical charges on the two particles respectively, ϵ is the relative permittivity, ϵ_0 is the permittivity of free space (given by $8.854 \times 10^{-12} \text{ C}^2/\text{Nm}^2$), and d is the distance of separation between the two particles.

If a charged particle encounters an uncharged particle, the first particle will induce an image charge on the surface of the second particle. The electrostatic force (F_c) between these particles is then calculated as follows.

$$F_c = \frac{q^2 \left(1 - \frac{d}{\sqrt{r^2 + d^2}} \right)}{16\pi\epsilon d^2} \quad (2)$$

where q is the electrical charge on the charged particle, r is the radius of the interacting particles, and d is the distance between the charged and uncharged particles.

When two solid materials of different **work functions** are separated (in vacuum) by a small distance (d), electrons transfer from the material with the lower work function to the material with the higher one. Equilibrium will be established eventually, in which the two work functions reach the same level. The forces of attraction (F_w) between these two solid materials can then be determined using the following equation.

$$F_w = \pi\epsilon r \frac{(\Delta U)^2}{d} \quad (3)$$

where (ΔU) is the potential difference arising from the difference in work functions between the two materials and r is the radius of the interacting particles.

3.2. Physicochemical properties

Drawing definite conclusions concerning the effects of one physicochemical property on **electrostatic** charge behaviour is difficult because of interactions among several variables related to the formulation parameters, dispersion conditions, and environmental conditions (Figure 1). Nevertheless, rational justifications for most of the observed effects are discussed below.

3.2.1. Resistivity

Surface resistivity is related to the **level** of charge a material can pick up/lose upon contact with another surface. **For materials** with high surface **resistivities**, charge **decay** slowly and therefore such materials have high electrostatic effects. Substances could be broadly **categorised** into three classes based on their resistivity, i.e., conductors (resistivity below $10^{10} \Omega\text{m}$), semiconductors (resistivity from $10^{10} \Omega\text{m}$ to $10^{13} \Omega\text{m}$) and insulators (resistivity above $10^{13} \Omega\text{m}$). The surface resistivity of a material is strongly dependent on the RH of the environment (LuKttgens and Glor, 1989). The adsorption of water into a particle could contribute free charge carriers and/or influence the material's carrier trapping characteristics. Thus, the resistivity of a material typically decreases with increasing **the environmental humidity** (Passi et al., 2001).

3.2.2. Particle size distribution

The effect of particle size and density on the electrical and nonelectrical charge-transfer efficiency was studied by several reports (Biehl and Barringer, 2004; Mayr and Barringer, 2006). It has been suggested that the energy required to transfer an electron between two insulating solid particles **depends** on particle size (Gallo and Lama, 1976; Schein, 1993). In this view, for particles of the same material, electrons are expected to transfer from large particles to smaller particles, **because** large particles have typically lower work functions than the smaller particles (Bailey, 1984). Therefore, large particles often charge opposite to smaller particles of the same material (Ali et al., 1998; Zhao et al., 2002). In general, **for** mixtures containing fine and coarse particles, fine particulates tend to charge negatively, whereas large particles tend to charge positively **regardless of whether the netcharge is positive or negative** (Ali et al., 1998; Engers et al., 2006; Glor, 1988; Trigwell et al., 2003). Although the precise reasons for this behaviour are not clear, a hypothetical mechanism for particle size dependent charging has been provided by (Lacks and Levandovsky, 2007). **The physical explanation described is based on the arguments that collisions allow electrons trapped in high-energy states on one particle to transfer to the vacant low-energy states on another particle (assuming that the surface density of trapped electrons is initially the same on all particles).**

Electrostatic forces become more significant and may even dominate over other particulate forces (including van der Waals forces) when the particle size is decreased at low environmental humidities. Therefore, small particles usually tend to carry a greater **level of netcharge-to-**

surface ratio (net-CSR) than the larger particles, i.e., powder charge is inversely related to particle mean diameter (Guardiola et al., 1996; Kaialy et al., 2014; Rowley, 2001). For example, under similar **fluidisation** conditions, (Karner and Urbanetz, 2013) showed the amount of netcharge accumulated on mannitol powders to increase with the fine fraction of small mannitol. This **agreed with** previous studies carried out by (Carter et al., 1992), (Eilbeck et al., 2000, 1999) and (Kwek et al., 2012) who showed the netcharge of lactose to increase with decreasing particle size. **This could be explained as the specific surface area (per unit mass) increases with decreasing particle diameter and this makes a higher netcharge-to-surface ratio (net-CSR) for smaller particles obvious.** Nevertheless, it should be kept in mind that the exact mechanism by which particle size distribution affects the electrostatic charge behaviour is complicated by the number of factors directly related to particle size. A difference in the work function between small and large particles was suggested (Gallo and Lama, 1974; Zhao et al., 2003), although such difference is believed to be very small (<0.01 %) for particles larger than 1 μm (Wood, 1981). The **differences** in the surface properties (such as crystal lattice, rugosity, surface energy and surface area) **among** particles of different sizes could also account for the different work functions obtained (Figure 1). Large particles have been reported to show relatively higher surface roughness (Kaialy et al., 2012a; Narayan and Hancock, 2005), higher amount of surface impurities (Boer et al., 2003), greater shape-irregularities (cracks and dislocations) (Shariare et al., 2011), decreased disorder in crystal lattice (Kaialy et al., 2012a; Pearce and Lewis, 1972) and lower moisture uptake (van Campen et al., 1983), as compared to smaller particles. In an endeavour to reduce as many of the linked parameters as possible, (Kaialy et al., 2014) evaluated the charging and **aerosolisation** properties of spherical spray dried mannitol (SDM) particles with identical shape and solid-state characteristics but of different sizes. The netcharge (netcharge-to-mass ratio (net-CMR) or charge density) of SDM particles was shown to increase from $(-0.1 \pm 0.1) \text{ nC/g}$ to $(2.3 \pm 0.8) \text{ nC/g}$ with decreasing the mean size of SDM particles from 122 μm to 45 μm (Figure 2). The authors attributed this effect to the higher particle-wall contacts (Rowley, 2001), the greater particle number density, and the higher specific surface (Zhu et al., 2007) **for** smaller particles, providing a significant increase in the overall surface area available for charge-transfer. (Saini et al., 2007) showed the percentage **number** of neutral particles **aerosolised** from a dry powder inhaler (DPI) to increase with the mean particle size. However, the **level** and sign of the electrostatic charge acquired by the inhaled particles as well as the

particle size measurements of **aerosolised** particles are all influenced by the interplay of several factors including the formulation and inhaler material. Thus, more controlled work is required in the further to understand the effect of these factors on the charge and size measurements of inhaled particles.

3.2.3. Particle shape distribution

Particle shape is the recognised pattern of relationships among **all the** points forming the external particle surface (Luerkens et al., 1987). Particle shape is one of the most uncontrollable factors in powder technology. Different production techniques (e.g., nonsolvent precipitation, spray drying, etc.) for one material will practically **continually** lead to the production of particles of different shapes, and even particles that have experienced similar treatments may exhibit different shapes. Most pharmaceutical solid particles are diverged from the spherical shape (Hickey and Concessio, 1997). Nevertheless, all equations that calculate the interparticle forces (either van der Waals, capillary or electrostatic forces) are built on the unrealistic situation, which assumes that particles of a predetermined shape interact under theoretical conditions (an interaction between perfect spheres with perfectly smoothed surfaces). Therefore, any effort to deduce an equation that accurately calculates the interparticle forces between the real irregular-shaped particles would prove to be unrealistic, although a qualitative assessment of the particulate interaction within a powdered system is possible using the simple principles generated from perfect situations.

Particle shape **distribution** could have a significant effect on powder charging (Murtomaa et al., 2004a). (Chakrabarty et al., 2008) argued that the possibility of a particle carrying a certain number of charges depends on its morphology, i.e., spherical particles are less prone to attain more charge than elongated particles of the same particle mass. The results **agreed** with our results, which compared the **electrostatic charging** of mannitol particles with a similar size range (63 μm to 90 μm) but two distinct morphologies (Kaialy et al., 2014). Spherical mannitol particles showed a considerably lower netcharge than irregular-shaped mannitol particles ($(0.7 \pm 0.2) \text{ nC/g}$ versus $(3.7 \pm 0.5) \text{ nC/g}$) (Figure 4). (Karner et al., 2014) also reported similar results for mannitol particles ($d_{50\%}$ (median diameter): 78.4 μm to 86.4 μm), i.e., particles with more elongated shapes carried a higher **level** of charge than less elongated particles.

Not only the amount of charge of individual particles differs considerably, but also the degree of nonuniformity of charge distribution on particle surface is likely to vary from particle to particle

due to the arbitrariness of tribocharging process. Thus, the concept of charge distribution on particle surface was proposed (Hays and Wayman, 1989). A uniform charge distribution on the surface of a spherical particle has been assumed in theoretical calculations due to the lack of information about detailed surface charge distributions (Feng and Hays, 2003). (Murtomaa et al., 2004a) showed the reproducibility of electrostatic charging to improve with homogeneous particle morphology. For non-spherical particles, particle morphology and charge distribution on particle surface are important factors for unipolar diffusion charging (Biskos et al., 2004).

3.2.4. Particle surface properties

Since charging is a surface phenomenon, particle surface characteristics could have a significant influence on **the charging behaviour of powders**. Surface area is considered a measure of surface geometry, whereas surface free energy represents the amount of energy needed to separate particles or surfaces (Fowkes, 1964). Many factors could deeply affect particle surface area, including particle size, shape, anomeric form and surface morphology (Figure 1). In general, particles with smaller size **distributions** and more surface irregularities have higher surface **areas** (Lowell and Shields, 1991). Powders with **higher specific surface areas** usually show higher moisture **uptakes** (Van Campen et al., 1983) and higher surface free **energies** (Sethuraman and Hickey, 2002). In the literature, the surface properties of a particulate material were shown to affect the materials' physical properties, such as its flowability (Han et al., 2011), cohesivity and adhesivity (Kaialy and Nokhodchi, 2013a). Additionally, several pharmaceutical processes, such as milling (Julien et al., 2011), blending (Rumondor et al., 2011) and **aerosolisation** (Kaialy and Nokhodchi, 2013b), were deeply influenced by the material's surface properties. The electrostatic charge characteristics of pharmaceutical powders have been correlated with surface energy measurements obtained using inverse gas chromatography (Jallo and Dave, 2015). Powders with higher specific surface **areas** (Murtomaa et al., 2004a) and higher surface free **energies** (Traini et al., 2012) demonstrated higher **levels of netcharge**.

Particle surface roughness **affects the overall charge-transfer because it affects the interparticle and particle-surface contact areas** (Vladykina et al., 1985). Theoretically, **for** insulator materials, electrostatic charges concentrate on the peaks of surface asperities leading to dissimilar charge distribution across the particle surface, i.e., regions with higher surface roughness would have higher energy states (Hogue et al., 2004; Kwok et al., 2005). This was

evident in the study by (Kwek et al., 2013) who showed the rough mannitol particles generated by spray drying to exhibit a higher surface potential in comparison to the smooth particles (-5.9 kV/m² versus 1.4 kV/m²). Such difference could be related to other physicochemical properties that varied along surface roughness. The rough mannitol particles showed a smaller mean **diameter** (2.7 μm versus 4.6 μm), a higher surface area (2.54 m²g⁻¹ versus 1.21 m²g⁻¹), a higher dispersive surface free energy (56.2 mJ.m⁻² versus 34.6 mJ.m⁻²), and an increased moisture sorption **compared to** the smooth particles. **Rough** mannitol particles were **also** prepared under higher atomising rates (670 NL.min⁻¹ versus 357 NL.min⁻¹) and lower inlet temperatures (145 °C versus 170 °C) **compared to** the smooth particles. With such complex interplay among physicochemical properties and operational factors, our understanding of the effect of surface roughness on electrostatics is far from complete, thus more controlled studies are needed in the future.

3.2.5. Polymorphic form

Polymorphism is the ability of a particle to exist in more than one form. About one-third of all drugs displays polymorphism (Henck et al., 1997). The polymorphic form of a material could influence its charging behaviour. **This is because** different solid forms (e.g., crystalline and amorphous) of the same pharmaceutical material may show different charge-transfer behaviours (Murtomaa et al., 2004a), **attributed** to their different **crystal packing**, surface **energies**, surface work **functions**, and moisture **contents**. **However**, the influence of crystallinity on the charging properties is not consistent throughout the literature. **(Carter et al., 1992) showed the spray-dried amorphous lactose to have lower levels of electrostatic charge than the fractionated crystalline lactose. In contrast, other studies reported an increase in electrostatic charging with increasing amorphous content.** For example, (Kwok and Chan, 2008) showed amorphous (spherical-shaped) salbutamol sulphate (SS) particles to be more charged than the crystalline (plate-like shaped) particles. (Murtomaa et al., 2002) **evaluated the influence of crystallinity on the tribocharging of lactose powders. The** charging behaviour of lactose ($d_{50\%}$: 45 μm to 55 μm) **was shown** to decrease with increasing crystallinity. (Murtomaa et al., 2004a) also showed that lactose particles with a higher amorphous content carried a higher **level** of electrostatic charge. **In the same line, (Shekunov et al., 2002) showed the supercritical fluid conditioned salmeterol xinafoate to have a higher crystallinity and reduced level of electrostatic charge compared to both granulated and micronised powders.** These inconsistencies show that other,

interrelating parameters must be in play. For example, particle **size and shape distributions** **were** not controlled in the latter studies. This was verified in a study by (Bennett et al., 1999) who showed that the **level** of electrostatic charge within two-component mixes of spray dried and crystalline lactose depends on particle size distribution of the resultant mix, i.e., charging increase with decreasing fine **particulate** content. In the study performed by (Murtomaa et al., 2004a), amorphous lactose particles were less homogeneous in shape and had wider size distributions in comparison to crystalline lactose particles. Furthermore, the influence of crystallinity on the charging behaviour is further complicated by their differences in moisture content. Amorphous and ‘partial amorphous’ particles usually have higher moisture contents than the crystalline particles (Figure 1), due to their less dense structure and increased ‘free’ volume into which water vapour could penetrate more easily (Ahlneck and Zografis, 1990). To eliminate this ambiguity, (Wong et al., 2014) conducted a more controlled study to evaluate the effect of crystallinity on the electrostatic charge properties of inhalable SS particles with a spherical shape and well-defined size distribution ($d_{50\%}$: 2.71 μm to 2.82 μm , span: 1.79 to 1.86). Amorphous SS was shown to have less consistent charging behaviour in comparison to crystalline SS.

The charge distribution on a particle surface is also influenced by crystallinity. Charge distribution is expected to occur faster on the surface of amorphous particles than on the surface of crystalline particles, because molecules’ mobility is higher for an amorphous material in comparison to a crystal lattice. Therefore, electrical charges may distribute homogeneously on the surface of spherical amorphous particles whereas most charges may concentrate on the tips and edges of crystalline irregular particles (Zeng et al., 2001) (Figure 3).

3.3. Hygroscopicity and relative humidity

Moisture uptake is **related to** relative humidity (RH) of the environment (an external factor), **as well as, both the chemical (e.g., hydrophilicity and hydrophobicity) and physical (e.g., powder specific surface area and particle anomeric composition) properties** (Van Campen et al., 1983). The role of the specific surface area in moisture sorption is particularly relevant to ‘adsorption’ and to a lesser extent to ‘absorption’. For absorption, it only increases the rate of moisture uptake. The risk of water sorption on the stability of pharmaceutical powders has been described in depth elsewhere (Coelho and Harnby, 1978; Hickey and Martonen, 1993; Maggi et al., 1999).

Moisture sorption behaviour is the ability of a hygroscopic material to absorb or release water vapour from or into the air until an equilibrium state is reached. The particle hygroscopicity and the environmental RH are both important factors influencing powder charge because moisture has a considerable effect on the electrical conductivity of particle surface (Zhu et al., 2007). The effect of RH on particle **electrostatic charging** is complex and depends on many factors (Kwok and Chan, 2008). Most studies showed the netcharge to decrease with the increase in RH, regardless of the contact surface (Elajnaf et al., 2006; Rowley and Mackin, 2003). However, such effect depends on **the material's hygroscopicity (which is an intrinsic property)** and moisture sorption behaviour **(which is a function of hygroscopicity as well as of physicochemical properties such as size distribution, shape distribution, porosity, solid-state, etc.)** (Kwok and Chan, 2008). A decreased surface resistivity and a consequent charge dissipation have been suggested in the case of a higher RH (Paasi et al., 2001). In addition, by increasing the RH, the absolute amount of water in the air (g/m^3) (and thus the air conductivity) increases leading to an enforced gas discharge (Karner and Urbanetz, 2011). In the context of **aerosolisation** performance, (Yurteri et al., 2002) suggested that there is an optimal RH, at which a balance between electrostatic and capillary forces exists, leading to minimal cohesive forces and thus an improved DPI dispersion behaviour.

3.4. Pharmaceutical processing

3.4.1. Milling

Milling is an important unit operation that is employed frequently in the pharmaceutical industry for the production of pharmaceuticals in the respirable size. In general, particle charging **increases** with the level of energy introduced to solid particles (Bailey, 1993). Milled particles usually exhibit high **levels** of electrostatic charge (ranging from 0.1 nC/g to 100 nC/g as given in the British Standard (Steele, 2001)), **potentially** leading to an increased interparticle cohesive forces and a consequent poor product performance (Brodka-Pfeiffer et al., 2003; Rasenack et al., 2004). Such **charging** generated on mechanically milled **powders** is induced by the interparticle and particle-wall collisions and sliding with different surfaces during milling (Feeley et al., 1998). Additionally, milling involves size reduction and thereby a milled powder typically contains an increased proportion of fine particulates compared to an unmilled powder (Figure 1). The effect of particle size distribution on charging characteristics is discussed previously (**chapter 3.2.2.**).

3.4.2. Spray drying

Spray drying is a drying technique in which a dry powder is produced by evaporating the liquid from the **atomised** feed when it mixes with a drying hot gas medium (Vehring, 2008). The separation of the product in the spray dryer usually takes place in the cyclone; however, other separation equipment such as electrostatic precipitators could be used (Patel et al., 2009). Several studies evaluated the **tribocharging** of spray dried products (Carter et al., 1998a; Cassidy et al., 2000; Murtomaa et al., 2002); nevertheless, the location where the static electrification takes place during spray drying was not clear. (Murtomaa et al., 2004b) concluded that spray drying generates a complex bipolar charging behaviour of the produced particles. It was argued that the static charge could be generated during the spray drying process in different parts of the spray dryer in different mechanisms: in the feed pipe (double layer charging), in the spray nozzle (double layer or induction charging), and at the walls of the spray cylinder and the cyclone chamber (contact and frictional charging). In general, spray drying produces particles with relatively high **levels of** electrical charge since the solutions prepared for drying are **aerosolised** into small droplets, which are next dried in a hot-air cyclone. Additionally, the differences in physicochemical properties (e.g., polymorphic form, size distribution, porosity, and surface properties) contribute to the considerable differences in **charging** properties between the spray dried and the parent particles (Carter et al., 1998a; Cassidy et al., 2000; Murtomaa et al., 2002) (Figure 1).

3.4.3. Sieving

Sieving (size fractionation) is a pharmaceutical process by which particles are passed through a series of sieves with progressively smaller square mesh sizes whereupon the particles are weighed and thereafter classified into size-fractions based on which mesh size they did not pass through. Sieving is a rough method in determining particle size. This is because sieving (especially mechanical sieving) cannot effectively separate all the fine particulates adhering to the surface of large particles (Kaialy and Nokhodchi, 2016; Kaialy et al., 2012b). Alternatively to mechanical sieving, the removal of fine particulates from the surface of coarse carrier particles has been achieved using air-jet sieving (Kaialy et al., 2012a; Kaialy et al., 2012b; Tee et al., 2000), air washing of the particles held on the top of a sieve (Zeng et al., 1999), and wet decantation (Islam et al., 2004).

In drug-carrier DPI formulations, the carrier particles are usually sieved into a size range of 63 μm to 90 μm or 70 μm to 100 μm (Kaialy et al., 2011; Kaialy et al., 2012a; Steckel and Bolzen, 2004). It is also common to subject the drug particles to sieving to remove any large drug agglomerates before mixing with coarse carrier particles. (Bechtold-Peters et al., 2005) showed the sieved **micronised** fenoterol drug particles to have greater electrostatic charge compared to the unsieved drug. Such charge acquisition of the sieved drug was subsequently reduced by surface treatment with sorbitan trioleate, leading to improved inhalation properties of fenoterol powders. (Noras, 2008) introduced a stackable Faraday pail by which the charging behaviour during sieving could be assessed.

In general, sieving produces **lower** levels of charge than other industrial processes such as **micronisation** and pneumatic conveying (Gibson, 1997). One reason for this is that the sieving process produces particles of a lower surface area-to-mass ratio in comparison to **micronisation** processes such as milling. For example, in contrast to milling, a significant particle size reduction is not typically involved during sieving (Figure 1). Mechanical sieving is typically not suitable for particles $<38 \mu\text{m}$ due to particle cohesiveness. Additionally, several process parameters (process time, the number of particle-particle collisions per unit time, etc.) could be involved in the difference in effect between the unit operations mentioned. For example, the amount of work done on a sieved powder is relatively less than that done on a milled powder. (Telko et al., 2007) evaluated the influence of several formulation parameters on the charging behaviour of SS-lactose binary mixtures. The propensity of negative charging was shown to increase when sieved lactose was used, whereas the use of milled lactose promoted positive charging. One reason for such variation in charge sign is that the sieved lactose (Respitose[®] SV003; $d_{50\%}[d_{10\%} \text{ to } d_{90\%}] = 60[30 \text{ to } 100] \mu\text{m}$) contains a lower proportion of fine particulates and different particle morphologies in comparison to the milled lactose (Respitose[®] ML001; $d_{50\%}[d_{10\%} \text{ to } d_{90\%}] = 55[4 \text{ to } 170] \mu\text{m}$), which indicates the need for more controlled investigations in the future.

3.5. Storage

Over time, the charge accumulated on a powder surface will decay (dissipate) to a certain limit (Malave-Lopez and Peleg, 1985). Charge decay is a complex phenomenon that has been measured by different techniques (Paasi et al., 2001). The timescale for electrostatic charge decay is an important factor. For example, there will be a higher probability of a considerable charge

build-up on a material when charge decay occurs slowly. The charge decay rate is a measure of the rate at which the electrostatic charge present on the surface of a material can migrate away (Chubb, 2002). The charge decay rate depends on many factors, including the material's electrical resistivity, the resistivity of the other material on contact, RH of the surrounding air, and the hold time (Bailey, 1993; Sharma et al., 2001a). The lower the material electron conductivity the longer the time needed for charge decay. A powder in contact with a conductive material will dissipate the charge quicker than the same powder in contact with an insulator. Since moisture adsorption makes a material more conductive, the charge decay rate increases with increasing RH due to a concurrent decrease in surface resistivity (Paasi et al., 2001). (Engers et al., 2006) showed the hold time (the time passed between the end of processing and dispensing the sample into the Faraday cup for charge measurement) as the most effective option of dissipating charge following the blending of eight different common pharmaceuticals in a stainless steel low-shear blender. (Kulvanich and Stewart, 1988) also showed a significant decrease in the adhesive forces of several model drug particles to the surfaces of hypromellose-coated glass beads during storage over 23 days due to charge decay.

Most pharmaceuticals are insulating organic materials (resistivities above $10^{13} \Omega\text{m}$) (Byron et al., 1997; Carter et al., 1998b), thus their charge relaxation times would broadly range from minutes to hours (Bailey, 1984). (Elajnaf et al., 2007) evaluated the charge decay characteristics of two drugs (SS ($d_{50\%} = 1.7 \mu\text{m}$) and ipratropium bromide monohydrate ($d_{50\%} = 1.7 \mu\text{m}$)) and one carrier (α -lactose monohydrate, $63 \mu\text{m}$ to $90 \mu\text{m}$) commonly used in DPI systems under different humidity conditions (RH = 0% to 86%). The decay behaviour results of the three materials showed ipratropium bromide to have the highest decay rate, whereas SS had the lowest. The decay rates of all materials were shown to increase with increasing the RH from 0% to 86%. The total drug–excipient adhesion forces were shown to decrease with the decay of electrostatic charge during storage. In another study, (Staniforth and Rees, 1982) showed that the electrical charges on lactose surface decay within a few minutes. This **agreed** with a study by (Carter et al., 1998b) who showed a rapid charge decay for lactose, whereas **micronised** SS retained substantial charge after 2 h. (Traini et al., 2012) showed the fine particle fraction (FPF) of SS **aerosolised** from the CyclohalerTM (at a flow rate of 60 L/min) to increase slightly after storage for 2–weeks at a RH of 45% and 20 °C, although such increase was not statistically significant. This was explained by charge relaxation during storage, with a consequent increase in aerosol performance.

After 6 months of storage at a RH of $32\% \pm 2\%$ and $21\text{ °C} \pm 1\text{ °C}$, (Murtomaa et al., 2004a) showed the Taifun™ inhaler to result in minimal changes in netcharge in comparison to Clickhaler™, attributable to the desiccant capsule in the Taifun™ inhaler device which can protect the formulation powder from environmental conditions during storage.

4. Electrostatics in inhalation powders

There has been an increased interest over the last few years in the measuring of electrostatic charge of pharmaceutical aerosols. Such measurements constitute an area of an important step in the development of pharmaceutical **aerosols** (Ehara et al., 1996; Emets et al., 1991; Flagan, 1998).

4.1. Drugs, carriers and contact surfaces

In the static state (i.e., before **aerosolisation**), the charge level and sign of drug–carrier inhalation powders was shown to be influenced by the type of drug, carrier and contact surface, as well as drug–carrier interparticle interactions. Powders in the respirable size ($\leq 5\text{ }\mu\text{m}$ in aerodynamic diameters) have large specific surface areas (several square meters per gram) **and therefore** respirable drug particles can carry large **levels** of charges (Mehrani et al., 2007) (Grosvenor and Staniforth, 1996; Peart, 2001a). A summary of the charge series of drugs and excipients established in the literature is provided elsewhere (Wong et al., 2013). In general, excipients tend to show lower **levels of** charge than drugs (Šupuk et al., 2012). In contrast to SS drug that carried an electronegative charge (Kaialy and Nokhodchi, 2016), several common carriers used in DPI systems such as lactose, glucose (Murtomaa and Laine, 2000) and mannitol (Kaialy et al., 2014) demonstrated an electropositive charge. The electrostatic charge of carrier particles (e.g., lactose, mannitol, glucose, etc.) could have a considerable influence on the **aerosolisation** behaviour of DPIs (Bennett et al., 1999). For example, (Mackin et al., 1997) showed the **electrostatic** charging of lactose ($63\text{ }\mu\text{m}$ to $90\text{ }\mu\text{m}$) and **micronised** salmeterol xinafoate before DPI–filling to reduce the respirable fraction of micronised salmeterol xinafoate **aerosolised** from the Diskhaler® at 60 L/min.

Typical drug–carrier DPI formulations consist of at least two different components (i.e., a drug and a carrier) which could result in complicated bipolar charging (Murtomaa and Laine, 2000). Following the addition of SS drug particles to mannitol carrier particles, drug–carrier DPI formulations demonstrated a higher netcharge than the carrier (Karner and Urbanetz, 2013).

(Elajnaf et al., 2006) studied the role of **tribocharging** in interparticle interactions between **micronised** SS and ipratropium bromide with lactose (α -lactose monohydrate, 63 μm to 90 μm) during mixing in different blending vessels. The charge of the drugs and the lactose carrier particles were shown to change following blending. SS acquired a high electronegative netcharge in contact with stainless steel, but an electropositive netcharge in contact with polymeric vessels (Elajnaf et al., 2006). Since lactose usually shows an electropositive charge behaviour (Kaialy and Nokhodchi, 2016; Palonen and Murtomaa, 2003), it could be assumed that the use of a metal equipment would encourage the formation of a SS–lactose **adhesive** mixture, whereas the use of plastic inhalers may promote SS–lactose detachment during **aerosolisation** (Peart, 2001b, 1996).

4.2. Dry powder inhalers

DPIs comprise a pharmaceutical dosage form of increasing popularity with attractive features such as the provision of a propellant-free means of drug delivery and such formulations have rapidly increased in number (Smith and Parry-Billings, 2003). In general, DPI performance is affected by **three** main factors: the design of the inhaler device (Dalby et al., 1996), inhaler powder formulation properties (with respect to the physicochemical properties of the drug and the carrier) (Kaialy and Nokhodchi, 2012; Kaialy et al., 2015; Kaialy et al., 2012c; Timsina et al., 1994), **and** patient airflow and inhalation manoeuvre (Chan, 2006). The DPI performance is most importantly affected by particle–particle interactions (Guchardi et al., 2008). Some of the most attractive methods to improve DPI performance include the use of engineered drug (Dhumal et al., 2009; Xu et al., 2012) and/or engineered carrier (Kaialy et al., 2015, 2010; 2012b) particles.

Drug particles usually separate from the larger carrier surface particles, or both the drug and carrier separate from the inhaler device, resulting in a netcharge on the particles (Telko et al., 2007). Indeed, the complete understanding of the relationships between electrostatic charge and DPI performance is still challenging due to the complexity of DPI systems and the heterogeneous nature of the particles used. Nevertheless, it could be anticipated that high resistance DPI devices (such as the Handihaler[®], Easyhaler[®] and Turbuhaler[®]) generate higher **levels of** electrostatic charge in comparison to low resistance DPI devices (such as the Rotahaler[®], Diskus[®] and Cyclohaler[®]), due to a higher shearing and consequently a higher particle **tribocharging** (Telko et al., 2007). (Byron et al., 1997) showed that the estimated charge **level** of respirable budesonide following **aerosolisation** from the Turbuhaler[®] is high enough to affect deposition. Battery-

operated DPIs have also been introduced, in which powder dispersion is enhanced using electrostatic technologies (Nilsson, 2000; Sun et al., 1999). (Ali et al., 2008) studied the charging behaviour of several commercially available DPIs (the Spiriva Handihaler[®], Pulmicort Turbuhaler[®] and Advair Diskus[®]) in real time using the electrical single particle aerodynamic relaxation time (E-SPART). However, the data interpretation is limited because the inhalers studied contain different formulations (i.e., different drug-excipient adhesive mixtures), thus more controlled studies are justified in the future.

4.3. Influence of powder charge on DPI performance

4.3.1. Blending and drug content homogeneity

Blending is an energy consuming process that shuffles individual particles, small particle groups, and large particle groups of two or more different portions of a material to produce a distribution of particles with a desired level of uniformity in the final mixture. Blending of dry pharmaceutical solids is an important step in the production of carrier-based DPI formulations (Saleem et al., 2008). Segregation and agglomeration are two main problems frequently faced in powder-mixing processes, resulting in drug content homogeneity problems (Cartilier and Moës, 1989). Recently, there has been increased attention towards the **tribocharging** phenomenon during powder blending processes (Karner and Urbanetz, 2012; Zhu et al., 2007). **The control of powder charge is important to maximise mixing efficiency** (Engers et al., 2007). This is because the electrostatic forces generated during powder mixing lead to an accumulated charge, which in turn can cause adhesion and/or agglomeration resulting in processing difficulties (Gibson, 1997; Muzzio and Alexander, 2005). Electrostatic forces have been shown to affect the number of agglomerates formed during mixing of powder systems. The decrease of electrostatic charges generated during mixing was shown to lead to a decrease in the intensity of interparticle attraction forces, leading to a reduced agglomeration tendency (Lachiver et al., 2006).

Powder mixing is broadly classified as **randomised** (Buslik, 1973; Lacey, 1997) and ordered mixing (Hersey, 1975), but there are good arguments to reject the term 'ordered' and to speak of 'adhesive' instead (Staniforth, 1987). In **randomised** mixtures, the mixing process is **often performed with (multi-component) mixtures of particles having approximately the same size distribution (to avoid segregation) in which gravitational forces exceed the interparticulate forces**. Adhesive mixtures are formed when small **drug** particles are mixed with large **carrier**

particles where they become tenaciously attached to the **carrier surface**, and so they would exhibit great resistance to being dislodged (Staniforth, 1987). In adhesive mixtures, the attractive forces holding the particles to the adsorption site **on the carrier surface** are greater than the gravitational forces. **Recently, it was proposed that the activity of surface sites on carriers for dry powder inhalation is a result of the interplay of the physicochemical properties of the carrier surface, as well as relevant formulation and dispersion conditions** (Grasmeijer et al., 2014). **Initially, the term 'ordered mixture' (introduced by (Hersey, 1975) to describe a new mixing mechanism) became popular to describe mixtures with a degree of homogeneity higher than theoretically possible on the basis of homogeneity equations derived (statistically) by (e.g.) (Buslik, 1973) and (Lacey, 1997). Later, it became generally acknowledged that ordered mixing is a concept and that such mixtures could be highly inhomogeneous too. Nevertheless, due to the high interaction forces between particles relative to the gravitational forces, adhesive mixtures are generally less prone to segregation than random mixtures. A real risk of adhesive mixtures is the loss of active material (mostly present in low concentrations) to the walls of the process equipment.**

Fine drug particles adhere to the surface of the coarse carrier particles by van der Waals, capillary, electrostatic or mechanical forces. Although van der Waals forces are the most important interparticle forces between the drug and carrier particles in the case of **adhesive** mixtures, manipulating the electrical properties was used to introduce electrostatic forces between the drug and the carrier particles and thereby reducing particle segregation tendency within an **adhesive** mixture (Staniforth and Rees, 1981, 1982). However, the properties of the final mixture depend on the type and physicochemical properties of the mixed materials. (Bennett et al., 1999) reported that the adhesion of fine lactose particulates ($<10\ \mu\text{m}$) to the inner surfaces of the charging instrument (stainless steel) can reduce the frequency of drug particle-surface interactions, leading to an increased drug–drug interparticulate interactions. Such increased interactions may be responsible for generating a heterogeneous bipolar system and thereby influencing the final netcharge.

The uniformity of blending is an essential factor for the uniformity of consequent dosing. During blending of the fine particulates with coarse particles, a competition is believed to take place between the cohesive (drug–drug) and the adhesive (drug–carrier) forces within a formulation (Dickhoff et al., 2002). The outcome of the resultant equilibrium was shown to be favoured

towards adhesion in the case of small drug and/or small carrier particles and carrier particles with rough surfaces (Staniforth, 1987). To achieve an even distribution of drug particles among the carrier particles, the drug–carrier adhesive forces should be stronger than the drug–drug cohesive forces. The ratio between the cohesive **forces** and the adhesive forces, i.e., the Cohesive-Adhesive Balance (CAB) ratio (Begat et al., 2004a, 2004b), was shown to have a dominant effect on the mixing efficiency and the **aerosolisation** performance of DPI formulations. A stable **adhesive** mixture could be expected when the CAB ratio of a drug–carrier combination is < 1 , i.e., adhesive drug–carrier forces $>$ cohesive drug–drug forces. In contrast, a less uniform mixture is expected when the CAB ratio is > 1 , i.e., cohesive drug–drug forces $>$ adhesive drug–carrier forces (Begat et al., 2004a, 2004b).

A reduced mixing efficiency could be anticipated in the case of drug and carrier particles with similar charge sign (both electropositive or both electronegative) due to an expected reduced drug–carrier adhesion (Zeng et al., 2001). In contrast, a stronger drug–carrier adhesion forces and therefore a promoted mixing efficiency and an improved drug content homogeneity are expected in the case of drug and carrier particles with opposite signs of electrical charges (Lachiver et al., 2006; Staniforth and Rees, 1981, 1982; Staniforth, 1995). For example, (Pu et al., 2009) showed that blends composed of positively charged excipient particles (e.g., lactose) and negatively charged drug particles (e.g., SS) demonstrated an improved drug content homogeneity due to a strengthened drug–carrier interparticle adhesion.

The mixing ratio of at least two different materials within a mixture is another factor that further complicates the tribocharging behaviour of powder mixture systems (Engers et al., 2007, 2006). Some reports examined the tribocharging behaviour of lactose in binary mixtures. When blended with SS, (Elajnaf et al., 2006) showed the netcharge of lactose powder to decrease because of adhesion to the mixing vessel surface. (Rowley, 2001) showed the **electrostatic** charge of SS–lactose binary mixtures to increase with decreasing the concentration of SS.

Recently, a mechanism governed by the electrostatic force has been proposed to understand the blending process of drug and carrier particles in DPI formulations using a discrete element method (DEM) (Yang et al., 2015). The number of drug particles adhering to coarse carrier particles was shown to decrease with decreasing charge and decreasing the vibrational velocity amplitude and frequency in a vibrating container. The difference between long-range and short-

range adhesive forces resulted in different mixing behaviours. The kinetics of particle charging in mixers have been described elsewhere (Zhu et al., 2007).

The pharmaceutical industry has rigorous regulations for satisfactory content uniformity. The efficiency and safety of the final DPI product are considerably influenced by electrostatic charge. In general, charged particles could be either attracted to or repulsed to each other, promoting powder agglomeration or segregation (Beeckmans et al., 1979), both have a detrimental influence on the homogeneity of powder mixtures (Pu et al., 2009). The electrostatic charge could lead to less dose homogeneity due to the forming of regions with different densities and flowabilities within a powder. Some researchers have shown that powder blends with higher **levels of netcharge** are more cohesive and have increased segregation **tendencies** (and thus reduced physical **stabilities**) (Staniforth and Rees, 1982). For example, (Pu et al., 2009) investigated the process of blending by using lactose (90 μm to 120 μm) as an excipient with caffeine (40 μm to 90 μm) as a drug after **tribocharging** with steel and polyamide contact surfaces. A strong correlation was established indicating that powders with higher **levels of netcharge** demonstrate poorer drug content homogeneities. This was confirmed by a recent study, which showed the coefficient of variation (CV) of SS content within SS–mannitol DPI formulations to increase with the increase of mannitol netcharge (Figure 5) (Kaialy et al., 2014). (Pu et al., 2009), (Hao et al., 2013) and (Kaialy et al., 2014) related the elimination or reduction of electrostatic charges to better homogeneity of the formulation blends.

4.3.2. Aerosolisation behaviour

In drug–carrier DPI systems, electrostatic forces may have a dominating influence on the adhesion, detachment (Staniforth, 1995) and deposition of fine drug particulates (Bailey, 1997).

Both the static (i.e., before **aerosolisation** – within the powder bed) and the dynamic (i.e., during **aerosolisation**) electrifications of DPI formulation powders should be considered and understood to enhance the performance of DPIs. The electrostatic forces are generally larger than the gravitational forces, but smaller than the dispersion forces. Before **aerosolisation**, both the type of materials that constitute the DPI formulation (Carter et al., 1998) (chapter 4.1) and the formulation physicochemical characteristics (Peart, 1996) (chapter 3.2) influence the charge behaviour of the final DPI dosage form, as discussed previously.

Drug and carrier particles generated from DPIs inevitably undergo **tribocharging** during frequent particle–particle physical contacts, particle contacts with the surfaces of the components of the inhaler device, and high impact velocities during their use, resulting in charged aerosols. Such charging could affect their dosing and **aerosolisation** performance (Karner and Urbanetz, 2011). **Tribocharging** occurs at this point in time of fluidisation of the powder bed through the inhaler device by the inspiratory airflow. In general, the **level** of charging increases with the energy input involved (Bailey, 1993; Šupuk et al., 2012). This has been evident during **aerosolisation** since several reports showed the powder netcharge to increase with increasing the pressure/airflow rate **employed during aerosolisation** (Chow et al., 2008; Hoe et al., 2010, 2009a, 2009b). The electrical charging of some pharmaceutical powders was shown to increase at least 100 times after **aerosolisation** induced by a turbulent airflow within an air cyclone. For example, (Staniforth and Rees, 1982) showed the absolute amount of netcharge of lactose particles (500 μm to 710 μm) to increase from 0.63 nC/g following pouring off a glass surface to -470.0 nC/g subsequent to **fluidisation** in an earthed brass cyclone. In another study, the electrostatic charges of an inhalation grade of coarse lactose (InhaLac[®] 230, $d_{50\%}$: 70 μm to 110 μm) were shown to be considerably higher in **level** following **aerosolisation** (from the Rotahaler[®] at flow rates ranging between 30 and 75 L/min) compared to the initial charges of the bulk and capsulated lactose (Chow et al., 2008). Therefore, because **aerosolisation** is more energetic than blending, it could be assumed that the initial charges of powders before **aerosolisation** could be negligible in **level** in comparison to the charges generated during powder dispersion. This explains why, for example, the original electrostatic charge levels of mannitol powders ($d_{50\%} = 3.5$ μm) tumbled in containers of different materials were inadequate to significantly influence the FPF of SS **aerosolised** from the Aerolizer[®] at a given flow rate (60 L/min) (Adi et al., 2010). This was also in line with a recent study by (Kaialy et al., 2014) who showed that the original electrostatic charges of several size-fractions of mannitol ($d_{50\%}$: 45 μm to 122 μm) before **aerosolisation** had no significant effect on the **aerosolisation** performance of SS from the Aerolizer[®] at 92 L/min.

Some reports confirmed that the charging behaviours of **aerosolised** drug–carrier formulations are very different to drug only formulations (Byron et al., 1997). Following the **aerosolisation** of lactose–beclomethasone dipropionate formulation from the Easyhaler[™], lactose particles were positively charged, whereas the drug particles (mostly) charged negatively (Palonen and Murtomaa, 2003). SS particles formulated with lactose were shown to charge negatively when

aerosolised from the Dryhaler[®] (Byron et al., 1997) and the Rotahaler[®] (Zhu et al., 2008). These observations are in line with many studies of **micronised SS aerosolised** from DPIs (Hoe et al., 2011; Young et al., 2007). Such results support the argument that drug and carrier particles will have a significant tendency to dynamic charge-transfer not only during blending (Elajnaf et al., 2006) but also during drug-carrier detachment upon **aerosolisation** (Kwok and Chan, 2009). These conclusions were further supported by theoretical and experimental studies which demonstrated that pharmaceutical aerosols acquire bipolar charge during **aerosolisation** (Kulon and Balachandran, 2001; Saini et al., 2007). It could be argued that the **micronised** drug deeply influence the charging characteristics of lactose and vice versa. However, evidence to corroborate such an explanation was not provided. The opposite charge signs of drug and carrier particles generated following **aerosolisation** could result from the dislodgement of fine drug particle from the surface of coarse carrier particles during **aerosolisation**, and it is expected to discourage drug-carrier detachment during **aerosolisation** (Peart, 2001a, 1996).

The reviewed literature has shown that the **tribocharging** of particles during **aerosolisation** is influenced by the interplay between several factors, including the particle physicochemical properties (Karner and Urbanetz, 2011), the inhaler type/design, drug/carrier type, the drug load, the capsule material and the inhalation flow rate (Byron et al., 1997; Palonen and Murtomaa, 2003). Furthermore, the influence of these several factors (such as capsule material, inhaler device, lactose carrier grade and mixing procedure) on the charging properties of drug-carrier DPI formulations were shown to be not strictly additive (Hoe et al., 2010).

At the clinical level, the electrostatic charge in DPI formulations could cause powder aggregation and **fluidisation** problems. This could result in an increased oropharyngeal drug deposition and consequently a reduced bioavailability and increased side effects, especially **for** corticosteroids (Noakes, 2004). The highly charged particles can deposit on the surface of the inhaler device by electrical precipitation. Therefore, the reduced bioavailability may also result from high amount of drug being retained by the DPI device. This was supported by (Byron et al., 1997) who showed the drug particles and the inhaler-mouthpiece to carry opposite charges following **aerosolisation**. In the same line, (Kaialy et al., 2014) showed that SDM carrier particles with higher **levels of** netcharge deposited higher amounts **of** drug (SS) on the inhaler device, inhaler-mouthpiece and induction port when **aerosolised** from the Aerolizer[®] at 92 L/min.

4.4. Influence of electrostatic charge on aerosol lung deposition

It has established that the charge of **aerosolised** particles could influence their deposition profiles in the airways (Matsusyama and Yamamoto, 2006; Melandri et al., 1983), thus the electrostatic charge of pharmaceutical aerosol particles is a subject for formulation **optimisation** (Melandri et al., 1983). The deposition of charged particles has been extensively studied using computational lung models (Hashish et al., 1994; Saini et al., 2004).

The deposition of **aerosolised** drug on the respiratory system is ruled by inertial impaction, gravitational sedimentation and Brownian diffusion (Gonda, 1991). **The deposition** may also occur by other less important mechanisms, such as electrostatic attraction (**for** charged particles) and interception (**for** elongated particles). The deposition by electrostatic attraction is small (contributing to < 10% of overall deposition) (Lippmann and Schlesinger, 1984; Schlesinger, 1995). This is because the electrostatic force is inversely related to the square of the distance between charged objects (Coulomb's law, Eq. 1) (Mansur and Mansur, 2011). Electrostatic attraction is relatively more relevant for the deposition on the lower airways, especially in the alveolar region (Balachandran et al., 1997; Gonda, 2004; Melandri et al., 1983).

DPI performance could be improved by taking advantage of electrostatic charges present on the particles. Several theoretical and experimental studies concluded that particles with higher **levels of** electrostatic charge have a higher probability to deposit on the airway surfaces due to higher attractive forces (Chang et al., 2012; Cohen et al., 1998, 1995; Fleming et al., 1996).

Electrostatic forces are divided into two different categories, i.e., *space charge* and *image charge* (Virtanen et al., 2001). Space charge refers to interparticle repulsion within the airstream. Although space charge has been reported to be more relevant at the upper airways **for** dense aerosol clouds (Yu, 1977), it has a considerably low contribution on the overall particle deposition on the upper airway regions in which inertial impaction is the **dominant** mechanism. Image charge is particle-image charge on a surface attraction. Processing and handling of powders during manufacture generate **tribocharging** and/or contact charging (Kulvanich and Stewart, 1987). When those charged particles pass through the lining of the respiratory tract (which is uncharged but electrically conductive), they induce an opposite image charge on the inner surface of the respiratory tract (Melandri et al., 1975). Since the image charge generated is of opposite sign to the original charge, a force of attraction to the airway surface is induced

accelerating drug deposition in this region (García-Hernández et al., 1998; Schlesinger, 1995). However, the latter mechanism is a minor contributor to the deposition of drug particles in the upper airway region in comparison to inertial impaction (Lippmann and Schlesinger, 1984). Particle deposition by image charge is only important in the alveolar airways **for** low-density particles (Koolpiruck et al., 2004). The use of electrostatic principles to improve the efficiency of pulmonary drug delivery has been discussed elsewhere (Chang et al., 2012; Koolpiruck et al., 2004; Wong et al., 2013).

5. Outlook and future directions

Most of the previous studies revised above focused on the factors affecting charge one-by-one, neglecting the potential interactions between them. Therefore, there is a need for methodological evaluations and predictive *in silico* investigations in the future to evaluate the significance of the factors affecting charge as well as the interactions between them. Additionally, there is an increased need to separate and measure the bipolar charges (i.e., to discern positively and negatively charged particles) of inhalation powders. The novel approach that has been recently developed in the Wolfson centre (University of Greenwich, UK) (Hussain et al., 2013) is a capable method to study the bipolarity of inhalation powders. This technique will improve the understanding of bipolar electrostatic charges to enhance pulmonary drug delivery (Kaialy and Nokhodchi, 2016; Kaialy et al., 2014). In time, the control of the effects of electrostatic charging in DPI devices is expected to become obligatory, although a systemic control of the charge sign and level in inhalation powders by **tribocharging** has not been reported yet. Additionally, up to now, the influence of electrostatic charge of aerosol particles on aerosol performance in human subjects has not been reported and therefore the role of electrostatic charge on **aerosolisation** performance is not yet fully ascertained. Finally, there are concerns of the reproducibility of electrostatic charge properties, i.e., the electrostatic charge properties measured in the laboratory may not be adaptable to the industrial scale.

6. Conclusions

Tribocharging is a popular phenomenon in inhalation solids that arises from particle–particle and particle–wall collisions. Charge generation phenomena in inhalation powders could be severe. The electrostatic charging phenomenon is complex and difficult to study and control. This is

because charging of inhalation powders depends on a combination of many physicochemical properties as well as the inhaler design and environmental factors, thus our understanding of electrostatic charging is not complete.

The **electrostatic** charging process is very sensitive to a multitude of factors and thus a slight difference in particle physicochemical properties or the measurement principles could lead to significant differences in the charge behaviour of inhalation powders. Moreover, in addition to interactions, the linkage between variables is a main complicating element in obtaining a fundamental understanding of **electrostatic** charging in adhesive mixtures for inhalation. However, the recognition that interactions among charging, formulations, and **aerosolisation** variables are pervasive is an important step towards the understanding of tribocharging of inhalation powders.

Charging during unit operations can cause agglomeration and lead to serious problems of quality control. Electrostatic charge has an influence on both particle transport and deposition on **the respiratory** airways due to space and image charge. Therefore, controlling the electrostatic charge of inhalation powders is crucial to improving the quality and efficiency of the inhalation product. Although the reduction of powder electrostatic charge may improve the future prospects of aerosol formulation powders, it is difficult to ascertain the influence of a single factor such as charge level/sign on DPI performance due to the complexity of DPI systems. Therefore, a substantial work is warranted to investigate the charging properties of drug and carrier particles of DPI systems as well as drug-carrier adhesive mixtures. The study of bipolarity in the drug-carrier inhalation powders could potentially play an important role in the technological advances in the design and development of dry powder inhalation formulations in the future. The fundamentals of charging as well as the agglomeration, deagglomeration, **and** deposition properties of charged drug and carrier particles have to be the subject of advanced examination.

7. References

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Legends to figures

Figure 1. Schematic, simplified presentation of some factors (and their inter-relationships) having an effect the electrostatic charging of pharmaceutical solids and adhesive mixtures for inhalation.

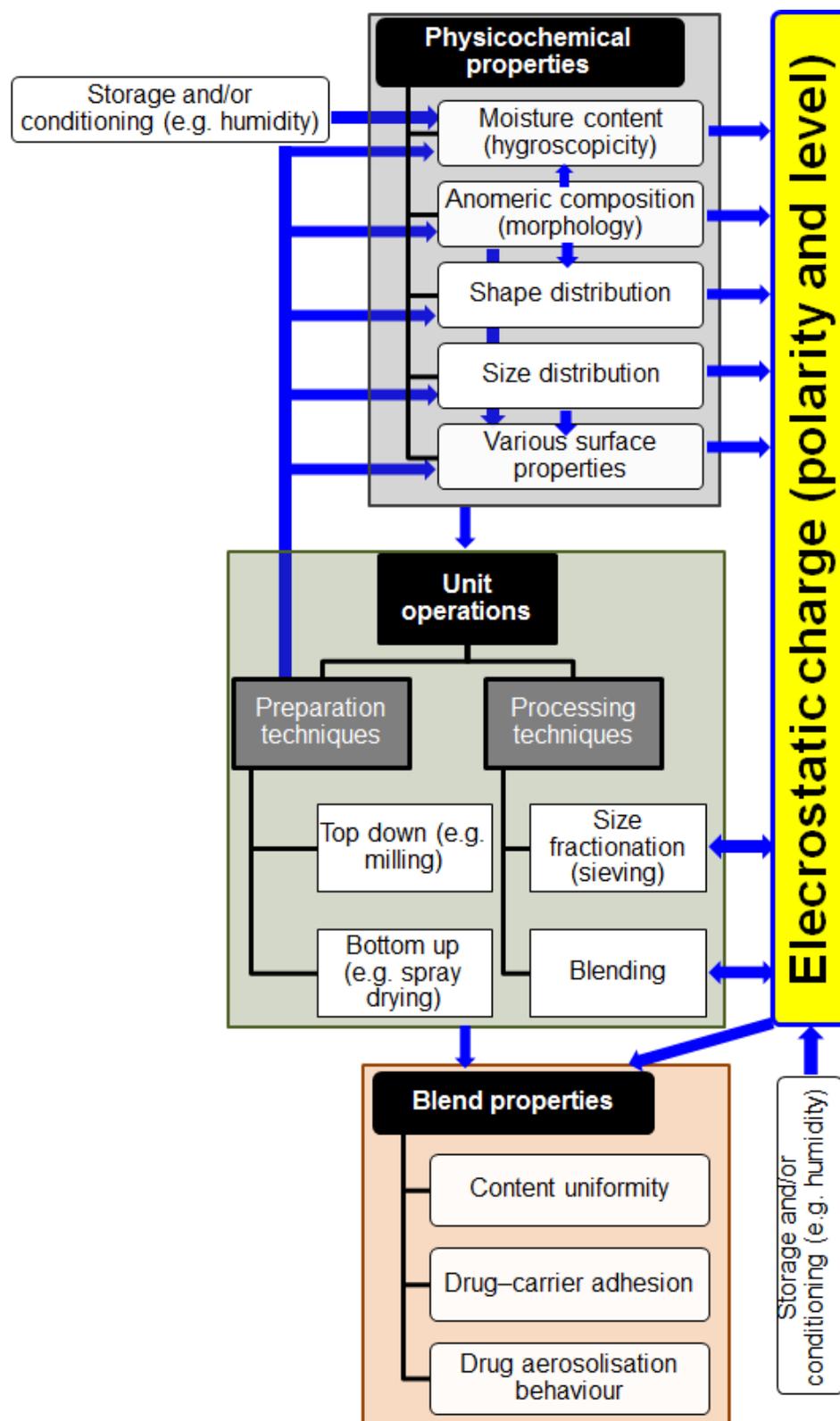


Figure 2. Netcharge (nano-coulomb/gram: nC/g, mean \pm SD, $n = 6$) in relation to volume mean diameter (\bullet) (mean \pm SD, $n = 10$) and BET specific surface area (\blacksquare) (mean \pm SD, $n = 3$) of different size-fractions of spray dried mannitol, i.e., SDM-A (90 μm to 125 μm), SDM-B (63 μm to 90 μm), SDM-C (45 μm to 63 μm) and SDM-D (20 μm to 45 μm) (Source: reproduced from with permission from (Kaialy et al., 2014)).

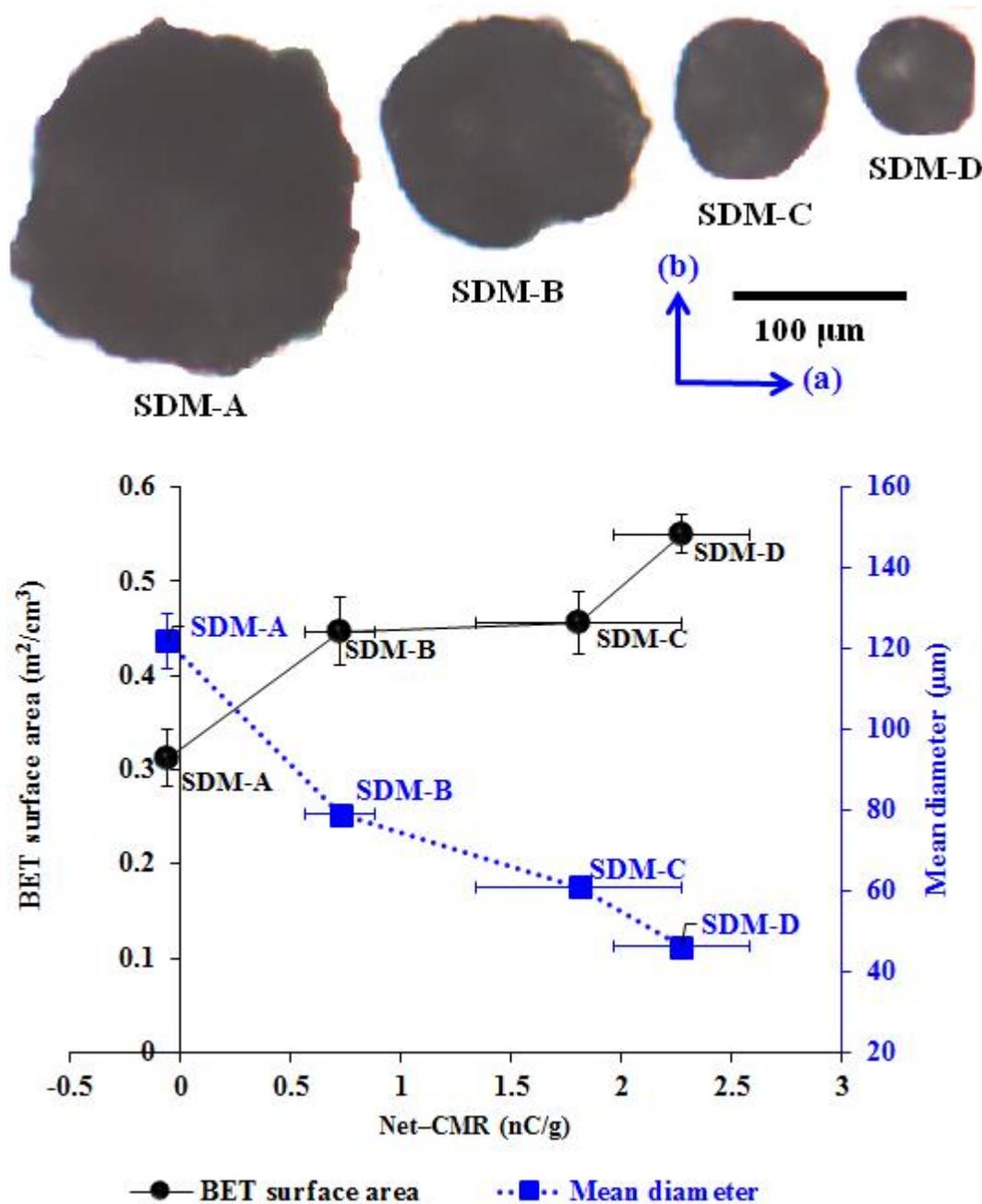
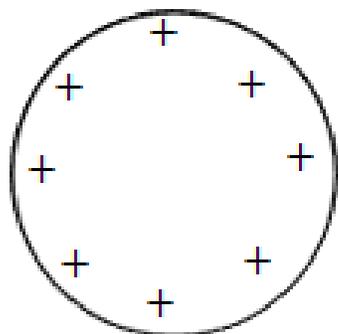
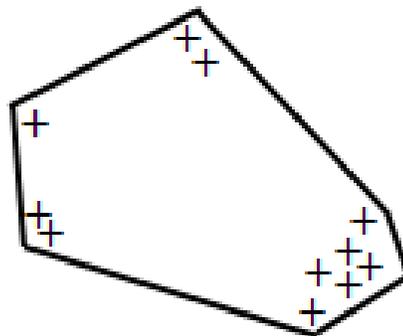


Figure 3. Schematic diagram showing theoretical charge distribution on the surface of spherical particles and angular particles.



Spherical particle



Irregular particle

Figure 4. Netcharge-to-mass ratio of mannitol particles with comparable particle size (63 μm to 90 μm) and two distinct shapes, i.e., spherical shape (spray dried mannitol, SDM) (**Source: reproduced from with permission from (Kaialy et al., 2014)**) and irregular shape (commercial mannitol, CM) (unpublished data).

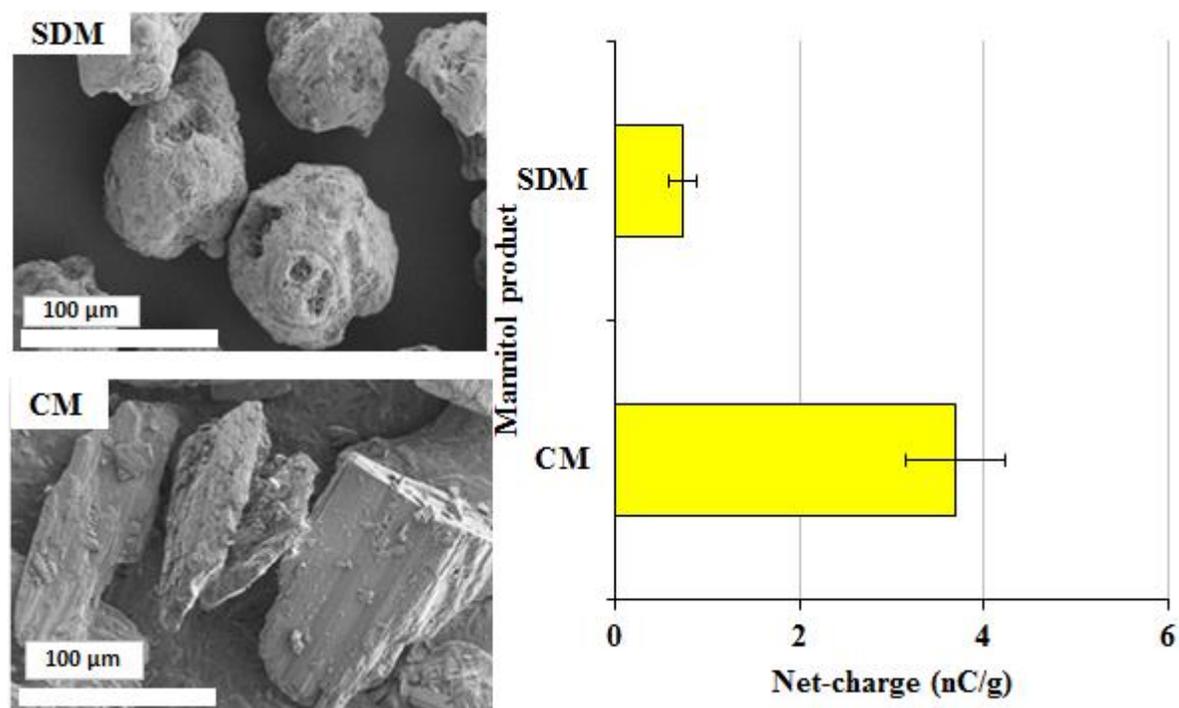


Figure 5. Coefficient of variation of salbutamol sulphate (SS) content in relation to netcharge of spray dried mannitol for salbutamol sulphate-spray dried mannitol DPI formulations (**Source:** reproduced from with permission from (Kaialy et al., 2014)).

