

British Journal of Pharmacy

www.bjpharm.hud.ac.uk

Critical Review

Triboelectrification of Pharmaceutical Powders: A Critical Review

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ARTICLE INFO

Received: 18/08/2018
Revised: 11/10/2018
Accepted: 15/10/2018
Published: 17/12/2018

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KEYWORDS:

Triboelectrification;
Powders; Charge;
Electrostatics

ABSTRACT

The majority of pharmaceutical and polymer powders are insulating materials that have the propensity to attain and then retain triboelectric charge. This phenomenon can potentially give rise to issues during handling and processing of materials. A comprehensive understanding of the mechanisms controlling charging behaviour can inform effective control of the process and potentially enhance the final product quality and performance. Therefore, the objective of this review article is to summarise the principles of triboelectric charging and to understand the various contributing factors. It is intuitively expected that the acquired understanding can be helpful in improving the efficiency, quality, performance and safety of powder processing phenomena and final products.

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INTRODUCTION

In pharmaceutical manufacturing, processing operations such as mixing, spray-drying, coating and pneumatic conveying, have a tendency to induce an electrostatic charge on powder particles due to inter and intra-particulate collisions (Carter et al., 1992). Fine powder particles, such as those used in inhalation, typically experience problems in flow and dispersion because of the small particle size. Moreover, electrostatic, capillary and Van der Waals forces play a critical role contributing to adhesion and cohesion (Bailey, 1993) with implications on transporting, filling, blending, drying, milling, and mixing; and subsequently, non-uniform dosages in the final product (Bennett et al., 1999; Elajnaf et al., 2007; Elajnaf et al., 2006; Rowley, 2001; Staniforth and Rees, 1982). Due to the potent nature of many APIs, there are strict quality control processes governing pharmaceutical production for acceptance of finished pharmaceutical product. A

single batch of powder worth hundreds of thousands of pounds is sometime discarded, if a number of APIs does not meet the pharmacopoeial standards. Therefore, the control of electrostatic charge is important to ensure the final product is safe and effective to use. Aside from the mechanical behaviour of charged particles, electrostatic discharges are also an area of concern as large quantities of powders being handled with high transfer rates in filling and emptying during tableting process. This can rapidly build up a charge and increases the probability of an electrical discharge. Additionally, fine pharmaceutical powder particles have a larger surface area which enhances the surface contact and that leads to charge accumulation and their distribution in the air provides the oxygen a chance of combustion. The combination of these elements is considered highly dangerous as it has the potential to ignite fires and explosions (Ohsawa, 2011). In 2012, an electrostatic spark discharge ignited a fire during a

pharmaceutical powder transfer operation. Following an investigation, the source was found to be a 15-year-old filter which was not appropriate for handling low minimum ignition energy powders (Kong, 2006). A statistical study about industrial dust explosions revealed that one dust explosion happens every day and every tenth explosion is caused by static electricity discharge (Glor, 2003). Similar statistics in Japan were found 70% of 153 industrial accidents that occurred over the past 50 years were attributable to static electricity (Ohsawa, 2011). A noteworthy finding was that these incidents were caused by isolating conductors, including workers, which led to spark discharges and could have been easily prevented with earthing (Wong et al., 2014a).

Despite the issues, there have also been several useful applications of electrostatics in the pharmaceutical industry. Blend homogeneity of powder mixes can be promoted by APIs and excipients with opposite charges as they tend to attract each other and segregation becomes unlikely (Pu et al., 2009; Staniforth and Rees, 1981, 1982). While the physicochemical properties determine the inherent polarity of charge gained, the magnitude of charge can be enhanced by charging processes. Conversely, homogeneity could be compromised if an opposite polarity is induced. Other critical parameters that should be considered, in particular for potent low-dose formulations, include the choice of an appropriate mixer, mixing time, and content uniformity (Venables and Wells, 2001). Pu et al. (2009) evaluated three different API blending procedures: (I) conventional blending without any charge control, (II) blending with simultaneous charge neutralisation, and (III) blending combined with a corona charging process. Variation in API content increased with specific charges, which suggested that uncontrolled electrostatic charging had an adverse effect. The elimination or minimisation of electrostatic charge did not resolve the problem, rather the mixing of oppositely charged components remained the only controlled charging that improved blend uniformity (Staniforth and Rees, 1982). Interestingly, there is a relationship between electrostatic charging and blend homogeneity and selection of the time points with the least charge variation were expected to correlate with relatively more uniform content, and

the authors proposed this as a useful monitoring tool in mixing processes (Chang et al., 1995).

Powder mixing is a fundamental, important and often the very first processing step, for many industrial processes and is one of the most common unit operations utilised in many industries such as pharmaceutical, chemical, food, cosmetic, cement, glass, and detergent. Mixing may be defined as the merger of two or more dissimilar portions of materials to attain a required level of uniformity in the final product (Swarbrick, 2007). There are three types of mixing namely, positive, negative and neutral. The first occurs spontaneously by diffusion, for example, in miscible liquids and gases where no energy is needed, whereas with negative mixing, such as the dispersion of insoluble solid particles within a liquid, work is required by stirring to maintain the dispersion. In the neutral mix, work must be done initially to mix the components as in a blend of powders. Specifically, the pharmaceutical industry uses powder mixing operations to incorporate active pharmaceutical ingredients in many pharmaceutical formulations, such as powders, granules, capsules and tablets. Powder mixing can be classified either as randomised or ordered mixing (Hersey, 1975). Random mixing is the process of repeatedly splitting and recombining a bed of particles until there is an equal chance of any individual particle being at any given point in the mix at any one time (Venables and Wells, 2001), Figure 1. Random mixing is based on the statistical randomisation of non-cohesive particles (Hersey, 1975). It is a rough estimate of disorder and does not result in an “ideal” mixture.

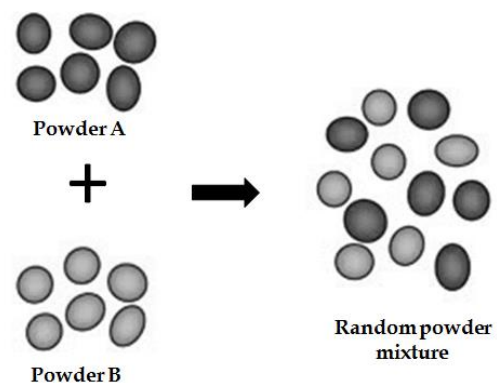


Figure 1. Schematic illustration of random powder mixture.

Conversely, when inter-particulate forces, either attraction or repulsion, are introduced during powder mixing the randomised distribution of component particles will be disturbed; this type of mixing is described as ordered mixing. The charge generated can be used to help with such mixing operations in industry (Swaminathan and Kildsig, 2000; Venables and Wells, 2001). Fine particles tend to charge oppositely to coarse particles during particle collisions with material surfaces. This results in fine particles adhering to larger carrier particles, known as ordered mixing (Figure 2). Ordered mixing is believed to result in a more homogeneous and stable system compared to that of a random mixture (Hersey, 1975). An ordered mixture is likely to retain its integrity if the bonds between the carrier and the fine particle are strong enough; in this case, handling problems are greatly reduced (Ghori et al, 2015; Ghori et al 2014a; Mäki et al., 2007; Hersey, 1975).

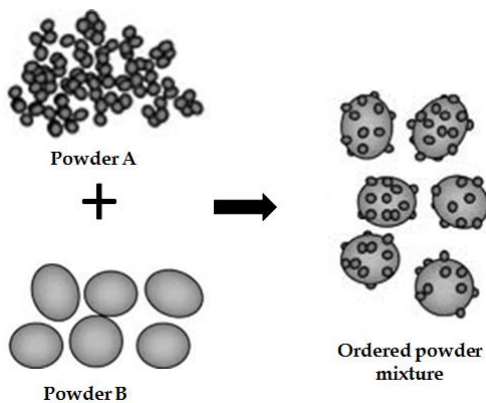


Figure 2. Schematic illustration of ordered powder mixture.

Pharmaceutical solids are mainly organic materials that have high resistivities ($> 10^{13} \Omega \text{ m}$) and charge relaxation times of minutes to hours (Bailey, 1993). The processing of pharmaceutical powders during manufacturing inevitably involves relative movement of particles against each other and alongside solid surfaces of processing equipment, hence providing ample opportunities for charge generation (Glor, 1985, Harper, 1967). Powder processing operations, including micronisation, fluidisation, sieving, conveying of powders through pipes, bags, and hoppers and spray drying, invariably generate triboelectric charges (Glor, 1985; Matsusaka et al., 2010; Matsusaka and Masuda, 2003). Usually, higher the energy involved in a procedure, the greater the magnitude of charge. This can instigate problems such as dust explosions, particle adhesion during manufacturing, alteration

in the dose uniformity of pharmaceutical dosage forms, particle accumulation on the surface and segregation (Šupuk et al., 2011; Staniforth and Rees; 1982, Glor, 2005; Glor, 1985). Surface adhesion (SA) of powder, is the propensity of dissimilar powder particles or contacting surfaces to cling together. SA during processing seems to be the root cause of other problems, having a direct relationship with the aforementioned problems related to binary powder mixtures especially where multiple powder materials containing excipients and APIs (active pharmaceutical ingredients) are mixed. The inter-molecular forces considered responsible for SA include van der Waals forces, electrostatic charges and bridging forces, mainly surface liquid capillary attractions (Cross, 1987). However, it was proposed that the main particle/substrate forces are van der Waals and electrostatic forces. These forces are strongly affected by surface properties (morphology, surface chemistry and contact area) and size of powder particles. For larger powder particles, gravity and inertia are generally greater than the adhesion force, hence they normally flow easily. However, for fine powder particles, the inter-particle adhesion force is substantial relative to gravity; therefore, they tend to adhere to one another and are difficult to handle (Lam and Newton, 1991; Podczeck, 1998). Hence, the evaluation of powder particle size and surface properties is important to control flowability of powders during pharmaceutical manufacturing.

Electrostatic charging

Electrostatic charging on solids arising from the contact between two surfaces is considered a one of the oldest manifestations of electricity. The concept of electrostatic charging has been known for centuries, as the ancient Greeks in the sixth century B.C. observed that the mineral amber can attract small objects after rubbing. The earliest experiments of Thales of Miletus, around 500 B.C., describe how amber attracted light bodies such as feathers and pieces of straw after rubbing with fur or wool (Arfken, 1984). In 1600, William Gilbert used the word 'electric' for the first time, originating from the Greek word "*elektron*" and differentiated electrical and magnetic phenomena. Gilbert also explained the generation of charge in a range of different materials and concluded that many materials other than amber can also be electrified. In 1733, Charles du Fay discussed the polarity of charge on glass and amber respectively, after rubbing with silk and introduced the terms 'vitreous' and 'resinous'. Subsequently, in 1750, Benjamin Franklin named these charges as positive and negative, respectively.

Around the same time Stephen Gray classified substances into two major groups, firstly, 'conductors' which were materials such as metals and water which allowed the charge to flow freely whereas 'insulators' was a group including wood, rubber and glass and did not allow charge to flow (Smith et al., 1966). A quantitative investigation of the electrical interaction between two charged particles was begun in 1785 when the French scientist Charles Augustin de Coulomb was able to establish an electrostatic force law or Coulomb's Law using a torsion balance (Arfken, 1984). According to this law, it was established that the force between two small electrically charged spheres, at rest, was inversely proportional to the square of the distance of separation. Furthermore, in 1843, Faraday conducted experiments on electrostatic induction using an ice-pail (Faraday well) connected to a gold-leaf electroscope and placed on an insulator. It was concluded that as a charged body was enclosed in a hollow conductor, it induced, on the inside of that conductor, a charge equal in magnitude but opposite in polarity to its own. He has also suggested that equal and opposite charges are produced when a body is electrified by rubbing (Chang et al., 1995).

Triboelectrification

Triboelectrification is intrinsically a dynamic, strenuous and dissipative phenomenon, arising due to the difference in electrical potential when two materials come into contact with each other (either by impact, friction or shear) and are then separated (Harper, 1967). There are two broad categories that are considered under triboelectrification: firstly, contact charging, which involves the direct contact and subsequent separation of two surfaces without rubbing. Secondly, frictional charging involves a relatively adjacent movement of two contacting surfaces. However, with regard to a mechanistic approach, these two modes of charging are difficult to differentiate and the term triboelectrification is conventionally used to describe the overall process, even though the prefix "tribo" literally means rubbing (Swarbrick, 2013; Cross, 1987). Mostly, pharmaceutical powders are insulators and are composed of fine powder particles, which come into contact with each other or with the surfaces of different processing equipment surrounding the powder leading to triboelectric charging. This charge generation arises due to the contact potential differences (CPD) between the bodies caused by the type of different materials but may also be influenced by particle size, surface roughness, environmental factors, contamination and type of

contacting surfaces (Karner and Urbanetz, 2011). The triboelectrification phenomenon can be classified into metal-metal, metal-insulator, and insulator-insulator contacts. A brief summary of different triboelectric charge generation theories has been summarised in Table 1.

Metal-metal contacts

The rationale for charge generation and transfer between two contacting metals is well known, however, quantification of triboelectric charging of metallic material is usually difficult, as the charge migrates quickly from the contact point. The charging process can be explained in terms of the work functions of the materials; when two dissimilar metal objects make contact, electrons will flow from the metal with the lower work function (W_{low}) to the metal having a higher work function (W_{high}), as illustrated in Figure 3. This is due to the CPD generated on contact between two surfaces having different energy levels (Matsusaka and Masuda, 2003).

Metal-insulator contacts

The theory of contact electrification between metals can be extended to metal-insulator contacts, as various authors have used the same concept to describe the metal-insulator charge generation mechanism (Matsusaka et al., 2010). However, this type of contact charging is less well understood, despite a considerable amount of research in this area. For instance, none of the literature on this subject discusses the exact mechanism of charge transfer, however, several charge transfer mechanisms have been proposed (Lowell and Rose-Innes, 1980), as described in the following subsections.

Electron transfer in metal-insulator contacts

Early experiments using insulators and metallic surfaces indicated a direct relationship between the charging propensity and the level of work function. Davies (1969) determined the charge density of insulator and dielectric polymer surfaces by contacting them with metallic surfaces having known work function. The charge density produced by each metal was plotted against the CPD of that metal with respect to gold as a reference. Results showed the dependence of charge density on the metal work function which revealed the movement of electrons.

Table 1. Summary of different theories of triboelectric charge generation.

Transfer theories	Description	Reference
Electron transfer theory	Electrons move from material having a low work function to that with a higher work function which causes a charge.	Davies, 1969 ; Murata <i>et al.</i> , 1979 ; Lowell and Rose-Innes, 1980 ; Lowell, 1979 ; Lang and Kohn, 1971
Ion transfer theory	On contact, the free movable ion (positively or negatively-charged) relocates to another surface.	Harper, 1967 ; Kornfeld, 1976 ; Matsusaka <i>et al.</i> , 2010 ; Robins <i>et al.</i> , 1980
Material transfer theory	A physical clump of material rubs onto an opposing surface of material bearing either positive or negative charges. This eventually determines the net overall charge of the resultant material bearing the detached material.	Jain and Bahadur, 1978 ; Tanoue <i>et al.</i> , 1999 ; Hogue <i>et al.</i> , 2004 ; Eilbeck <i>et al.</i> , 2000 ; Baytekin <i>et al.</i> , 2013 ; Piperno <i>et al.</i> , 2011

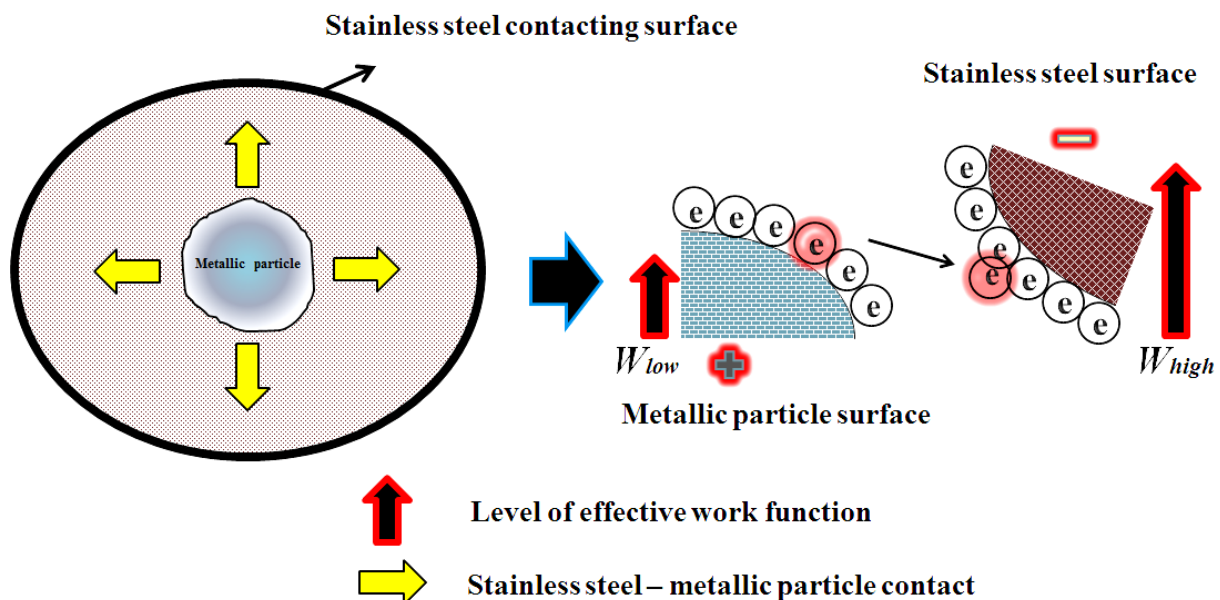


Figure 3. Schematic illustration of charge generation during metal-metal contact.

Murata and Kittaka (1979) presented evidence for electron transfer being the mechanism for contact electrification of polymers and metals by measuring photoelectric emission. According to Lowell and Rose-Innes (1980), charges acquired by an insulator, when in contact with a metal, are generally attributed to electron transfer. During the contact charging process, the valence electron energy state of powder particles on an atomic scale is designated as the Fermi level whilst the vacuum energy level is a thermodynamic state of electrons far from the atom and can be considered as a reference point.

The difference between the Fermi level and vacuum energy level equates to the work function (W), which is a unique surface property of materials and refers to the minimum energy difference required for the liberation of loosely bonded electrons present in the outer electron shells of an atom (Lowell, 1979). When inter- or intra-particulate contacts of powder particles are established, electrons flow from the lower work function (W_{low}) material towards the material with higher work function (W_{high}), consequently, a CPD ($W_{high} - W_{low}$) is generated across the particle surface (Lang and

Kohn, 1971). Moreover, this leads to the generation of electrostatic charge, which is exclusively a surface phenomenon (Lowell and Rose-Innes, 1980). A schematic illustration of electron transfer theory is described in Figure 4a.

Ion transfer in metal-insulator contacts

Ion transfer has been suggested by various researchers as a mechanism of charge transfer during insulator and metal contact (Harper, 1967; Robins et al., 1980). The fundamental principles of this theory are based on the fact that insulating materials contain free, movable ions in their body or on their surface. These ions can be transferred by diffusion- relative affinities and the kinetic effect arising from shearing and can cause one member of a pair of positive and negative ions to relocate to the other surface, which can be an insulator or a metal. This will then determine the magnitude and polarity of triboelectric charge on the contacting material surfaces (Matsusaka et al., 2002). A schematic illustration of ion transfer theory is described in Figure 4b.

Furthermore, it was assumed that insulators contain an internal electric field. The charged defects present in their lattice structure and the ions present in the atmosphere compensate for this internal electric field which leads to the formation of a surface layer. Friction between the two materials amalgamates their respective surface layers. Finally, the compensation of the intrinsic field of the two bodies is disturbed and the insulator gains a triboelectric charge (Kornfeld, 1976). However, ion transfer is usually not regarded as a dominant cause of triboelectric charging (Harper, 1967).

Material transfer in metal-insulator contacts

According to this theory, material in the nanometre to the micrometre range can be transferred during contact and that dislodged material is expected to bear the charge. Any impact or friction between two surfaces can break bonds and this is particularly true for brittle and friable particles, such as pharmaceutical powders, and this eventually determines the net overall charge of the resultant material bearing the detached constituent

(Matsusaka et al., 2010). Jain and Bahadur (1978) probed the impact of material transfer in polymer-polymer sliding as a function of time, speed and load. It was concluded that material transfer occurred under all conditions of rubbing. Material transfer may also contribute to charge transfer between a metal and an insulator (Tanoue et al., 1999). Electrons in insulators do not possess single energy levels like conductive materials. Electron energy can be explained as a function of its physical position, surface impurities, and the material's chemical and atomic structure (Hogue et al., 2004). Research investigating the impact of surface impurities has shown that cleaning a container surface with acetone to remove surface impurities during the experiments can have a significant effect on the triboelectric charging of particles. This study suggested that charge transfer is not solely an intrinsic feature of the material (Eilbeck et al., 2000). However, recently experimental data using X-ray photoelectron spectroscopy and Raman spectroscopy support the material transfer model mechanism of charge generation (Baytekin et al., 2013; Piperno et al., 2011). A schematic illustration of the material transfer theory is shown in Figure 4c, in which a physical clump of material rubs onto the opposing material surface bearing either positive or negative charges.

Insulator-insulator contacts

The experimental and theoretical principles of charging generation during insulator-insulator contact have been exploited in toner charging (Lowell and Rose-Innes, 1980; Yoshida et al., 2003; Yoshida et al., 2006). The mechanism of charge generation is similar to that for metal-insulator contacts, but in this particular scenario, the movement of electrons and ions is more restricted (Matsusaka et al., 2010). According to Castle, (1997), all three aforementioned mechanisms (electron transfer, ion transfer, and material transfer) may occur during insulator-insulator contacts. Moreover, another theory associated with insulator charging may also be involved. According to that theory, to generate charging between two insulating surfaces, there must be donor and acceptor sites near the surface of the non-conductive particles (Bailey, 1984). In order for insulators to charge, surface impurities must be present if the particles are to

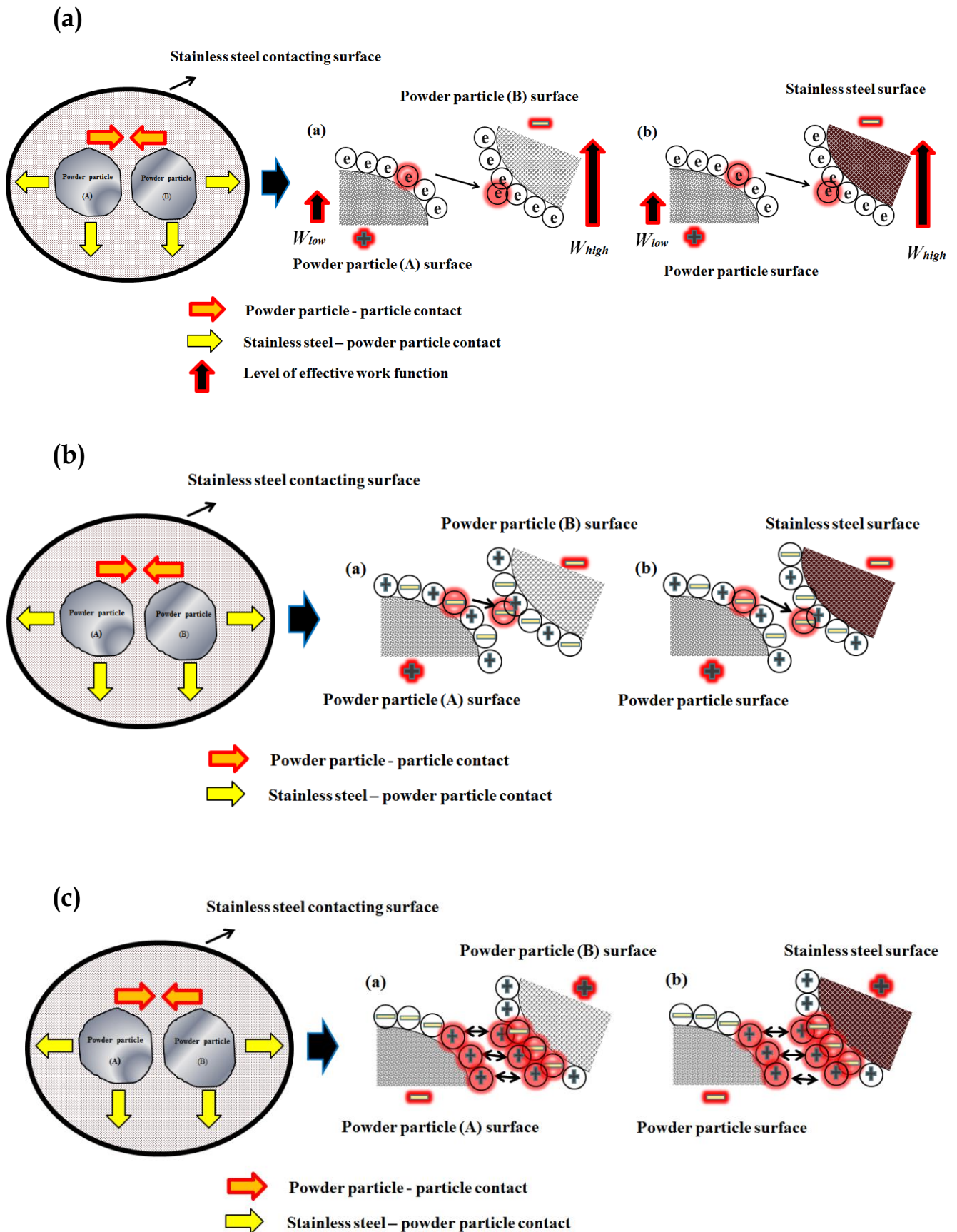


Figure 4. Schematic illustration of (a) electron transfer (b) ion transfer and (c) material transfer theory of triboelectric charge generation.

charge when in contact with each other. According to Bailey (1984), tests carried out using perfect insulators showed that no charging occurred and when slight impurities were added charging became detectable. Hogue et al., (2004) state that many materials are hydrophilic and have a thin layer of water molecules on their surfaces; this is where ions can exist which play a role in charge exchange.

Factors affecting triboelectrification

The electrostatic charging of powder particles in relation to the manufacturing and use of pharmaceutical products is usually considered due to a triboelectrification phenomenon. Triboelectrification and its associated adhesion of powder particles are complex processes affected by different factors. In this section, the principal factors that can affect electrostatic charge transfer and powder SA will be discussed; however, a summary of all the major contributing factors has been given in Table 2.

Nature and work function of contacting surfaces

The earliest research work demonstrated conflicting evidence regarding the relationship between work function and electrostatic charging (Elsdon and Mitchell, 1976) but with progress in the area, there is now evidence to show that there is a relationship between work function and electrostatic charge generation and transfer. Davies (1969) studied the charge densities generated on dielectric surfaces, polycarbonate, polytetrafluoroethylene (PTFE), polyvinyl chloride (PVC), polyimide, polyethylene terephthalate (PET), polystyrene (PS) and nylon, and studies revealed that the dielectric surfaces were directly related to the work function of the respective contacting surface, as described earlier. Lowell (1976) studied the mechanism of charge generation and transfer between platinum, gold, nickel, rhodium, and aluminium and three kinds of polymers (polyethylene, PTFE and PET), using a single non-sliding contact, repeated non-sliding contacts and a sliding contact. The results demonstrated that in a single non-sliding contact, the charge did not depend on the work function. However, on repeated contact, or if the metal slides

on the polymer, then the resultant charge density has a linear relationship with the work function of contacting surfaces. Electrostatic charging of aluminium, copper, gold, magnesium and platinum electrodes was investigated by Nordhage and Bäckström (1977) against sodium chloride. It was found that the charge density transferred to the metals was increased with increasing work function of each respective metal. A study using lactose of different surface type and distinct different levels of work function revealed that it charged differently as the contacting surface changed. The triboelectric charge was -13.23 , -18.76 and $+76.90 \times 10^{-9}$ C/g when the contacting surfaces were brass, steel and cellulose, respectively (Carter et al., 1992). The authors explained that metals generally donate electrons due to a high work function, whereas insulators accept electrons because of lower work function. So, in this particular study, the difference in triboelectric charge generation is entirely due to a difference in work function (Carter et al., 1992). Bennett (1998) investigated the electrostatic properties of salbutamol sulphate which acquired negative and positive charges following agitation in stainless steel and polypropylene, respectively. The polarity of charge was found to depend on the magnitude of the work function of the contacting surface (Bennett 1998). Furthermore, the triboelectrical properties of α -lactose monohydrate powder particles were investigated by Eilbeck et al. (1999) using a cyclone separator at < 10 % RH. It was found that α -lactose monohydrate gained a higher magnitude of negative charge following contact with stainless steel than with acetal, and a higher positive charge following contact with polyvinylchloride (PVC) than with polypropylene, thus again demonstrating that charge generation and transfer have a linear relationship with the level of work function. Li et al., (1999) also concluded that the charge transferred for a synthetic mineral against a copper surface had a linear relationship with work function. Similar conclusions have been drawn by Akande and Adedoyin (2001), Elajnaf et al. (2006), Engers et al. (2006), Greason (2000) and Zhu et al. (2007).

More recently, Šupuk et al. (2012) studied the triboelectric charging of numerous pharmaceutical materials, including lactose and

hydroxypropylcellulose (HPC), using glass, PTFE and stainless steel surfaces. This study again demonstrated that the work function plays an important role in determining the magnitude and polarity of triboelectric charging of powder particles and the powders, themselves and a 50:50 binary mixture was found to charge positively against PTFE, but negatively against glass and stainless steel. These findings suggest the need for careful selection of storage containers or processing surfaces keeping in view their work function or place in the triboelectric series.

Contact surface roughness

Coste and Pechery (1981) investigated the effect of contact surface roughness of polyethylene terephthalate (PET) on the electrostatic charge density acquired through contact with metal. This study demonstrated that the charge density increased as the PET powder particles collided with the smooth metal surface. Additionally, the experiments conducted by Eilbeck et al., (1999) investigated the effects of contact surface roughness on triboelectrification using α -lactose monohydrate charged against a rough and smooth stainless steel cyclone separator at < 10% RH. The results showed that the α -lactose monohydrate acquired a highly negative charge against the smoother stainless steel surface.

Contact surface contamination

Contact surface contamination and the procedure for cleaning surfaces can affect the triboelectrification process and hence the charge acquired by contacting powders. Early work by Harper (1953) showed the electrification of powders was affected by the cleaning procedure and any contamination on the surfaces. Eilbeck et al., (2000) investigated the effect of contamination of pharmaceutical equipment on powder triboelectrification following contact with a stainless steel cyclone separator. Charging of α -lactose monohydrate was studied without cleaning between experimental runs and there was a decrease in the net negative charge acquired by the lactose with replicated experiments, due to an increase in the extent of powder adhesion to the

cyclone surface. Murtomaa et al., (2002a) studied the triboelectrification of glucose powder in a glass pipe, and the impact of adding smaller particles of lactose, magnesium stearate, dicalcium phosphate or starch 1500 of different size fractions to the glucose. Mixtures of different ratios were charged by sliding them down a glass pipe into a Faraday well and differences were obtained in the polarity and magnitude of transferred charge after mixing. For example, when the glucose was mixed with lactose, the particle charge changed from positive to negative due to contact between glucose particles and adhered lactose particles. Also Murtomaa et al., (2000) investigated the triboelectrification of microcrystalline cellulose and PS spheres in contact with stainless steel pipes washed with several different detergents. The results clearly indicated that some detergents left a residue on the pipe surface that had a significant effect on the polarity and the magnitude of the transferred charge.

Particle Size

The effect of particle size on the charging behaviour of powders has been studied extensively for many years. In general, particle size affects many industrial processes; a small size improves drug bioavailability, but may lead to flow problems and segregation. In the literature, there are contradictory findings on the effect of particle size on triboelectrification.

Gallo and Lama (1976) proposed that the work function decreases with an increase in particle size, suggesting that, under some experimental conditions, the difference in work function between small and large particles of the same material will result in charge generation and transfer. The tendency for such charge exchange is greatest when one of the particles is very small and the other is comparatively large (Gallo and Lama, 1976). It was also suggested that electrons should transfer from larger particles, due to their lower work function, to smaller particles when they contact each other and therefore, the smaller particles should charge negatively and the large particles positively. The studies conducted by Duff and Lacks, (2008); Engers et al. (2006); Lacks et al. (2008); Lacks and Levandovsky (2007); Rowley (2001) and Lacks and Sankaran (2011) proposed mechanisms for particle

Table 2. Summary of studies investigating factors affecting triboelectric charging.

Factors	Effects	References
Nature and work function of contacting surface	Work function is considered the principal driving force for the generation of triboelectric charge.	Akande and Adedoyin, 2001 ; Bennett, 1998 ; Carter <i>et al.</i> , 1992 ; Davies, 1969 ; Eilbeck <i>et al.</i> , 1999 ; Elajnaf <i>et al.</i> , 2006 ; Elsdon and Mitchell, 1976 ; Engers <i>et al.</i> , 2006 ; Greason, 2000 ; Li <i>et al.</i> , 1999 ; Lowell, 1976 ; Šupuk <i>et al.</i> , 2012 ; Zhu <i>et al.</i> , 2008
Contact surface roughness	The smooth contact surface leads to higher magnitude of triboelectric charge.	(Coste and Pechery, 1981, Eilbeck <i>et al.</i> , 1999)
Contact surface contamination	Contamination of contacting surface impacts the polarity and magnitude of triboelectric charge.	Eilbeck <i>et al.</i> , 2000 ; Harper, 1953 ; Murtomaa <i>et al.</i> , 2002a ; Murtomaa <i>et al.</i> , 2002c
Particle size	A decrease in particle size enhances the magnitude of triboelectric charge. However, some studies report an increase in particle size enhances the magnitude of triboelectric charge.	Bailey, 1984 ; Carter <i>et al.</i> , 1992 ; Duff and Lacks, 2008 ; Eilbeck <i>et al.</i> , 1999a ; Engers <i>et al.</i> , 2006 ; Gallo and Lama, 1976 ; Karner and Urbanetz, 2012 ; Karner and Urbanetz, 2013 ; Kwek <i>et al.</i> , 2013 ; Lacks <i>et al.</i> , 2008 ; Lacks and Levandovsky, 2007 ; Lacks and Sankaran, 2011 ; Rowley, 2001b ; Smeltzer <i>et al.</i> , 1982 ; Staniforth and Rees, 1982 ; Zhao <i>et al.</i> , 2003) (Carter <i>et al.</i> , 1998 ; Fasso <i>et al.</i> , 1982 ; Nieh and Nguyen, 1988)
Particle shape and roughness	A rougher particle surface leads to higher magnitude of triboelectric charge.	Afzal <i>et al.</i> , 2018 ; Kwek <i>et al.</i> , 2013 ; Matsusaka <i>et al.</i> , 2000 ; Murtomaa <i>et al.</i> , 2004 ; Trigwell <i>et al.</i> , 2008)
Material chemistry	The chemical structure, functional groups and surface chemistry can significantly affect triboelectrification.	(Kamiyama <i>et al.</i> , 1994 ; Mazumder <i>et al.</i> , 2006a ; Sharma <i>et al.</i> , 2007 ; Sharma <i>et al.</i> , 2003 ; Shinohara <i>et al.</i> , 1976 ; Trigwell <i>et al.</i> , 2003)
Crystallinity and amorphicity	Higher crystallinity leads to higher propensity of triboelectric charging	Carter <i>et al.</i> , 1998 ; Cassidy <i>et al.</i> , 2000 ; Kwok and Chan, 2009 ; Murtomaa <i>et al.</i> , 2002a ; Shekunov <i>et al.</i> , 2002 ; Wong <i>et al.</i> , 2014b)
Mixing ratio	Increasing fraction of excipients in powder mixtures with APIs tends to decrease the final triboelectric charging.	(Asare-Addo <i>et al.</i> , 2013b ; Engers <i>et al.</i> , 2006 ; Ghori <i>et al.</i> 2014c ; Murtomaa and Laine, 2000 ; Pingali <i>et al.</i> , 2009 ; Rowley, 2001 ; Sarkar <i>et al.</i> , 2012 ; Zhu <i>et al.</i> , 2007)
Frequency of contacts	Increasing frequency of powder particle contacts increases the magnitude triboelectric charge	Cunningham and Goodings, 1986 ; Engers <i>et al.</i> , 2006 ; Harper, 1953 ; Lowell, 1976 ; Lowell and Akande, 1988 ; Matsusaka <i>et al.</i> , 2000 ; Watanabe <i>et al.</i> , 2007 ; Zhu <i>et al.</i> , 2007)
Atmospheric conditions	As the RH decreases, the charge on a powder sample increases. However, some studies report increased propensity of charging with increased RH	Eilbeck <i>et al.</i> , 2000 ; Greason, 2000 ; Nguyen and Nieh, 1989 ; Nieh and Nguyen, 1988 ; Nomura <i>et al.</i> , 2003 ; Rowley and Mackin, 2003 ; Smeltzer <i>et al.</i> , 1982 ; Turner and Balasubramanian, 1976) Wiles <i>et al.</i> , 2004 ; Boschung and Glor, 1980

size dependent charging. In most cases, smaller particles charged negatively whereas larger particles charged positively and these findings are in complete accordance with the theory of Gallo and Lama (1976). However, this theory is contradicted by Ali et al. (1998) who reported that for a specific polymer powder tested, small particles charged positively and the larger ones charged negatively. It could be argued that if the charging is the result of ion transfer rather than electron transfer, the Gallo and Lama Theory may still be valid (Bailey, 1984).

Many studies have shown an inverse relationship between particle size and charge, i.e., as particle size is decreased, the charge on a powder particle increased (Carter et al., 1992; Eilbeck et al., 1999; Engers et al., 2006; Ghori et al 2014a; 2014b; 2014c Ghori et al, 2015; Smeltzer et al., 1982; Staniforth and Rees, 1982; Rowley, 2001; Zhao et al., 2003). The study conducted by Staniforth and Rees (1982) found that recrystallised lactose acquired negative charges, which increased with decreasing sieve fraction from 710-1000 μm to 500-710 μm . Smeltzer et al. (1982) investigated the effect of particle size on the charging of glass beads during pneumatic transport along a pipe, with an increase in charge transfer, as the particle size decreased from 150 to 75 μm . This was thought to be due to a higher number density, giving an increased number of collisions for smaller particles. Carter et al. (1992) investigated the triboelectrification properties of α -lactose monohydrate against a stainless steel and brass cyclone separator. The specific charge values were inversely related to particle size. Eilbeck et al. (1999) investigated the triboelectrification of lactose after contact with a stainless steel and PVC cyclone separator at < 10% RH. The mean specific charge for the α -lactose monohydrate sieve fraction samples increased with decreasing particle size, over the range 90-1000 μm . Rowley (2001) proposed that as the lactose sieve fraction size decreased from 355-500 μm to 90-125 μm , there was an increase in the specific charge following contact with a stainless steel surface and likewise for fractions 355-500 μm to 125-150 μm in contact with a PVC surface.

Zhao et al. (2003) investigated the effect of particle size on charge-to-mass ratio of polymer powders using fluidized beds. It was observed that smaller particles charged negatively and possessed a high

charge-to-mass ratio, whilst the larger particles charged positively and possessed lower charge-to-mass ratios. Engers et al. (2006) investigated the effect of particle size of dicalcium phosphate dihydrate on the specific charging of powder samples. The study revealed that the specific charge was significantly higher for the sample containing a higher proportion of fines than that observed for particles in the size range of 425 – 800 μm . Ghori et al. (2014a) reported that when the particle size of MC/HPMC blends decreased from 150-250 μm to 90-150 μm the charge was increased. The studies carried out by Karner and Urbanetz (2012, 2013) and Kwek et al. (2013) reach the same conclusions, the fine powder particles acquired a higher magnitude of the charge.

Conversely, other studies have shown a direct relationship between increasing particle size, and the specific charge (Carter et al., 1998a; Fasso et al., 1982; Nieh and Nguyen, 1988). In a study by Fasso et al. (1982), the electrostatic charge and charge distribution of glass beads was measured in a freeboard and the main charge for glass beads (30 to 55 μm) at various flow velocities was found to be enhanced with the increase in particle size. Nieh and Nguyen (1988) studied the electrostatic charging of flowing glass beads (137 to 550 μm). The results showed that large particles acquired a higher charge, but lower specific charge and the mean surface charge density of the particle remained almost constant over a wide particle size range. Carter et al. (1998a) investigated the triboelectrification for both fractionated crystalline and spray-dried lactose samples. The results showed that the magnitude of charge on the lactose samples increased with increasing particle size, over the range 45-125 μm and 63-180 μm for crystalline and spray dried lactose, respectively. This was due to particle adhesion to the contact surface which caused increased particle-particle interactions and reduced particle-contact surface collisions.

Particle shape and roughness

The transfer of charge takes place between surfaces in contact and the shape and surface morphology of powder particles play an important role in the exchange of triboelectric charges. Transferred charge is proportional to the maximum contact area

in an impact process; consequently, the particle shape is extremely important (Matsusaka et al., 2000; Trigwell et al., 2008). The rougher the surface of the particle, the smaller the area of contact and surface-charge density, which is transferred between the materials in contact. In reality, most pharmaceutical materials have rough surfaces, containing many asperities. When such surfaces are in contact, there will be a small distance between the materials in contact, known as the effective distance. The flatter the contact surfaces of the powders, the smaller the effective distance will be (Trigwell et al., 2008). Murtomaa et al. (2004) investigated triboelectric charging of lactose with different particle morphology, finding that the overall reproducibility was improved with homogeneous particle morphology. However, the study could not clearly explain the effect of shape and morphology of lactose on the triboelectric charging. Recently, Kwek et al. (2013) studied the triboelectrification properties of mannitol, comparing smooth and rough surfaces using shaking and aerosolisation techniques. This study revealed that the mannitol powder particles with a rougher surface had a higher magnitude of surface charge than those with a smoother surface. Moreover, the porous powder materials for example mesoporous silica have attained a widespread popularity in developing pharmaceutical formulations. Recently, Afzal et al., 2018 described that the mesoporous silica (SBA-15) powder particles have very low triboelectric charge and it has been demonstrated in the study that with the inclusion of SBA-15 in a binary system the net triboelectric charge of the flurbiprofen has been decreased.

Material chemistry

The chemical structure, functional groups and surface chemistry (Kamiyama et al., 1994; Mazumder et al., 2006; Shinohara et al., 1976) can significantly affect the tribo-electrification and subsequent particle SA processes. Kamiyama et al. (1994) investigated the tribo-electrical properties of polymeric materials by introducing different ions on their surface, demonstrating that the change in surface chemistry can significantly impact the materials' triboelectrification properties. Furthermore, Sharma et al. (2003 and 2004) and

Trigwell (2003) determined that the magnitude and polarity of charge exchange between two dissimilar materials are directly related to the chemical nature of the polymer powders. Recently, Ghori et al. (2014a; 2014b; 2014c) reported that the substitution groups of methylcellulose/hydroxypropyl methylcellulose (MC/HPMC) have a significant impact on the triboelectrification properties.

Crystallinity and amorphicity

Theoretically, amorphous and crystalline materials have different crystal packing which would lead to varied surface energies that may influence charge transfer behaviours. Cassidy et al. (2000) investigated the triboelectrification of spray-dried lactose prepared from different feedstock concentrations (10 - 50% w/v), following contact with a stainless steel surface, using either a mixing vessel or cyclone separator. Increasing the feedstock concentrations from 10 to 50% decreased the mean specific charge on lactose from -20.8 to -1.3 nC/g and 54.9 to -4.1 nC/g for the mixing vessel and cyclone separator, respectively. This was attributed to differences in the crystal form of the spray-dried lactose powder samples. Carter et al. (1998a) investigated triboelectric charging of spray-dried amorphous and fractionated crystalline lactose. Both the materials had significantly different charging tendencies, with crystalline lactose gaining a higher triboelectric charge than spray-dried amorphous lactose. Shekunov et al. (2002) compared micronized and supercritical fluid-conditioned salmeterol xinafoate, Murtomaa (2002b) studied the triboelectrification properties of lactose and Kwok and Chen (2008) studied amorphous spray-dried salbutamol sulphate (spherical shape) and crystalline jet-milled salbutamol sulphate (plate-like). In all studies, the triboelectric charge decreased as the crystalline component of respective powder samples increased. All of these studies have fail to provide a mechanistic understanding of charging. However, a study carried out by Wong et al. (2014) has, for the first time, attempted to resolve this ambiguity. Electrostatic charging was characterised in two ways, firstly, through aerosolisation from an inhaler and secondly, by tumbling in containers composed of different materials. Following aerosolisation, crystalline

salbutamol sulphate showed more consistent charging and mass deposition (process in which materials are deposited as a layer) than the amorphous formulation. Alternatively, the tumbling experiments found the net charge of crystalline salbutamol sulphate correlated linearly with work function. This correlation was not obvious for amorphous salbutamol sulphate. It is possible that the long-range crystal packing in crystalline salbutamol sulphate leads to more predictable charging behaviour.

Mixing ratios

The quantification of triboelectric charge of different powder blends is a difficult task as due to different mixing ratios; the component powder particles of a powder blend have complex charging kinetics. Additionally, the tendency of one material to coat either the equipment surface or other particles leads to unpredictable behaviour, if the surface area of the container is bigger than the powder mass, particle-particle contacts may be negligible (Zhu et al., 2007). Pingali et al. (2009) concluded that the composition of powder blends can significantly impact triboelectric charging properties.

Rowley (2001) investigated the effect of different salbutamol sulphate concentrations (0.5, 1.0 and 5.0% w/w) in a binary mixture with α -lactose monohydrate carriers charging against steel and polyamide contacting surfaces. The magnitude of triboelectric charge decreased as salbutamol sulphate concentration increased from 0.5 to 5% w/w, and the values were -38 to -91 nC/g for steel and -10 to -42 nC/g for polyamide.

Lactose and glucose are widely used excipients in the pharmaceutical industry. It was reported that pure glucose became positively charged on sliding through the glass pipe, but as soon as lactose was introduced, the accumulated net charge on the powder mixture became negative. The mixture charged negatively if the amount of lactose was between 20 and 40 % w/w, but became positively charged again when the amount of lactose was increased further (Murtomaa and Laine, 2000). Engers et al. (2006) reported that specific triboelectric charging of powder mixtures can be controlled by using compatible excipients. Sarkar et

al. (2012) observed a reduction in triboelectric charge on the incorporation of additives (L-ascorbic acid, magnesium stearate, and stearic acid). Moreover, Sarkar et al. (2012) also proposed that the extent of charge reduction appeared to relate to moisture content and levels of effective work function. Šupuk et al. (2010) concluded that binary mixtures of α -lactose monohydrate and hydroxypropyl cellulose charged to significantly higher magnitudes with increasing concentrations of α -lactose monohydrate in a binary mix. Asare-Addo et al. (2013), Ghori et al. (2014a) and Ghori et al., 2015 confirm that HPMC has antistatic properties as with higher polymer concentration it has the ability to dissipate the charge of drug particles.

Mixing speed/frequency of contact

Cunningham and Goodings (1986); Harper (1953) and Lowell (1976) have shown that an increase in the number of contacts may increase the propensity of triboelectric charging on the surface of powder particles. Cunningham and Goodings (1986) demonstrated that repeated contact increased the quantity of net charge transferred between a gold probe and a polymer. Moreover, Lowell and Arkande (1988) also found that repeated contact increased the extent of triboelectric charging. Watanabe et al. (2006, 2007) found that the amount of triboelectric charge generated during single particle impacts under different impact velocities and angles relates to the normal component of the impact velocity. Furthermore, an equilibrium initial charge was quantified, where no charge transfer took place on impact due to the surface potential of the contacting bodies. Similar results were reported by Matsusaka et al. (2000) using 30 mm rubber balls. Zhu et al. (2007) investigated the contact energy as a function of the rotation speed of a mixer, finding that it was not influenced by the rotation speed. This is because the rotation speed of the mixer only influences the frequency of particle contact. Thus, the time required to attain saturation increases with a decrease in rotation speed, but the total amount of saturated charge is defined by the surface potential difference of the contacting bodies and, therefore, cannot be influenced by the rotation speed. These

results are in agreement with the blender studies performed by Engers et al. (2006).

Atmospheric conditions

Most authors have shown an inverse relationship between RH (relative humidity) and charge. (e.g. Eilbeck et al., 2000; Greason, 2000; Smeltzer et al., 1982; Nguyen and Nieh (1989); Nieh and Nguyen, 1988; Nomura et al., 2003; Mackin et al., 1993, 1994; Rowley and Mackin, 2003; Turner and Balasubramanian, 1976). Conversely, Boschung and Glor (1980) measured the charge of more than two hundred different types of materials including glass, different types of resins and polymers and concluded that charge increased linearly with RH. Also, the investigations of Wiles et al. (2004) on polystyrene drew the same conclusion. In a study carried out by Turner and Balasubramanian (1976), a lower electrostatic charge on glass spheres was found at higher levels of relative humidity. Similarly, Smeltzer et al. (1982) investigated the effect of RH (25 to 65%) on the charging of glass beads (75-150 μm) during pneumatic transport along a pipe and showed a greater charge was generated at the lower RH. Nieh and Nguyen (1988) found that the mean particle charge on 550 μm glass beads flowing in a copper pipe fell with an increase in RH from 4 to 76 %. This may be due to the moisture around the dielectric particles, increasing their surface conductivity, and thereby enhancing the transfer of electrons upon contact with an earthed pipe wall. Nguyen and Nieh (1989) investigated the effect of carrier gas RH on the electrostatic charges of glass beads flowing in a continuous copper pipe loop. As RH increased from 0 to 65%, electrostatic charges decreased; this was attributed to sorbed moisture on the glass particle surface, providing an earthing path to the metal walls during particle/metal collisions and it was proposed that hydrated ions and water vapour would act as charge carriers to redistribute the surface charge into free space. Eilbeck et al. (2000) investigated the effect of moisture contamination of the contact surface on the charge of α -lactose monohydrate (180-212 μm) following triboelectrification within a stainless steel cyclone separator at 2 and 100% RH. There was a decrease in the net negative charge on the lactose at the higher RH. There was a decrease in net charge as

the RH % and the temperature increased after rolling a stainless steel sphere (1.27 cm diameter) in tubes constructed from glass, quartz, PTFE, acrylic, polycarbonate, and nylon at range of 10-30°C and RH range from 10 to 70% (Greason, 2000). The decrease in the triboelectric charge can be attributed to a decrease in the volume and surface resistivities of the insulators caused by an increase in temperature and RH. Nomura et al. (2003) studied the effect of environment humidity on the triboelectrification of a ferrite powder coated with silicone resin following rotating samples in cylindrical nickel vessels and showed a decrease in the specific charge on the powder with increasing humidity. With a variety of contact surfaces, Rowley and Mackin (2003) showed that for the relatively non-hygroscopic excipients α -lactose monohydrate and dextrose monohydrate, there was a negligible change in charge values over the RH range 0-80 %, however a hygroscopic excipient, sodium starch glycolate, exhibited a decrease in electrostatic charge from RH 0 to 80 %. There was no relationship between moisture sorption and charge for an intermediately hygroscopic material, spray-dried sorbitol. Care must be taken when considering total sorption data for predicting electrostatic charge behaviour, where significant proportions of total moisture are present as absorbed moisture, as may be the case with porous spray-dried sorbitol. When nylon, Teflon® and polyacetal pellets were fired at a metal target at temperatures ranging between ambient temperature conditions and 230 °C, Bailey and Smedley (1991) found there was little effect of temperature on triboelectrification between metal and insulator contacts.

CONCLUSIONS

Triboelectric charging has been reviewed from both mechanistic and theoretical points of view. It can be concluded that the triboelectric charging of powder particles is a sensitive property where multiple factors can impact the overall magnitude and propensity. A slight change can potentially lead to substantial variation in triboelectric charging of powder particles and thus impact the handling and processing. Therefore, reliable triboelectric charge measurement techniques are essential. Moreover, it can be concluded that there are many areas within the fundamentals of triboelectric charging which are

still elusive and require some research attention. However, the positive applications of triboelectric charging are also reviewed and it can be successfully employed in electrostatic separation, dry powder coating, electrophotography and development of electrostatic charge assisted drug delivery systems.

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