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NOVEL INDUSTRIAL-SCALE ELECTROSTATIC CHARGE ELIMINATION METHOD FOR INHALATION PRODUCTS

In this article, Orest Lastow, PhD, Chief Technical Officer at Iconovo, describes a novel technique for removing the built-up charge from dry powder inhaler components, offering a potential solution to the issues caused by static charges in these devices, including decreased performance, altered powder properties and increased variability in delivered dose.

INTRODUCTION

According to US FDA guidance,[1] "*interparticulate interactions between the drug substance and excipients and with the container closure/device constituent part at a microscopic level (e.g. cohesive and adhesive properties, surface activity, specific surface area, static charge properties of the formulation) can also be important. These properties and interactions can affect, for example, blend uniformity, powder flow and delivered dose.*" This is one of many indications as to how important a role electrostatics play in the field of dry DPIs.

The manufacturing of a DPI includes processes that generate surface charges on the plastic parts of the device and on the dry powder formulation. Injection moulding exposes the material to very high temperatures and shear forces. This leads to parts experiencing a high level of triboelectric charging.[2] Freshly injection moulded parts can become charged to such an extent that they can jump up from a collection bin simply due to electrostatic repelling forces. Plastic parts have very low conductivity, which makes them retain the charges for a very long time.

Any handling of a dry powder will generate surface charges due to high triboelectric charging. The high surface area of a powder makes it very susceptible to this charging. Formulations for inhalation can have some degree of conductivity, leading to a low rate of dissipation of the charge. Lactose, which is a primary constituent of many inhaled formulations, can slowly dissipate charges.

When observing the electrostatic properties of a DPI, a great variability can be seen. A study by Byron *et al* measured the charge of the powder aerosol exiting a Bricanyl© (terbutaline, AstraZeneca) Turbuhaler.[3] The charge on the aerosol was measured from five different inhalers and showed a variability from 51 pC to -44 pC. Most surprising was that the charge showed two polarities. When measuring the aerosol charge of Pulmicort (budesonide, AstraZeneca), the variability was lower but still considerable – 55 pC to 89 pC.

Another study, by Kwok *et al*, investigated the charge level of different particle sizes.[4] Bricanyl and Pulmicort Turbuhalers were compared and tested at different relative humidities (RHs). Both groups showed a bipolar charge distribution with respirable particles having positive polarity and larger particles being negative. The charge on Pulmicort was more or less independent of RH but Bricanyl showed a strong RH dependence. A low RH generated a much higher charge for all particle sizes, whereas a high RH showed a lower charge level.

A study by Hoe *et al* investigated the impact of inhalation flow rate on the electrostatic properties.[5] Again, Bricanyl and

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Pulmicort Turbuhalers were investigated. When the flow rate was varied from 30 L/min to 90 L/min, the net charge of Pulmicort increased by about a factor of four. For the same flow rate range, Bricanyl varied by a factor of eight to ten. A futher study by Telko *et al* also showed that the actuation of the DPI generates significant triboelectric charging of the powder.[6] Lastly, a study by Melandri *et al* demonstrated that electrostatic charge greatly enhances the deposition of the inhaled powder in the patient's airways.[7]

These studies indicate that electrostatic properties depend on different inhalers, on the RH at which the dose is taken and on the inhalation flow rate. They also show that the formulation and API play a key role. In many studies, Bricanyl showed higher variability than Pulmicort. Together with the variability of the device charge, this can have a strong negative impact on the dose uniformity of the DPI and on the dose delivered to the lung.

The electrostatic effects on the performance of a DPI are many and are predominantly caused by either adhesion of the powder to the plastic surfaces of the device or altered formulation properties in terms of cohesivity, density and flowability. The adhesion of powder to the charged plastic components increases the retention of powder during the de-aggregation process and during transport of the aerosolised powder through the inhaler. This retention affects the dose delivery uniformity and particle size distribution of the delivered dose. A charged powder, together with charged plastic components, can also severely impair accurate and reproducible dose metering in a reservoir dry powder inhaler (Figure 1).

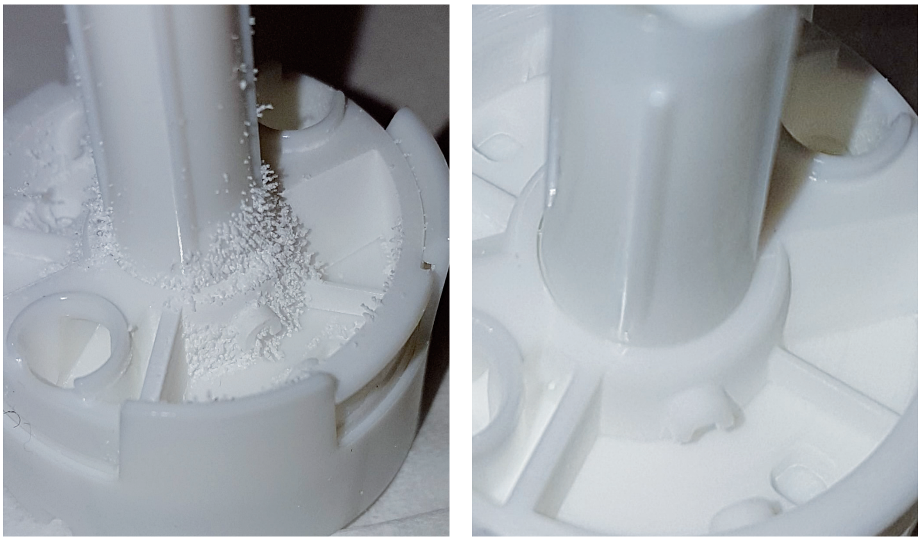

Figure 1: Dose metering feature in ICOres© before charge removal (left) and after charge removal (right).

Electrostatic effects are also present during the manufacturing process, presenting many challenges and quality issues. Electrostatic problems can come and go and are dependent on climate and season. Electrostatic effects cannot be avoided but can be controlled and their effect minimised by effective charge removal. When dealing with electrostatic issues, a good approach is to ascertain that it is actually an electrostatic problem and then prove that the remedy works in a robust and consistent way.

CHARGE REMOVAL BY PRESSURE REDUCTION

This section describes a novel charge removal process suitable for high-throughput industrial applications. The removal is permanent, and charges are removed from all surfaces that are exposed to air. The process works equally well for assembled devices and blisters. The scientific basis of the charge removal is a Townsend-like discharge around a charged dielectric surface.[2,8–13]. The discharge is induced by reduction of air pressure.

"The method to remove surface charges by facilitating ionisation of the surrounding air by reducing the pressure was first described by the author in 2000."

The method to remove surface charges by facilitating ionisation of the surrounding air by reducing the pressure was first described by the author in 2000.[13] Free electrons are always present in air, moving in the presence of an electric field and by diffusion. When electrons are accelerated in an electric field, they gain energy. Eventually, the electrons collide with molecules in the air and, if they have sufficient energy, one or more electrons are ejected from the molecule. The ejected electrons can then be accelerated and eject new electrons, forming an electron avalanche. A large number of avalanches combined result in an electrical breakdown of air. When the air breaks down, a large number of ions move towards the oppositely charged surface and neutralise the surface's charge.[13]

This process takes place spontaneously and continuously until an equilibrium is reached. Equilibrium is reached when the acceleration of the electrons provides insufficient energy to ionise the molecules. The process is very quick, and it can thus be assumed that an equilibrium has been reached in the surrounding air.

The parameter governing the ionisation is dependent on the mean free path of air and the present electric field. In air, the mean free path is directly proportional to the pressure, with the parameter able to be expressed as the electric field strength (E) to pressure (p) ratio, E/p. For a set gas and a set electric field, p and E will determine whether the breakdown criteria is fulfilled or not. Breakdown takes place when E/p exceeds a critical value, $[E/p]_{critical}$. When $E/p \leq [E/p]_{critical}$, the system is in equilibrium.

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When p is reduced, the mean free path increases, giving the electrons a longer distance over which to accelerate, meaning that the energy threshold for breakdown can be reached. The value of E/p increases with decreased p until $E/p > [E/p]_{critical}$ and a discharge takes place. The ejected electrons then travel in the electric field and eventually reach the charged surface and discharge the surface's charge. As long as $E/p > [E/p]_{critical}$, the discharge will continue and the charged surface will be discharged. E will decrease and, consequently, E/p will decrease. The process will continue until the equilibrium level is reached. To induce further discharging, the pressure must be reduced further. If the pressure is increased, nothing happens – the system stays in equilibrium.

The value of $[E/p]_{critical}$ cannot be generally given, as it depends on from which point in space $E(r)$ is defined. Since E increases closer to the surface, it can be argued that, when a breakdown has been initiated, its intensity should increase as the ions move towards the surface.

An experiment was performed to support this theory.[13] A charged dielectric object, a polytetrafluoroethylene (PTFE) disc, was placed on a conductive base (Figure 2 A–B). The charges in the conductor were disassociated, leaving excess charges of the same polarity as the charged dielectric object. The base was connected to an electrometer (Figure 2C) and the excess charges were earthed.

When an ion impacted on the surface, it neutralised some of the charges on the surface of the charged dielectric object (Figure 2D). The image charges in the conductor then become excess charges that could be measured. The measured charge was of the same polarity as the neutralising ions. Using this method, the time of ion impaction and the magnitude of neutralising ions could be measured. However, this method only measures the net charge neutralisation – it does not discriminate between an equal number of positive and negative charges and no charges at all.

A further experiment was performed to measure the ion impaction on a dielectric disc as a function of pressure in real time. A PTFE disc was rubbed against a polyvinylchloride (PVC) disc and a surface charge of approximately -1 $\mu C/m^2$ was obtained. The whole set-up was put into a vacuum chamber and the pressure signal was logged, together with the charge signal (Figure 3).

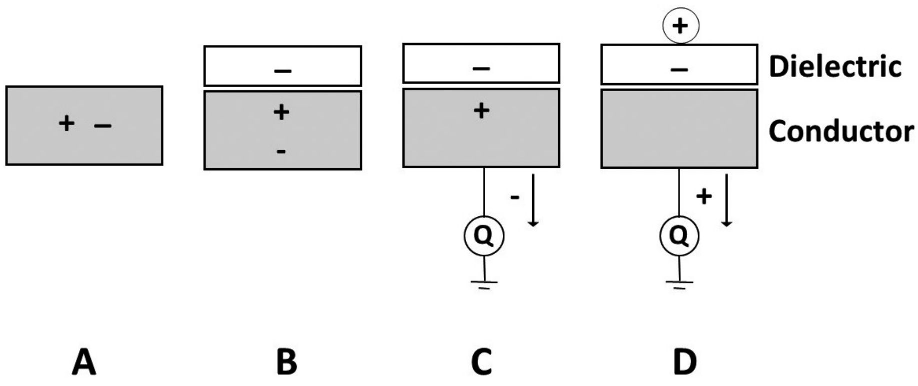

Figure 2: Experimental set-up.[13]

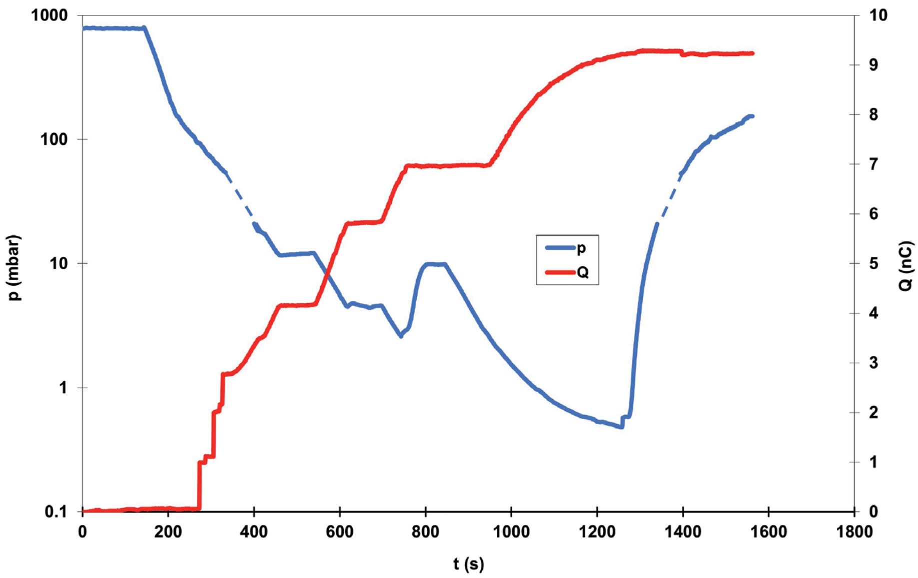

Figure 3. Diagram of charge versus pressure over time.[13]

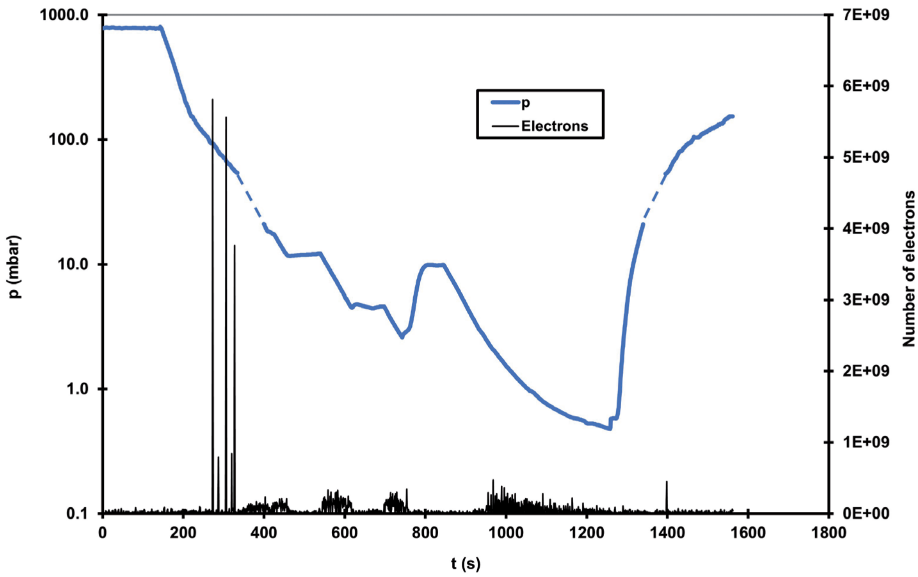

Figure 4. Diagram of the number of electrons versus pressure over time.[13]

Initially, as the pressure was reduced, no discharging could be observed. When a threshold level was reached, a clear discharging could be seen. When the pressure reduction stopped, the discharging stopped. At one point, the pressure was increased to verify that mere pressure change did not trigger any discharging; only when the pressure was reduced again – below the original pressure – did the discharging start again (Figure 4).

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A number of strong, clear discharges could be seen early in the pressure reduction sequence. After that, only minor discharging could be seen. These experiments support the concept of pressure-induced discharging and suggest the possibility of using this phenomenon in a large-scale industrial charge removal.

The method is to place injection moulded parts, or fully assembled devices, in a vessel and reduce the pressure. The process duration is dependent on the capacity of the vacuum pump and the volume of the vessel. The plastic parts or devices can be placed in an open bag or container inside the vessel. After the treatment, the bag or container is removed. All surfaces that are exposed to air during the pressure reduction will become permanently discharged.

The low-pressure charge-removal process is part of an approved US patent[14] and a PTC patent application by AstraZeneca.[15] In the application, it is shown that the use of low-pressure treatment can increase the delivered dose, reduce the amount of drug retained in the DPI and lower the variability of the dose (Figure 5). The degree of improvement is highly dependent on the device, formulation and API. Published data show that, in the case of a Bricanyl Turbuhaler, the dose increased by 15% and the variability decreased by 5%.

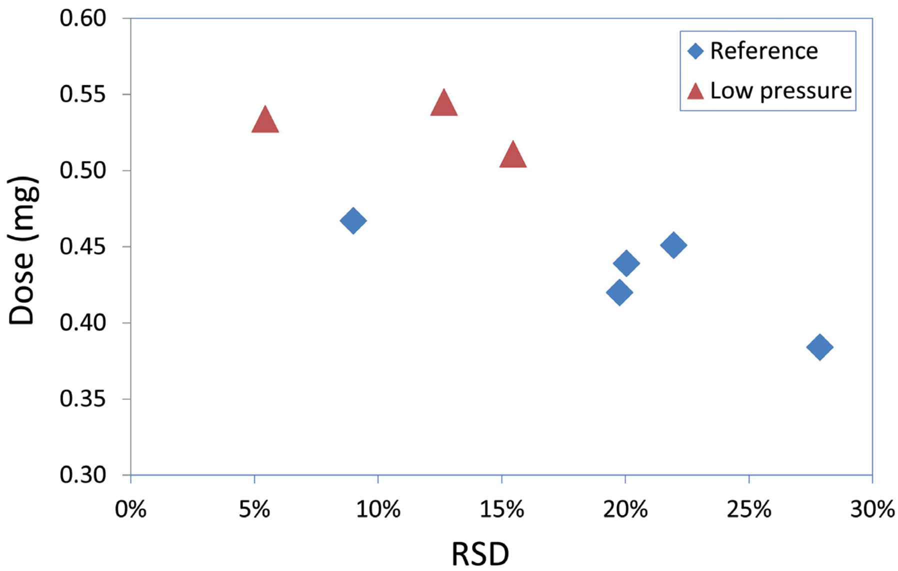

Figure 5: Performance improvement after low-pressure treatment.[14,15]

CONCLUSION

The electrostatic charging of a DPI during manufacturing and handling can have a strong influence on the performance and the dosing uniformity. An effective removal of the triboelectric charge improves the dose size and decreases drug retention in the device, as well as reducing the dose variability. Using the pressure reduction method is suitable for efficient large-scale industrial charge elimination.

ABOUT THE COMPANY

Iconovo develops novel inhaled pharmaceutical products in collaboration with international pharmaceutical companies. The company provides several types of patent-protected inhalers, with significant commercial opportunities in the development of novel pharmaceuticals and in patent expirations for established pharmaceuticals. Iconovo has in-house capabilities in the development of inhalation products – design tools for inhalers, and dry-powder formulation equipment for measuring and mixing, and characterisation testing using next-generation pharmaceutical impactor and high-perfomance liquid chromatography methods. Possessing a unique combination of engineering and pharma expertise, Iconovo can provide the optimal combination of customised inhalers and tailored formulations.

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ABOUT THE AUTHOR

Orest Lastow, PhD, has more than 30 years' experience in inhalation development, mainly at AstraZeneca. He has invented more than nine different inhaler devices and been involved in the development of 13 different inhaler devices. Dr Lastow is the inventor behind more than 40 patents and patent applications, and has published several research articles and books. He also co-authored the ISO standard for inhaler devices and is frequently an invited speaker at inhalation conferences. Dr Lastow founded Iconovo in 2014.

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