EVALUATION STUDIES OF A SENSING TECHNIQUE FOR
ELECTROSTATIC CHARGE POLARITY OF PHARMACEUTICAL
PARTICULATES

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Abstract: Electrostatic charge due to inter-particle and particle-wall contacts may generate significant hazards during the processing of particulates within the pharmaceutical industry. Although charge behaviour of particulates is erratic and not easy to predict, it would be desirable to characterise the tendency of tribocharging prior to manufacturing. The work reported in this paper concentrates on a new and novel techniques for the detection of the active ingredient and excipient in a bipolar material. Three different case studies are presented for demonstration of the applicability of the method in different practical situations. Work confirmed through an experimental rig set-up indicates that materials that accumulate opposite charge via contact and rubbing can be detected from their charge sign as well as their relative magnitude. The results reported clearly demonstrated that the developed method for charge characterisation is a useful tool to understand how the charges are distributed in a population of particles showing a number of advantages over conventional methods.

1. Introduction

Charging of particulates due to inter-particle contacts and particle to wall contact during industrial handling is a common phenomenon in industry and has great influence on material behaviour in many cases [1]. The impact of electrostatic charge generation can be felt in many industrial applications, however the pharmaceutical industry is particularly prone to electrostatic charging issues because of the small particle size, light weight particles, as well as the presence of
relatively small quantities of a fine material which is being processed over several handling steps [2-4]. The problems caused by electrostatic charge (both the magnitude and polarity) observed in the form of agglomeration, segregation, particle adhesion to the processing equipment etc., may result in cases of batch failure in product quality control and can influence formulation [4-7]. Therefore, characterisation of charging properties of particulate materials is helpful to provide essential information relating to the behaviour of particulate materials with different contact surfaces and handling procedure to improve the quality of the final product [8]. For example, it has been demonstrated that the homogeneity of drug content within dry powder inhaler formulations improves with decreasing the charge density of mannitol excipient [9].

However, the identification of the role of tribocharging by characterising the charging tendencies in particulate materials is still a major challenge that has been the subject of intensive research recently [6, 8, 10-16]. Several laboratory test methods for charge measurement have been developed to investigate tribocharging, but they all suffer from limitations in practice [4, 6, 17, 18]. In many cases when the particulate material acquired bipolar charge distribution, the intensity of problem caused by electrostatic charge during industrial handling is not identified correctly [4]. When particulate materials acquire a bipolar charge distribution the net charge information can lead to misleading results for example, agglomerated particles may be characterised with a very low level of overall charge although agglomeration may be due to strong bipolar charge [3, 17].

At present, the most popular assessment of tribocharging problems is generally gained from the Faraday pail method which provides only limited information in the form of net charge to mass ratio. The Faraday pail method is robust and highly accurate when materials are charged unipolar. But in the case when particulate materials acquire bipolar charge distribution, the charge measurement using traditional method for example the Faraday pail is not an accurate indicator to assess the intensity of the possible effect of electrostatic charging of the particulate materials [3]. Due to complex nature of charge transfer process between particles the European Pharmaceutical Aerosol Group has recognised the need of better method to understand charging phenomenon [19]. Bipolar charging is more likely to occur in industrial processes of particulates where the materials are prone to bipolar charging (such bipolar charging is likely to be observed in most products such as pharmaceutical mixtures consisting of two materials with opposite or same charging tendencies) [3, 10]. A conclusion based on net charge to mass ratio without understanding the inter-particle electrostatic forces is less helpful [4]. In contrast, accurate charge distribution information across the population of particles will provide a better understanding of the role of tribocharging in process assessment [17]. The presently poor understanding of change distribution across a population of
particles is attributable to the fact that the generation of electrostatic charge is a multifaceted process, i.e., it depends not only on the work function of materials but is also influenced by other factors such as surface impurities, contact area, particle size or humidity [18, 20]. Additionally, limited methods are currently available for systematic experimental investigations and instruments for bipolar charge characterisation.

This paper presents the applicability of a novel instrument recently developed at the Wolfson Centre [4, 17] to characterise charge properties of several particulate materials in the form of charge distribution. The major advantage of this method of charge sensing is its high sensitivity (charges on the particles equal or more than to $30 \times 10^{15}$ C are detectable) and quick measurement (less than 60 seconds) and it does not disturb the particle flow. Evaluation studies (by considering pharmaceutical industries) were carried out not only to demonstrate the ability of the method in different practical situations but also to highlight the importance of bipolar charging during the tribocharging process. The first case study was about tribocharging property detection of several excipients commonly used in pharmaceutical industry including lactose, mannitol, glucosamine hydrochloride and sorbitol.

The second case study explained the charging behaviour of two model API materials, i.e., salbutamol sulphate and budesonide. The last case study investigated the charging characteristics of several drug-carrier binary formulation blends, i.e., lactose-salbutamol sulphate, lactose-budesonide, mannitol-salbutamol sulphate and mannitol-budesonide. The results showed that the existence of bipolar charging in formulation mixtures following blending may not be only obtained by mixing oppositely charged materials but also by mixing two materials carrying the same charging polarity. It is believed that the existence of bipolar charge even when mixing two different materials carrying the same charge polarity attributes to the complex nature of charge transferring process between particles of same and different species and particle to wall contacts.

2. Materials and method

2.1 Materials

Polystyrene beads of average size 1.7 mm were used as charged particles. Other materials included Lactose (DMV International, the Netherlands), mannitol (Fisher Scientific, UK), glucosamine hydrochloride (Sigma-Aldrich, USA) and sorbitol (Roquett, France). Micronized salbutamol sulphate and budesonide were purchased from LB Bohle, Germany and IVAX...
Pharmaceuticals, Ireland respectively. All API (active pharmaceutical ingredient) and excipient samples were stored in a polypropylene container.

2.1.1 Preparation of DPI formulation blends: Commercial lactose and commercial mannitol were separately blended with either salbutamol sulphate or budesonide drug in a ratio of 67.5:1, w/w (in accordance with the ratio used in commercial Ventolin Rotacaps®, GSK). Each blending process was carried out at standard mixing conditions in a cylindrical aluminium container (6.5 cm × 8 cm) using a Turbula® mixer (Willy A. Bachofen AG, Basel, Switzerland) at a standard mixing condition, i.e., 100 rpm mixing speed and 15 minutes mixing time.

2.2 Methods

The novel instrument recently developed at the Wolfson Centre [4] to characterise the charge distribution in a population of particulate material was used to investigate the charging properties of different samples/formulations under investigation. All experimental work was carried out inside walk in environmental chamber where the relative humidity and temperature can be controlled.

The developed method is based on the electrostatic inductive sensor, which has been studied and investigated in detail [4]. Electrostatic induction sensing has been successfully used for many different purposes, for example, velocity measurement, flow measurement and charge measurement [21-23]. In particle charge determination, particles are dispersed and fed into the probe so the charged particles can be determined separately. Due to the non-homogenous sensitivity distribution of the sensor, particles moving under peripheral flow induce 7% higher charge on the sensor compared to the particles moving under central flow condition [4]. As a result, the developed method is only able to measure relative charge on moving particles. It was assumed that all particles moved through the centre of the sensor to minimise the influence of variation in sensitivity due to particle position inside the sensor.

The speed of vibratory feeder is adjustable, for example, very cohesive and micronized materials need a higher vibration speed because of their inter-particle forces, mechanical interlocking or agglomeration. The charge amplifier is configured as a pure integrator so ideal waveforms can be achieved which is the key to detecting the charge distribution across a population of particles.

As the charged particles pass through the sensor they induce a current that is amplified by a charge amplifier. The direction of the induced current peaks in the signal infer the polarity of
charged particles moving whereas the amplitude of the peaks indicates the level of charge carried by the particles. The signal processing methodologies were adapted to obtain the information relating to charge distribution and charge to mass ratio when a mass of particles moves through the sensor. The overview of the test facility is shown in Figure 1.

Figure 1: Schematic overview of experimental test facility

Figure 2 represents the charge signal when solid charged particles (polystyrene beads) pass moving through the sensor; the positive and negative peaks in the signal correlate to the charge polarity of the moving particulate through the sensor.

The beads were charged in a plastic vial (9 cm in length and 2.5 cm in diameter) by using a “vortex-mixer” (PV-1 personal vortex mixer, Cambridge). The charge ($Q$) can be calculated by taking the voltage magnitude from the baseline obtained as a result of charged particles moving through the sensor using the following equation:
where $\Delta V$ is the difference between the minimum (baseline) and maximum voltage (the peak value either positive or negative), $C_{\text{INT}}$ is the integrating capacitor and $G$ is the gain of the amplifier.

The charged signal acquired as shown in figure 2 for polystyrene beads, the integrating capacitor value used was $C_{\text{INT}} = 10$ pF and gain ($G$) of two was used.

The relative level of charge of the particles can be determined by the voltage amplitude of the charge signal from the baseline. In the case of a population of charged particles, the sensor can show the voltage peaks in the signal which indirectly but linearly represents the charges on the particles moving through the sensor. The direction and magnitude of these positive and negative peaks represent the polarity and level of charges on individual particles, therefore the distribution and level of charge on the moving particles can be determined from the voltage signal recording of the individual peaks. The relative charge calculation for multiple charged particles is given in equation 2.

$$Q = C_{\text{INT}} \Delta V \left( \frac{1 + G}{G} \right)$$  \hspace{1cm} \text{Equation 1}

$$Q_{\text{Total}} = C_{\text{INT}} \left( \frac{1 + G}{G} \right) (\Delta V_1 + \Delta V_2 \ldots \Delta V_n)$$  \hspace{1cm} \text{Equation 2}

where $Q_{\text{Total}}$ represents the relative charge because of non-homogeneous sensitivity distribution across the pipe cross section and unknown particle position. Because of the number of particles in an individual test, signal processing software was designed to extract the information of interest from the charge signal obtained as a result of the moving charged particles. The software can determine two groups of information; the position of the peaks in a time sequence and the amplitude of the individual peaks from the baseline. The amplitude of the peaks was used to calculate the charges in the presence of a population of charged particles.

Figure 2 illustrates the raw and processed signals arising from the multiple charged particles moving through the sensor. In the processed signal, it can be clearly seen that the voltage signal produced as red-cross labelled peaks show positive charge and green cross labelled peaks show negative charge. From the positive and negative peaks and their magnitude, the total charge level, ratio of positive or negative charge and bias of bipolar charge distribution can also be determined. Frequency distribution of charges in population of particles presented in (Figure 3) is obtained based on the charge distribution information (Figure 2).

Special care was taken by considering the adhesion property of particles with the wall of the sensor. A fresh sample was used for each test experiment in a humidity and temperature controlled
laboratory (RH = 50 %, 22 °C). The positive charge is the sum of positive charges whereas the negative charge is the sum of negative charges. The net charge is the sum of positive charges and negative charges. The charge–to–mass ratio (CMR or charge density) is defined as the charge (negative charge for N–CMR, positive charge for P–CMR and net charge for net–CMR) per unit mass, in nC/g. Each material investigated was tested 15 times. The data were expressed as the mean ± standard deviation (SD).

Figure 2: Raw data acquired as particles moving through sensor (a) Raw signal (b) Processed signal
2.3 Drug homogeneity assessment

After blending, ten randomly selected samples were taken from different spots with each formulation powder under investigation for the quantification of drug content. Each sample weighed (27.5 ± 0.5) mg (which is equivalent to a unit dose of 400 µg, in accordance with Ventolin Rotacaps®) and was dissolved in 100 mL distilled water (salbutamol sulphate) or ethanol (budesonide) in a volumetric flask. For each formulation, % potency was calculated as the percent amount of drug to the nominal dose, whereas the degree of SS content homogeneity was expressed in terms of percent coefficient of variation (% coefficient of variance (CV)). Salbutamol sulphate [24] and budesonide [25] were quantified as described previously.

3. Results and discussion

3.1 Charging properties of excipients

Materials were taken directly from polypropylene container which was stored under ambient conditions ((20±3) °C; RH = (45±5) %) to investigate initial charging properties of uncharged material. The charge properties of several commercial excipients were tested prior to blending. Figure 4 shows, the distribution of CMR values of glucosamine HCl, sorbitol, mannitol and lactose. Reported results in figure 4 indicate an overall unipolar (positive) charging behaviour for lactose and glucosamine HCl whereas negatively charged material was also detected in sorbitol and mannitol but at a low level.
Figure 4: Charge distribution (CMR) value for different excipients under investigation i.e., glucoseamine HCl, sorbitol, lactose and mannitol.

Figure 5 represents the net CMR value obtained from Faraday pail and developed method, across excipients tested, glucosamine HCl demonstrated the highest positive CMR and the highest net CMR whereas lactose demonstrated the lowest positive CMR, the lowest negative CMR and the lowest net CMR. The relatively small standard errors for the data obtained reflect a satisfactory degree of reproducibility for the method applied (Figure 4 and Figure 5).

Figure 5: Net charge (CMR) value for excipients under investigation i.e., glucoseamine HCl, sorbitol, lactose and mannitol.

Results presented in Figure 5 showed that Faraday pail indicated higher charge value in comparison to the charge sensing method and also clearly provides evidence that two methods are in agreement. Results reported in Figure 5 for lactose are similar to those previously reported by [26] in the case of glass as a contact surface. The results reported for lactose was + 0.3 nC/g.
compared to + 0.35 nC/g in this work. Charge distribution and net CMR value of excipients obtained by using developed method are presented in tabular form in Table 1.

Table 1: Charge distribution and net CMR value of excipients in tabular form

<table>
<thead>
<tr>
<th>Material</th>
<th>Mean Q/M [nC/g]</th>
<th>Standard Error</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Lactose</td>
<td>-0.00002</td>
<td>0.35195</td>
</tr>
<tr>
<td>Mannitol</td>
<td>-0.00992</td>
<td>0.41912</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>-0.02323</td>
<td>0.54955</td>
</tr>
<tr>
<td>Glucosamine HCl</td>
<td>-0.00268</td>
<td>0.74844</td>
</tr>
</tbody>
</table>

Karner, investigated the influence of particle size and contact surface on mannitol in mixing time process [27]. The results reported for the propensity of mannitol when the contact surface is polypropylene is comparable from the results reported in this work. When the mixing time is 5 minutes the net CMR was 0.5 nC/g for the particle size range (100 to 125) µm and 1.1 nC/g for the particle size range (63 to 80) µm. In this work mannitol was directly taken from polypropylene container and net CMR value is 0.42 nC/g.

A study of influence of humidity on electrostatic charge behaviour of sorbitol was investigated by Rowley [28]. This study confirmed that spray-dried sorbitol acquired a negative charge when contact surface is polypropylene but his study does not describe the reason for this behaviour. The polarity mentioned in the study undertaken by Rowley is different from this work however the charge magnitude is not considerably different from the results reported in this work [28]. The only possibility of different result it is may be the sorbitol was spray dried and study conducted by Murtomaa concluded that the process of spray drying increased the possibility of acquiring bipolar charge [2].

The results reported in figure 4 for electrostatic charge behaviour of mannitol are of the same order as those previously reported by Karner [27]. The presented results for charge characteristics of excipients are in agreement with previously published articles [11, 26, 29] in terms of charge level. Previous research has identified that the polarity of particulate material depends on contact surface. For example lactose exhibited positive charge behaviour when the contact surface was non-metal and acquired negative charge when the contact surface was metal.
3.2 Charging properties of APIs

For the second case study, commercial budesonide and salbutamol sulphate were tested. Both API materials are cohesive and showed a degree of self-agglomeration as can be seen from scanning electron microscopic (SEM) images in Figure 6. Materials were taken directly from polypropylene container which was stored under ambient conditions ((20±3) °C; RH = (45±5) %) to investigate initial charging properties of uncharged material.

Figure 7 illustrates the positive and negative charge to mass ratios (CMR) and error bars show the variation. Figure 8 presented the net charge to mass ratio and error bars for budesonide and salbutamol sulphate. Budesonide showed very weak bipolar charge behaviour, yet the value of positive CMR is much higher than the negative CMR. Budesonide demonstrated considerably higher net charge density in comparison to salbutamol sulphate (Figure 7 and 8). This may explain the high agglomeration tendency of budesonide particles compared to salbutamol sulphate particles as evident by SEM (Figure 6).

![Figure 6: Scanning electron microscopic (SEM) images of micronized budesonide and salbutamol sulphate](image)

The net charge to mass ratio charge properties of budesonide obtained from charge sensing method and Faraday pail are presented in Figure 7. The results obtained from developed method are in agreement with the results obtained from Faraday pail method. The results obtained illustrated that the charging tendency of the API materials was higher than the charging tendencies of the excipients tested. Such findings are in agreement with previous studies [11], and may be partly attributed to the considerably small size of drug particles investigated in comparison to excipient particles.
Charge distribution and net CMR values for API materials obtained from developed method are reported in Table 2 in tabular form.

Table 2: Charge distribution and net CMR value of API materials in tabular form

<table>
<thead>
<tr>
<th>Material</th>
<th>Mean Q/M [nC/g]</th>
<th>Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>BUD</td>
<td>-0.36123</td>
<td>20.41118</td>
</tr>
<tr>
<td>SS</td>
<td>-4.54758</td>
<td>0.004095</td>
</tr>
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</table>
3.3 Charging properties of blends

Following the understanding of charge distribution of excipients and drugs, four different blends were prepared and evaluated in terms of electrostatic properties and drug content homogeneity. The tests for charging characteristics in different blends were repeated 15 times; the results presented in Figure 9 shown the positive and negative CMRs. Bipolar charging behaviour was observed for all formulations, even when mixing two particulate materials having tendencies of acquiring the same charging polarity. Figure 10 presented the net charge to mass ratio and error bars value of all formulations. For example, results in Figure 9 illustrated bipolar charging distribution when budesonide is mixed with lactose, even though they both have the same charging tendency of positive charging behaviour prior to mixing. Such bipolar charging behaviour could be due to inter-particle contact of same and opposite species and particle to wall contacts during blending or just a difference in work function between the two elements. The results indicate that the charge characteristics are not only dependent on the material but also on the handling process of the material and the contact surfaces. During blending/mixing processes, charges may be transferred between the same or different types of particulates as well as to and from the surface of the blender body and impeller [30]. Therefore, it would be illuminating to evaluate the charge properties in real time in the processes. However to the best of the author’s knowledge, there is not any existing method that can achieve this target. Table 3 presents the charge distribution and net CMR values obtained from developed method in tabular form.

![Charge Distribution of Blended Samples](image)

Figure 9: Charge distribution (CMR) value for lactose-budesonide, lactose-sulbutamol sulphate, mannitol-sulbutamol sulphate and mannitol-budesonide
Figure 10: Net Charge (CMR) value for lactose-budesonide, lactose-sulbutamol sulphate, mannitol-sulbutamol sulphate and mannitol-budesonide

Table 3: Charge distribution and net CMR value of blends in tabular form

<table>
<thead>
<tr>
<th>Material</th>
<th>Mean Q/M [nC/g]</th>
<th>Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Man-BUD</td>
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<td>0.5426</td>
</tr>
<tr>
<td>Man-SS</td>
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<td>0.7651</td>
</tr>
<tr>
<td>Lac-SS</td>
<td>-0.5688</td>
<td>0.7694</td>
</tr>
<tr>
<td>Lac-BUD</td>
<td>-1.0996</td>
<td>1.1276</td>
</tr>
</tbody>
</table>

Drug homogeneity assessments indicated that the homogeneity of drug content was inversely proportional to net-CMR (Figure 11). This can be explained as particle electrostatic charge might lead to less dose uniformity due to forming of different regions of the powder with different densities and flow ability. Charged particles can be either attracted to or repulsed from each other promoting powder agglomeration or segregation which might have detrimental influence on homogeneity of the powder mixture [31].
4. Conclusions

The evaluation case studies for the developed method for charge measurement are presented to determine the charging properties of different particulate materials. Characterisation of charging properties of particulate materials both in terms of magnitude and polarity can be helpful to provide essential information related to charge behaviour of material.

The study of the developed method for charge assessment has clearly demonstrated the advantages in terms of bipolar charge detection over the other existing charge measurement methods. It showed the mixing/blending process is prone to produce bipolar charge distribution and hence need an advanced charge characterisation method to assess the charging properties. The major advantage of the inductive sensor is its ability to measure charge magnitude and polarity of individual particles for a bulk of particulate samples in a very short period of time. There are a few limitations to the developed system such as the requirement for an effective feeding method in order to disperse the material effectively. It is proposed that an extension to the work reported in this paper can utilise the established charge sensors in the Wolfson Centre to verify a proposed technique for the real-time monitoring of a typical batch manufacturing process in the pharmaceutical industry. Such a technique could help indicate whether the start, duration, and end of a batch manufacturing process...
had the correct proportion of active ingredient as well as early indications of relatively high charge accumulation (for example: a change in the excipient from one batch to the next).

5. References


