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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

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33 relatively small quantities of a fine material which is being processed over several handling steps
34 [2-4]. The problems caused by electrostatic charge (both the magnitude and polarity) observed in
35 the form of agglomeration, segregation, particle adhesion to the processing equipment etc., may
36 result in cases of batch failure in product quality control and can influence formulation [4-7].
37 Therefore, characterisation of charging properties of particulate materials is helpful to provide
38 essential information relating to the behaviour of particulate materials with different contact
39 surfaces and handling procedure to improve the quality of the final product [8]. For example, it has
40 been demonstrated that the homogeneity of drug content within dry powder inhaler formulations
41 improves with decreasing the charge density of mannitol excipient [9].

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

51 At present, the most popular assessment of tribocharging problems is generally gained from the
52 Faraday pail method which provides only limited information in the form of net charge to mass ratio.
53 The Faraday pail method is robust and highly accurate when materials are charged unipolar. But in
54 the case when particulate materials acquire bipolar charge distribution, the charge measurement
55 using traditional method for example the Faraday pail is not an accurate indicator to assess the
56 intensity of the possible effect of electrostatic charging of the particulate materials [3]. Due to
57 complex nature of charge transfer process between particles the European Pharmaceutical Aerosol
58 Group has recognised the need of better method to understand charging phenomenon [19]. Bipolar
59 charging is more likely to occur in industrial processes of particulates where the materials are prone to
60 bipolar charging (such bipolar charging is likely to be observed in most products such as
61 pharmaceutical mixtures consisting of two materials with opposite or same charging tendencies) [3,
62 10]. A conclusion based on net charge to mass ratio without understanding the inter-particle
63 electrostatic forces is less helpful [4]. In contrast, accurate charge distribution information across the
64 population of particles will provide a better understanding of the role of tribocharging in process
65 assessment [17]. The presently poor understanding of charge distribution across a population of

66 particles is attributable to the fact that the generation of electrostatic charge is a multifaceted
67 process, i.e., it depends not only on the work function of materials but is also influenced by other
68 factors such as surface impurities, contact area, particle size or humidity [18, 20]. Additionally,
69 limited methods are currently available for systematic experimental investigations and instruments
70 for bipolar charge characterisation.

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

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

90

91 **2. Materials and method**

92 **2.1 Materials**

93 Polystyrene beads of average size 1.7 μ m were used as charged particles. Other materials
94 included Lactose (DMV International, the Netherlands), mannitol (Fisher Scientific, UK),
95 glucosamine hydrochloride (Sigma-Aldrich, USA) and sorbitol (Roquett, France). Micronized
96 salbutamol sulphate and budesonide were purchased from LB Bohle, Germany and IVAX

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97 Pharmaceuticals, Ireland respectively. All API (active pharmaceutical ingredient) and excipient
98 samples were stored in a polypropylene container.

99 2.1.1 Preparation of DPI formulation blends: Commercial lactose and commercial
100 mannitol were separately blended with either salbutamol sulphate or budesonide drug in a ratio of
101 67.5:1, w/w (in accordance with the ratio used in commercial Ventolin Rotacaps[®], GSK). Each
102 blending process was carried out at standard mixing conditions in a cylindrical aluminium container
103 (6.5 cm × 8 cm) using a Turbula[®] mixer (Willy A. Bachofen AG, Basel, Switzerland) at a standard
104 mixing condition, *i.e.*, 100 rpm mixing speed and 15 minutes mixing time.

105 2.2 Methods

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

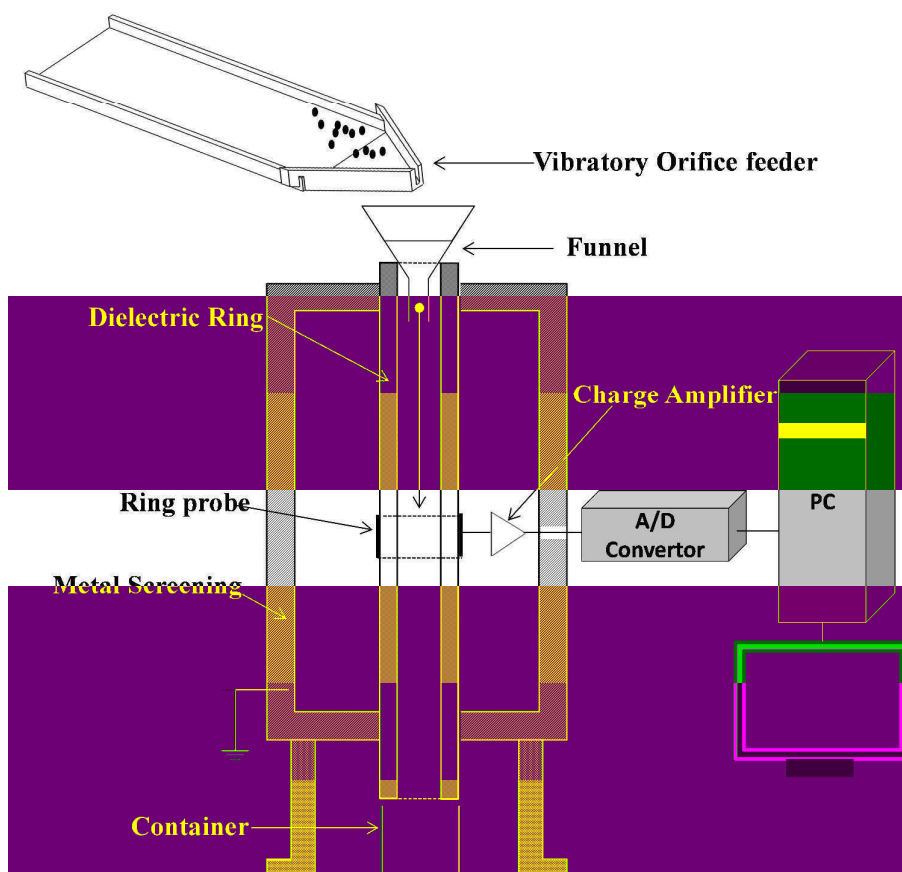
111 The developed method is based on the electrostatic inductive sensor, which has been studied
112 and investigated in detail [4]. Electrostatic induction sensing has been successfully used for many
113 different purposes, for example, velocity measurement, flow measurement and charge measurement
114 [21-23]. In particle charge determination, particles are dispersed and fed into the probe so the
115 charged particles can be determined separately. Due to the non-homogenous sensitivity distribution
116 of the sensor, particles moving under peripheral flow induce 7 % higher charge on the sensor
117 compared to the particles moving under central flow condition [4]. As a result, the developed
118 method is only able to measure relative charge on moving particles. It was assumed that all particles
119 moved through the centre of the sensor to minimise the influence of variation in sensitivity due to
120 particle position inside the sensor.

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

126 As the charged particles pass through the sensor they induce a current that is amplified by a
127 charge amplifier. The direction of the induced current peaks in the signal infer the polarity of

128 charged particles moving whereas the amplitude of the peaks indicates the level of charge carried
129 by the particles. The signal processing methodologies were adapted to obtain the information
130 relating to charge distribution and charge to mass ratio when a mass of particles moves through the
131 sensor. The overview of the test facility is shown in Figure 1.

132



133

134 *Figure 1: Schematic overview of experimental test facility*

135

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

139 The beads were charged in a plastic vial (9 cm in length and 2.5 cm in diameter) by using a
140 “vortex-mixer” (PV-1 personal vortex mixer, Cambridge). The charge (Q) can be calculated by
141 taking the voltage magnitude from the baseline obtained as a result of charged particles moving
142 through the sensor using the following equation:

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

143 where ΔV is the difference between the minimum (baseline) and maximum voltage (the peak value
 144 either positive or negative), the C_{INT} is the integrating capacitor and G is the gain of the amplifier.
 145 The charged signal acquired as shown in figure 2 for polystyrene beads, the integrating capacitor
 146 value used was $C_{\text{INT}} = 10$ pF and gain (G) of two was used.

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

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

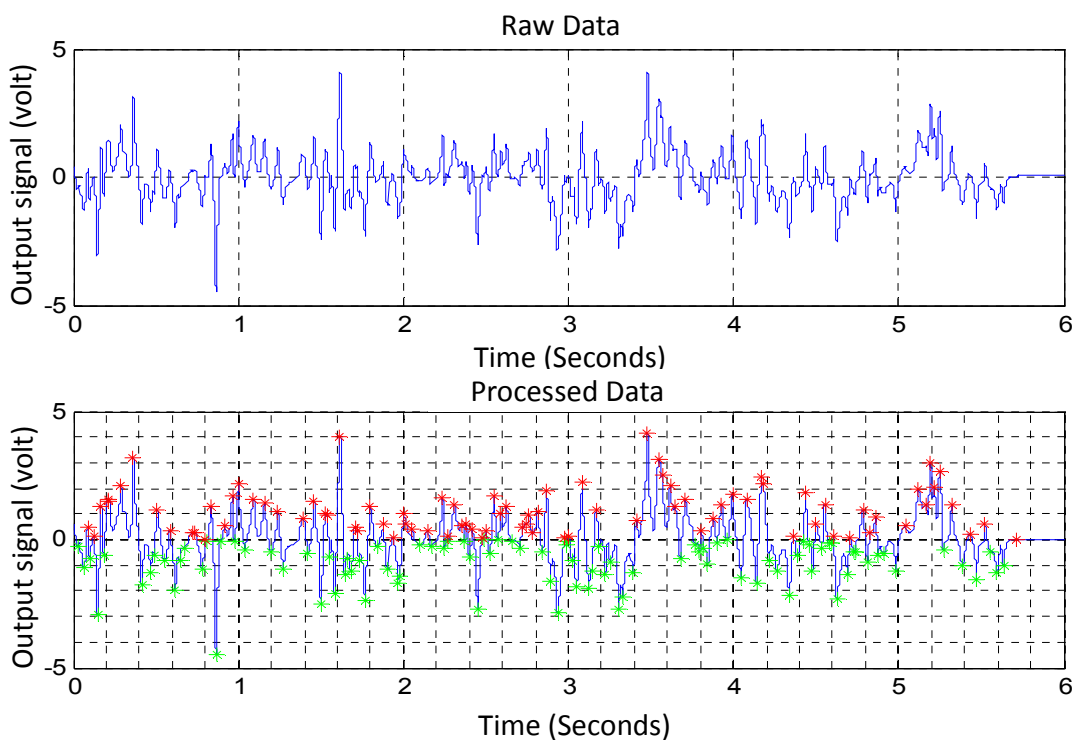
155 where Q_{Total} represents the relative charge because of non-homogeneous sensitivity distribution
 156 across the pipe cross section and unknown particle position. Because of the number of particles in
 157 an individual test, signal processing software was designed to extract the information of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

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

169 Special care was taken by considering the adhesion property of particles with the wall of the
 170 sensor. A fresh sample was used for each test experiment in a humidity and temperature controlled

171 laboratory (RH = 50 %, 22 °C). The positive charge is the sum of positive charges whereas the
172 negative charge is the sum of negative charges. The net charge is the sum of positive charges and
173 negative charges. The charge-to-mass ratio (CMR or charge density) is defined as the charge
174 (negative charge for N-CMR, positive charge for P-CMR and net charge for net-CMR) per unit
175 mass, in nC/g. Each material investigated was tested 15 times. The data were expressed as the mean
176 \pm standard deviation (SD).

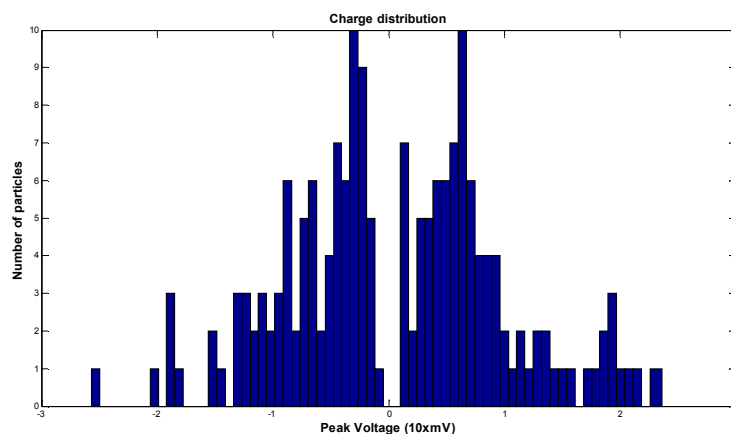
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178

179 *Figure 2: Raw data acquired as particles moving through sensor (a) Raw signal (b) Processed signal*

180



181

182 *Figure 3: Charge distribution information obtained from processed signal based on single particles*

183

184

2.3 Drug homogeneity assessment

185 After blending, ten randomly selected samples were taken from different spots with each
186 formulation powder under investigation for the quantification of drug content. Each sample
187 weighed (27.5 ± 0.5) mg (which is equivalent to a unit dose of 400 μg , in accordance with Ventolin
188 Rotacaps[®]) and was dissolved in 100 mL distilled water (salbutamol sulphate) or ethanol
189 (budesonide) in a volumetric flask. For each formulation, % potency was calculated as the percent
190 amount of drug to the nominal dose, whereas the degree of SS content homogeneity was expressed
191 in terms of percent coefficient of variation (% coefficient of variance (CV)). Salbutamol sulphate
192 [24] and budesonide [25] were quantified as described previously.

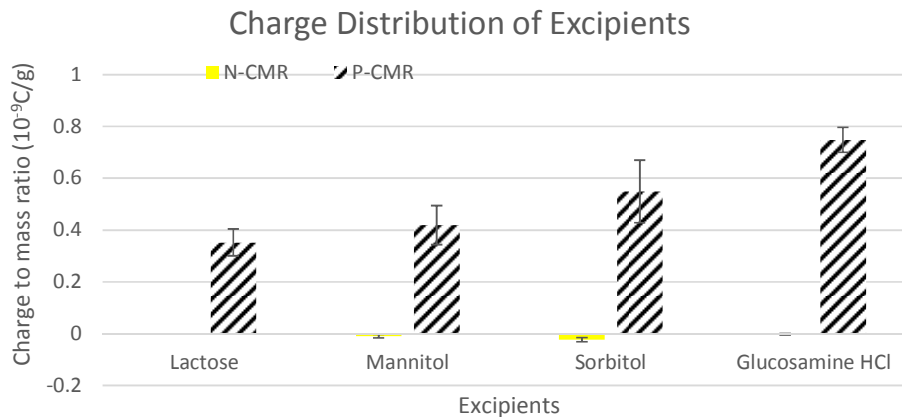
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3. Results and discussion

194

3.1 Charging properties of excipients

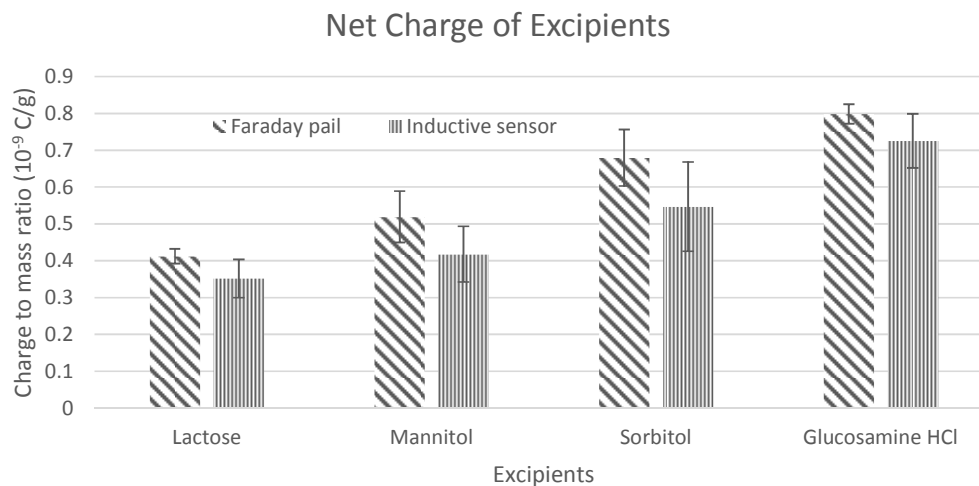
195 Materials were taken directly from polypropylene container which was stored under ambient
196 conditions ((20 ± 3) °C; RH = (45 ± 5) %) to investigate initial charging properties of uncharged
197 material. The charge properties of several commercial excipients were tested prior to blending.
198 Figure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



202

203 *Figure 4: Charge distribution (CMR) value for different excipients under investigating i.e., glucosamine HCl, sorbitol, lactose and*
204 *mannitol*

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



210

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

212 Results presented in Figure 5 showed that Faraday pail indicated higher charge value in
213 comparison to the charge sensing method and also clearly provides evidence that two methods are
214 in agreement. Results reported in Figure 5 for lactose are similar to those previously reported by
215 [26] in the case of glass as a contact surface. The results reported for lactose was + 0.3 nC/g

216 compared to + 0.35 nC/g in this work. Charge distribution and net CMR value of excipients
217 obtained by using developed method are presented in tabular form in Table 1.

218

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

Material	Mean Q/M [nC/g]			Standard Error		
	-	+	Net	-	+	Net
Lactose	-0.00002	0.35195	0.35193	±0.00002	±0.05165	±0.05165
Mannitol	-0.00992	0.41912	0.41767	±0.00696	±0.07536	±0.07559
Sorbitol	-0.02323	0.54955	0.54687	±0.00770	±0.12070	±0.12098
Glucosamine HCl	-0.00268	0.74844	0.72521	±0.00268	±0.04784	±0.07335

220

221 Karner, investigated the influence of particle size and contact surface on mannitol in mixing
222 time process [27]. The results reported for the propensity of mannitol when the contact surface is
223 polypropylene is comparable from the results reported in this work. When the mixing time is 5
224 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
225 particle size range (63 to 80) μm . In this work mannitol was directly taken from polypropylene
226 container and net CMR value is 0.42 nC/g.

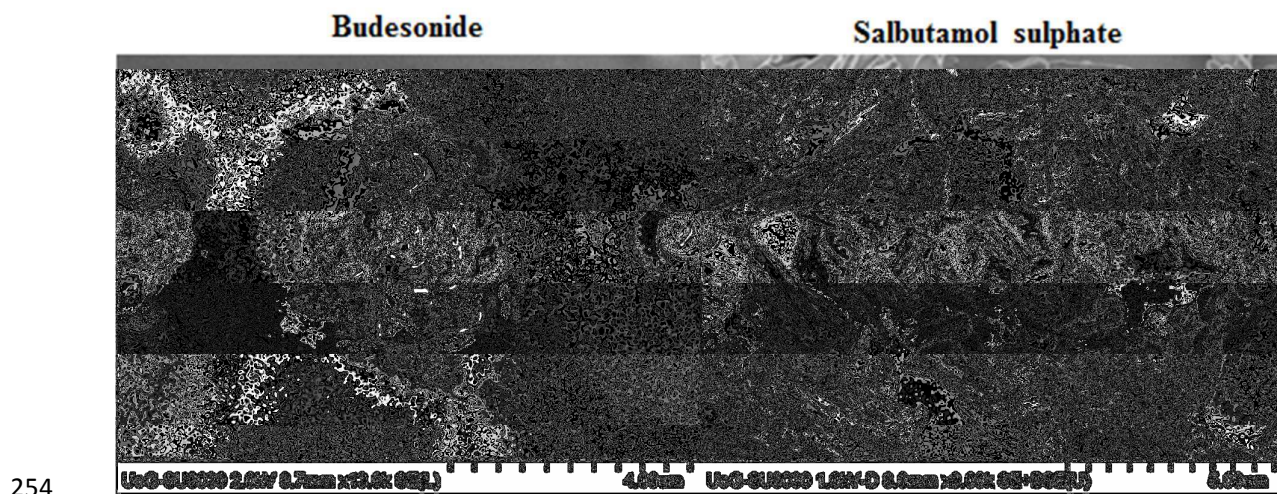
227 A study of influence of humidity on electrostatic charge behaviour of sorbitol was
228 investigated by Rowley [28]. This study confirmed that spray-dried sorbitol acquired a negative
229 charge when contact surface is polypropylene but his study does not describe the reason for this
230 behaviour. The polarity mentioned in the study undertaken by Rowley is different from this work
231 however the charge magnitude is not considerably different from the results reported in this work
232 [28]. The only possibility of different result it is may be the sorbitol was spray dried and study
233 conducted by Murtomaa concluded that the process of spray drying increased the possibility of
234 acquiring bipolar charge [2].

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

241 3.2 Charging properties of APIs

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

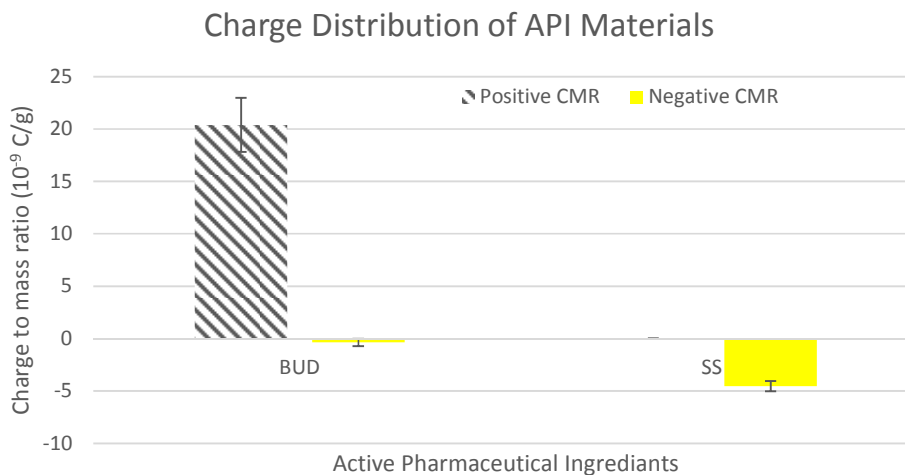
247 Figure 7 illustrates the positive and negative charge to mass ratios (CMR) and error bars
248 show the variation. Figure 8 presented the net charge to mass ratio and error bars for budesonide
249 and salbutamol sulphate. Budesonide showed very weak bipolar charge behaviour, yet the value of
250 positive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



255 *Figure 6: Scanning electron microscopic (SEM) images of micronized budesonide and salbutamol sulphate*

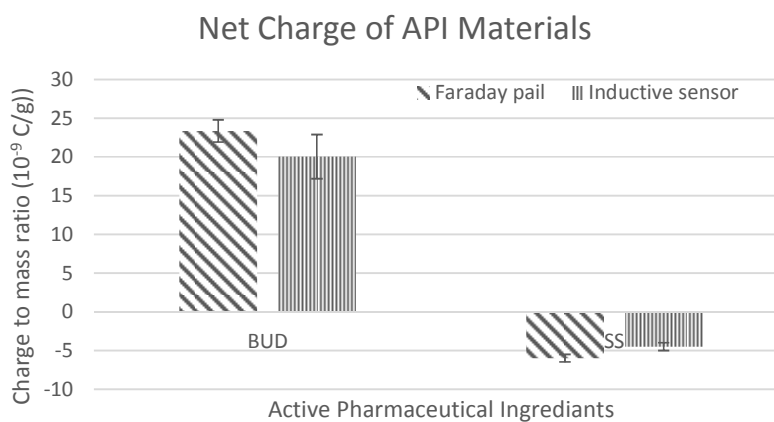
256 The net charge to mass ratio charge properties of budesonide obtained from charge sensing
257 method and Faraday pail are presented in Figure 7. The results obtained from developed method are
258 in agreement with the results obtained from Faraday pail method. The results obtained illustrated
259 that the charging tendency of the API materials was higher than the charging tendencies of the
260 excipients tested. Such findings are in agreement with previous studies [11], and may be partly
261 attributed to the considerably small size of drug particles investigated in comparison to excipient
262 particles.

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263

264 *Figure 7: Charge distribution (CMR) value for budesonide and salbutamol sulphate*



265

266 *Figure 8: Net charge (CMR) value for budesonide and salbutamol sulphate*

267

268 Charge distribution and net CMR values for API materials obtained from developed method are
269 reported in Table 2 in tabular form.

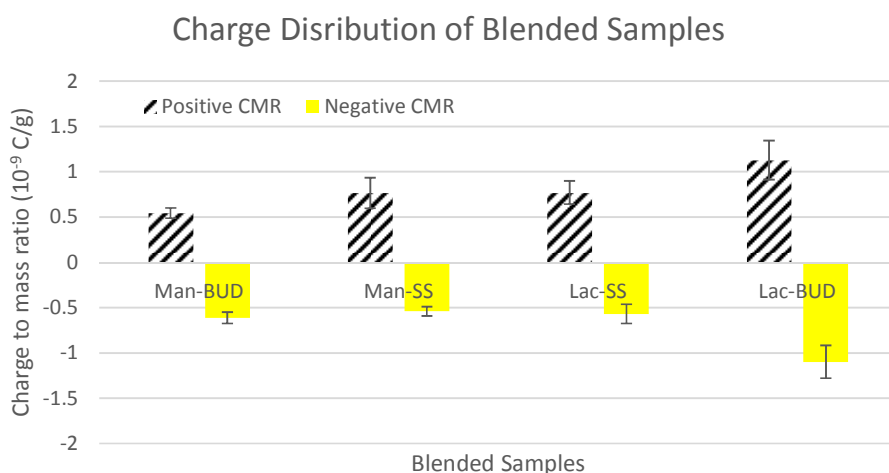
270 **Table 2: Charge distribution and net CMR value of API materials in tabular form**

Material	Mean Q/M [nC/g]			Standard Error		
	-	+	Net	-	+	Net
BUD	-0.36123	20.41118	20.04994	±0.353774	±2.587065	±2.85157
SS	-4.54758	0.004095	-4.48615	±0.489761	±0.001761	±0.504567

271

272 3.3 Charging properties of blends

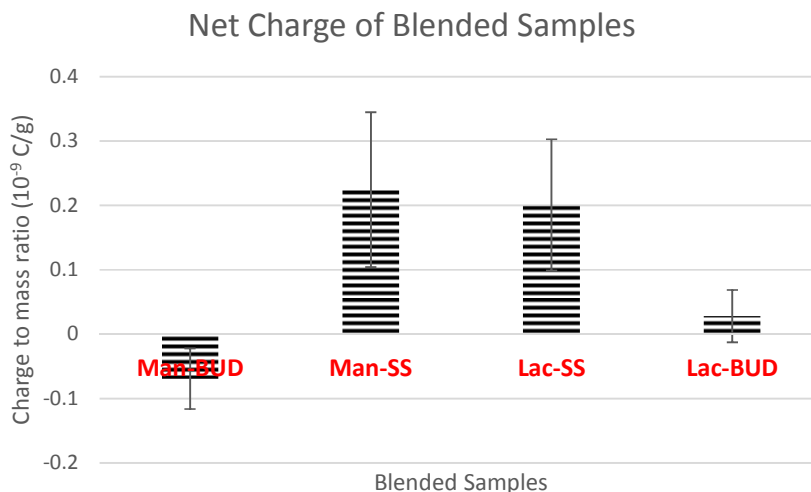
273 Following the understanding of charge distribution of excipients and drugs, four different
 274 blends were prepared and evaluated in terms of electrostatic properties and drug content
 275 homogeneity. The tests for charging characteristics in different blends were repeated 15 times; the
 276 results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



291

292 *Figure 9: Charge distribution (CMR) value for lactose-budesonide, lactose-sulbutamol sulphate, mannitol-sulbutamol sulphate and*
 293 *mannitol-budesonide*

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294

295 *Figure 10: Net Charge (CMR) value for lactose-budesonide, lactose-sulbutamol sulphate, mannitol-sulbutamol sulphate and*
296 *mannitol-budesonide*

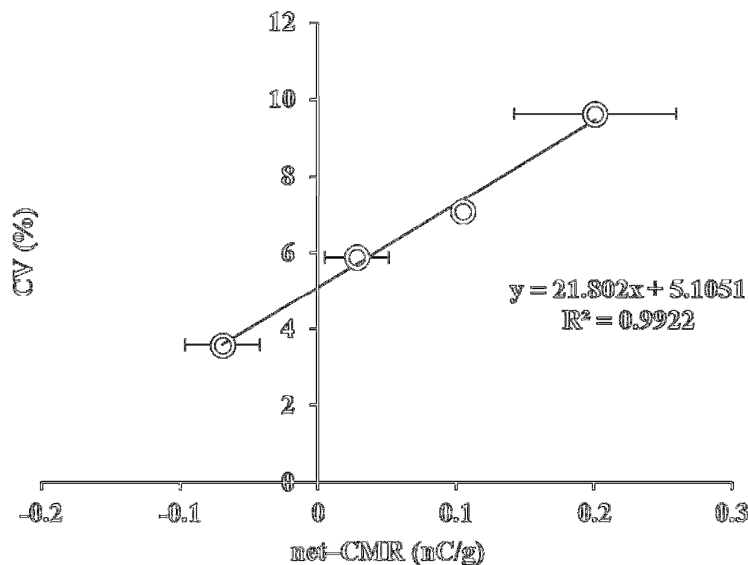
297 **Table 3: Charge distribution and net CMR value of blends in tabular form**

.Material	Mean Q/M [nC/g]			Standard Error		
	-	+	Net	-	+	Net
Man-BUD	-0.6119	0.5426	-0.0692	± 0.0576	± 0.0641	± 0.0470
Man-SS	-0.5406	0.7651	0.2245	± 0.1701	± 0.0525	± 0.1202
Lac-SS	-0.5688	0.7694	0.2006	± 0.1282	± 0.1066	± 0.1020
Lac-BUD	-1.0996	1.1276	0.0280	± 0.2140	± 0.1810	± 0.0404

298

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

305



306

307 *Figure 11: Relationship between coefficient of variation of drug content and net charge to mass ratio (CMR) for different*
 308 *formulations under investigation*

309

310

311 4. Conclusions

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

316 The study of the developed method for charge assessment has clearly demonstrated the advantages
 317 in terms of bipolar charge detection over the other existing charge measurement methods. It showed
 318 the mixing / blending process is prone to produce bipolar charge distribution and hence need an
 319 advanced charge characterisation method to assess the charging properties. The major advantage of
 320 the inductive sensor is its ability to measure charge magnitude and polarity of individual particles
 321 for a bulk of particulate samples in a very short period of time. There are a few limitations to the
 322 developed system such as the requirement for an effective feeding method in order to disperse the
 323 material effectively. It is proposed that an extension to the work reported in this paper can utilise the
 324 established charge sensors in the Wolfson Centre to verify a proposed technique for the real-time
 325 monitoring of a typical batch manufacturing process in the pharmaceutical industry. Such a
 326 technique could help indicate whether the start, duration, and end of a batch manufacturing process

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327 had the correct proportion of active ingredient as well as early indications of relatively high charge
328 accumulation (*for example: a change in the excipient from one batch to the next*).

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330 5. References

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