

# Chargeability Measurements of Selected Pharmaceutical Dry Powders to Assess their Electrostatic Charge Control Capabilities

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## ABSTRACT

The purpose of this study was to develop an instrument (the Purdue instrument) and the corresponding methodologies to measure the electrostatic charge development (chargeability) of dry powders when they are in dynamic contact with stainless steel surfaces. The system used an inductive noncontact sensor located inside an aluminum Faraday cage and was optimized to measure the charging capabilities of a fixed volume of powder (0.5 cc). The chargeability of 5,5-diphenyl-hydantoin, calcium sulfate dihydrate, cimetidine, 3 grades of colloidal silicon dioxide, magnesium stearate, 4 grades of microcrystalline cellulose, salicylic acid, sodium carbonate, sodium salicylate, spray-dried lactose, and sulfapyrazone were tested at 4 linear velocities, and the particle size distribution effect was assessed for 3 different grades of colloidal silicon dioxide and 4 different grades of microcrystalline cellulose. The chargeability values exhibited a linear relationship for the range of velocities studied, with colloidal silicon dioxide exhibiting the maximum negative chargeability and with spray-dried lactose being the only compound to exhibit positive chargeability. The instrument sensitivity was improved by a factor of 2 over the first generation version, and the electrostatic charge measurements were reproducible with relative standard deviations ranging from nondetectable to 33.7% (minimum of 3 replicates). These results demonstrate the feasibility of using the Purdue instrument to measure the electrostatic charge control capabilities of pharmaceutical dry powders with a reasonable level of precision.

**KEYWORDS:** Powders, charge control, electrostatic, chargeability, triboelectricity, excipients.

## INTRODUCTION

The goal of mixing in pharmaceutical operations is homogeneous, nonsegregating mixes, but this desired result is not always attained. The solid systems of excipients and active ingredients can suffer electrostatic charging by contact or friction electrification (tribocharging) caused by interactions among particles or between particles and the surfaces that contain them. These interactions can affect formulation, manufacture, powder flow, and packing behavior and can reduce fill and dose uniformity during final use by patients in products such as inhalers.<sup>1-3</sup> In addition, it has been reported that electrostatic charges are also responsible for problems in blend uniformity.<sup>4,5</sup>

Electrostatic charge can result in poor powder-flow properties during filling or emptying of pulmonary drug delivery devices (inhalers).<sup>6</sup> These devices, when using the pulmonary route to administer systemic drugs, use ordered mixtures of fine drug particles adhered to larger carrier particles. The drug particles are in the size range of 1.0 to 2.0  $\mu\text{m}$  and therefore have a tendency to carry a high surface charge, increasing the cohesiveness of the mixture and affecting the powder-flow properties. These properties can be improved during the formulation by selecting the proper excipients that will be accompanying the active compound<sup>2</sup> or during the design of the dispenser material to minimize the effects of the powder/internal-surfaces interactions. In addition, the study of chargeability (the physical property of a material to charge electrostatically when subject to contact, friction, or sliding) of pharmaceutical powders is important to understanding the mechanism for the release of active pharmaceutical ingredients (API) from the carrier particles in dry powder inhalers.

The development and use of appropriate methods for the characterization of different excipient functions is an important part of the excipient design by particle engineering. One of these methods characterizes the tendency of dry powder to become charged electrostatically, and this net positive or negative tendency is called chargeability. The literature does not have a database of chargeability of dry powders that allows the comparison of their values because the instrumentation and the methodologies used are so diverse that it is very difficult to compare results from different studies.

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There is no standard instrument for the measurement of the chargeability of dry powders, which contrasts with other industrial applications of chargeability of materials, such as the electronics industry, where there are standards for quantifying material electrostatic discharge.

Because of the importance of the study of chargeability and the need for comparable measurements of this parameter for different pharmaceutical powders, this study presents the development of an instrument and the corresponding methodology to measure the charge-control capabilities of several common excipients and active ingredients.

## MATERIALS AND METHODS

### Materials

The 16 pharmaceutical compounds used in this study and their physical properties are listed in Table 1. All the compounds were received in the original manufacturer packaging and tested prior to their expiration date. Spectrophotometric grade acetone (Mallinckrodt Inc, Hazelwood, MO) was used

to clean the internal surface of the charging pipe. The temperature of the processing environment was (mean  $\pm$  SD)  $22.02^{\circ}\text{C} \pm 0.73^{\circ}\text{C}$ , and the relative humidity (RH) was  $46.6\% \pm 10.3\%$ . A laboratory-quality compressed air cylinder (BOC Gases, Murray Hill, NJ) with 10 ppm maximum moisture content was used to convey the powder to the sensor.

### Chargeability Measurement Instrument

The instrument was designed and constructed in the Purdue Air Pollution Laboratory and was based on a previous model developed in the same laboratory.<sup>15</sup> In this study the instrument and the corresponding protocol were modified in order to improve the instrument sensitivity and precision. The instrument consisted of 3 systems: airflow control system, charging pipe, and measuring-data acquisition system (Figure 1).

### Airflow Control System

The airflow control system, consisting of a pressure-regulated dry-air gas cylinder supplying air at 206.84 kPa, was used to avoid any oil or particle contamination. Other equipment

**Table 1.** Physical Properties of the Compounds Analyzed\*.<sup>7</sup>

Compound	Density		Specific Surface Area m <sup>2</sup> /g	Mean Diameter $\mu\text{m}$	Moisture Content %	Manufacturer	Lot
	Abs. (g/cc)	Bulk (g/cc)					
<b>Microcrystalline cellulose (Avicel):</b>							
Grade: PH 101	1.586 <sup>†</sup>	0.29 <sup>‡</sup>	1.122 <sup>†</sup>	50	$\leq 5.0$	FMC Corp.	1656
Grade: PH 102	1.568 <sup>†</sup>	0.30 <sup>‡</sup>	1.069 <sup>†</sup>	100	$\leq 5.0$	FMC Corp	2940
Grade: PH 105	1.581 <sup>†</sup>	0.22 <sup>‡</sup>	2.73 <sup>†</sup>	20	$\leq 5.0$	FMC Corp	5904
Grade: PH 200	1.561 <sup>†</sup>	0.345 <sup>‡</sup>	1.106 <sup>†</sup>	180	$\leq 5.0$	FMC Corp	M910C
<b>Colloidal silicon dioxide (Cab-O-Sil):</b>							
Grade L-90	2.2	0.0481 <sup>§</sup>	$90 \pm 10^8$	0.007		CABOT Corp	1A308
Grade M5	2.2	0.0355	$200 \pm 25^8$	0.007		CABOT Corp	1I268
Grade EH-5	2.2	0.040 <sup>§</sup>	$380 \pm 30^8$	0.007		CABOT Corp	1F205
Cimetidine, unmilled <sup>9</sup> (Tagamet)	1.28	0.4621	0.67	19		Smith Kline and French labs	809-CETG-L1K6
Calcium sulfate dihydrate (Compactrol)	2.32	0.9400	3.15	17		Mendell (a Penwest Co.)	5022CX
Lactose S.D. No. 315	1.552 <sup>10</sup>	0.6700	$0.24-0.25^{10}$	$99.2^{11}$	4.8-5.2	Foremost Farms	9RD420
Magnesium stearate NF	1.092 <sup>10</sup>	0.1515	$8.2^{10}$	$9.61^{11}$		Mallinckrodt Inc	2256KTTX
Salicylic acid (Crystals)	1.443 <sup>12</sup>	0.3653 <sup>§</sup>	0.256			Mallinckrodt Inc	2028 KVET
Sodium salicylate	2 <sup>13</sup>	0.8339 <sup>§</sup>	0.1245			Mallinckrodt Inc	2094 Adi
Sulfinpyrazone (Anturane)		0.3796 <sup>§</sup>	1.1848			CIBA Pharmaceuticals	B76-26
Sodium carbonate	2.53 <sup>14</sup>	1.1893 <sup>§</sup>	1.0381			Sigma Chemicals	32H0313
5,5 -Diphenyl-hydantoin		0.4683 <sup>§</sup>	0.8634			Sigma Chemicals	16F0215

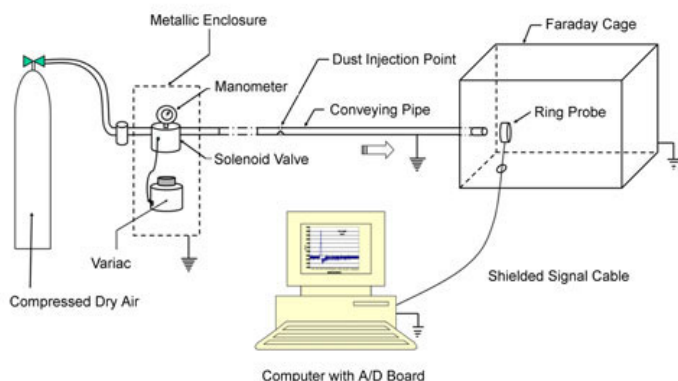
\*Note: All data are from Wade and Weller except where it is noted differently.

<sup>†</sup>Written communication of Mr. Jian-Xin Li, from FMC Corporation Technical Service, Philadelphia, PA, March 2003.

<sup>‡</sup>Manufacturer lot certificate of analysis for each Avicel grade.

<sup>§</sup>Measured by Juan Carlos Ramirez, Civil Engineering Air Pollution Laboratory, Purdue University, West Lafayette, IN.

|| Measured by Juan Carlos Ramirez using a Micromeritics accelerated surface area analyzer; ASAP 2010.



**Figure 1.** Powder chargeability instrument. A/D indicates analog-to-digital.

included a solenoid valve, a needle valve to adjust the air flow, and a calibrated air rotameter (RMC series, 40-400 SCFH, 10 SCFH resolution, Dwyer Instruments Inc, Michigan City, IN). All of these elements, except the dry-air cylinder, were installed in a portable grounded aluminum case.

### Charging Pipe

The charging device consisted of a horizontally oriented, electrically grounded 304 stainless steel pipe, 11.89-mm inner diameter, and 1.22 m long. Stainless steel was chosen because it is the industry standard for handling these materials. The sample inlet port was located at the top of the pipe, 1.041 m from the end. This is another feature that differentiates this design from the Gajewski and Szaynok<sup>16</sup> design, in which the sample powder was placed at the end of the pipe and then conveyed pneumatically through the sensor ring without emphasizing powder-surface interaction. Five identical stainless steel pipes were obtained from the same production batch to ensure the same internal surface roughness and composition. The charging pipe was grounded at one end only. The pipe's exit end entered into a Faraday cage through a rubber ring isolated hole at 6.35 mm (0.25 inches) from the sensor ring.

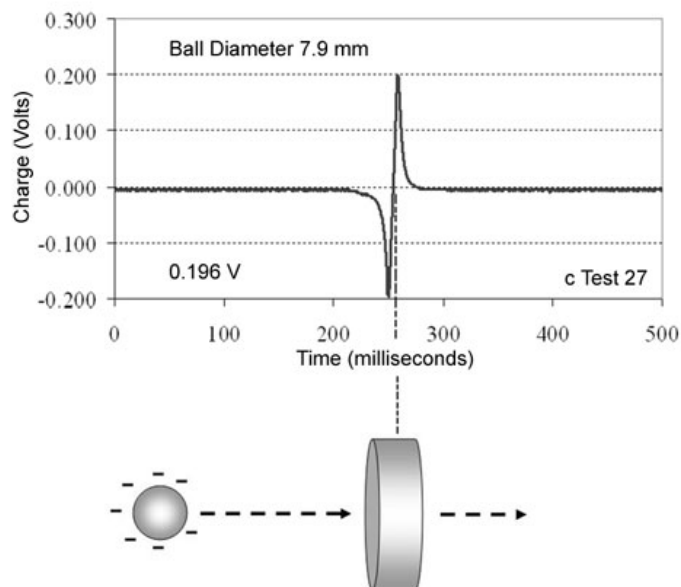
### Faraday Cage

The sensor system included the Faraday cage, the sensor ring, and the data acquisition system. The Faraday cage was constructed of aluminum with internal dimensions of 540-mm wide, 292-mm deep, and 324-mm high, for a total volume of 51 L. Every part of the cage was grounded. Finally, a copper screen cage door, which was electrically connected to the cage allowed the conveying air to exhaust outside (for non-active or hazardous compounds). A careful cleaning procedure was followed before each test using a high efficiency particulate (HEPA) filter.

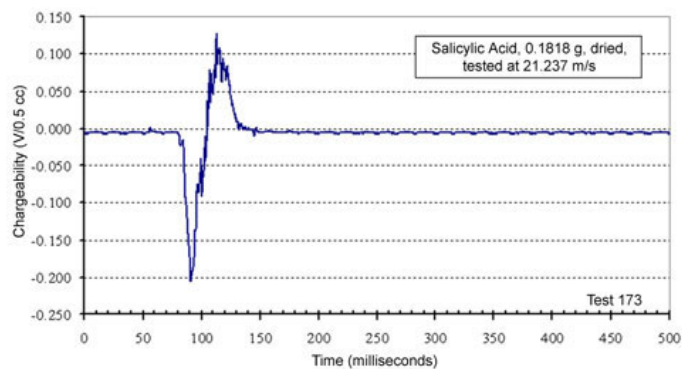
### Charge Sensor

The electrostatic charge sensor consisted of a copper ring with a 25.4-mm outer diameter, 12.75 mm in length, with 3.175-mm wall thickness. This is the same ring design used by Ghosh<sup>15</sup> on the first generation of this instrument, and it was a modification of a design presented by Gajewski and Szaynok.<sup>16</sup> The Purdue design used a clean stainless steel pipe for each sample tested, so the sample powder was always in contact with a clean surface. A shielded coaxial cable was connected to the sensor ring to collect the voltage signal induced by the powder cloud as it traveled through the center of the sensor ring. This signal was processed in an analog-to-digital converter and recorded as volts.

Figure 2 and Figure 3 show examples of the voltage data measured by the sensor ring versus time. Figure 2 was obtained using a steel ball charged negatively with corona-generated unipolar ions, which presents a clear symmetry because the electric charge is concentrated on the surface of the ball. The recorded chargeability is the value of the first absolute-maximum or absolute-minimum generated when the charged ball is approaching the sensor ring, which defines the polarity of the ball—in this case a negative polarity. The second peak, a positive peak, is generated when the ball moves away from the sensor ring. In the same way, Figure 3 shows the voltage induced by a cloud of salicylic acid crystals. Because we used a sample of powder that is blown using air, the cloud was assumed to have a shape close to a sphere. This assumption was verified by Gajewski and Szaynok<sup>16</sup> using high-speed photography.



**Figure 2.** Signal spectrum obtained using a charged steel ball of 7.9 mm (0.3125 inches) diameter.



**Figure 3.** Example of signal spectrum obtained during a salicylic acid chargeability test.

### Data Acquisition System

The data acquisition system involved a Computer Boards analog-to-digital (A/D) converter board and its companion software (Computer Boards Inc., Westford, MA). The converter board was calibrated to set the gain of the instrument to the range of voltages ( $\pm 1250$  mV) measured during the preliminary tests. The A/D converter board had a resolution of 12 bits.

Data were collected at a 2.5 kHz signal sampling rate during 3.2 seconds. The signal-to-noise ratio of the instrumentation was improved in order to measure the chargeability of compounds that develop a weak signal even when tested at the intended maximum velocity. This improvement was achieved by using a different strategy for grounding and shielding the sensor ring and signal cable, resulting in a 2-fold improvement. The average baseline signal range of the prior design was  $\pm 5$  mV and the value obtained with the improved design was  $\pm 2.5$  mV and the zero offset of 5.74 mV. All data collected from the sensor ring were corrected for this zero offset.

In order to verify the repeatability of the instrument readings through all the tests, a blank test was run periodically to confirm the level of base-line signal noise. These blank tests were performed under the exact same conditions, except that no powder was in the charging pipe; the tests showed the noise level invariant.

### Methodology

#### Sample Conditioning and Weighing

Powders were dried on a glass culture dish for 60 hours at 40°C in a BlueM Electric Co digitally controlled oven (BlueM Electric, Watertown, WI). This temperature was selected because some compounds can lose their water of crystallization above this temperature. The depth of the powder bed in the glass Petrie dish was kept at a maximum of 5 mm as recommended by the United States Pharmaco-

peia (USP) Loss on Drying Method.<sup>17</sup> Samples of pure compound were stored in a desiccator over silica gel and kept in the dark until they were used for the chargeability tests. Powders were weighed with a Mettler Toledo precision balance with 0.1 mg precision (model AB204, Mettler Toledo, Columbus, OH). The powders were taken out of the desiccator just before the weighing procedure, exposing the sample for approximately 3 minutes to the laboratory ambient air. Weighing paper (VWR Scientific Products Corp, West Chester, PA) was used to weigh the powder sample, and the same paper was carefully folded to deposit the powder sample into the conveying pipe through a 6.35-mm hole. An antistatic wrist strap was used to keep the researcher grounded, which yielded a noticeable improvement in the gravimetric measurement reliability.

From a previous study by Ghosh,<sup>15</sup> it was established that the chargeability of powders was more related to the powder volume than to the powder mass. Therefore, a powder sample volume of 0.5 cc was used in this study to measure the powder's chargeability. Using the powder bulk density, the mass corresponding to a volume of 0.5 cc of powder was calculated. For some compounds, the bulk density was measured in the Civil Engineering Air Pollution Laboratory following the General Method I - Measurement in a Graduated Cylinder - for Bulk Density of the USP.<sup>17</sup>

### Flow Characterization

The solid loading, defined as the mass solid flow divided by the mass gas flow, was in the very dilute regime, exhibiting a value of 0.262 g of solids per gram of air.

During powder transport through the pipe, the airflow was in the fully turbulent regime with a Reynolds number greater than 6600, which increases the particle-to-pipe contact.

### Charging Pipe Cleaning

Previous research has demonstrated the importance of surface contaminants such as powder particles and moisture,<sup>18</sup> and the type of liquid used to clean the surfaces,<sup>19</sup> on the chargeability of pharmaceutical powders. To control these effects, the stainless steel pipe was first dry cleaned with a nylon cylindrical brush and rinsed with spectrophotometric grade acetone. Immediately before the test, the pipe was washed using dry air for 15 seconds. Every test was performed with a clean pipe in order to expose the powder sample to a clean surface.

### Charge Measurement

After the pipe was introduced into the Faraday cage and positioned 6.35-mm from the sensor ring, the powder sample

was introduced into the pipe's sample inlet port. The air-flow control solenoid valve was activated for 10 seconds to blow the powder sample through the pipe, thereby tribocharging the powder, which was the fundamental difference of this approach with previous research.<sup>16</sup> This tribocharging process simulated the industrial conditions of the friction present in pneumatic conveying and mixing processes.

The sensor ring, located inside a Faraday cage, was protected from external electromagnetic interferences. The sensor ring was connected via coaxial cable to the analog-to-digital converter computer board. The charged powder cloud generated a voltage signal when passing through the sensor ring.

### Testing Active Compounds

To test the active compounds such as 5,5 diphenyl hydantoin, a suspected carcinogen, a containment system was designed, which included the Faraday cage powder "receiver" and filters housed within a standard laboratory hood.

## RESULTS AND DISCUSSION

### The Velocity Effect of Chargeability

Table 2 shows the average data for the 11 compounds studied at varying air velocities, with 3 replicas minimum per compound and per velocity. The volume specific chargeability (expressed as mV/0.5 cc) was used to calculate the statistical parameters.

**Table 2.** Mass and Volume Specific Chargeability Values of 11 Compounds at 4 Different Air Speeds\*

Compound	Air Velocity m/s	Replicates n	Sample Weight Average (g/0.5 cc)	Powder Chargeability				
				VSC				
				VSC mV/0.5 cc	SD mV/0.5 cc	CV %	95% CI mV/0.5 cc	MSC mV/g
Spray-dried lactose, NF	5.72	5	0.3354	24.28	3.86	15.9	3.38	72.38
	10.62	5	0.3356	65.78	8.69	13.2	7.62	195.99
	15.52	4	0.3355	111.19	11.40	10.3	11.17	331.40
	21.24	5	0.3354	131.21	16.41	12.5	14.39	391.20
5,5 Diphenyl-Hydantoin	10.62	7	0.2337	-7.46	ND	ND	ND	-31.90
	15.52	5	0.2351	-14.29	4.01	28	1.57	-60.80
	21.24	3	0.2346	-22.45	5.71	25	3.73	-95.70
Calcium sulfate dihydrate (Compactrol)	10.62	5	0.4705	-10.87	2.18	20.1	1.91	-23.11
	15.52	5	0.4706	-17.71	3.18	18.0	2.79	-37.64
	21.24	5	0.4706	-40.17	9.23	23.0	8.09	-85.36
Cimetidine (Tagamet)	15.52	4	0.2360	-14.78	1.99	13.5	1.95	-62.65
	21.24	3	0.2348	-26.99	2.44	9.1	2.76	-114.96
Colloidal silicon dioxide (Cab-O-Sil M5)	5.72	4	0.0167	-35.53	5.08	14	4.98	-2127.73
	10.62	4	0.0147	-72.15	12.69	18	12.43	-4925.20
	15.52	3	0.0154	-282.52	3.73	1	4.22	-18 345.58
	21.24	4	0.0173	-598.28	31.52	5	30.89	-34 582.51
Magnesium stearate	21.24	3	0.0751	-10.39	0.03	31	2.79	-138.34
Microcrystalline cellulose (Avicel PH 101)	5.72	3	0.1603	-13.96	1.40	10	1.59	-87.09
	10.62	4	0.1604	-42.86	5.08	12	4.98	-267.19
	15.52	5	0.1607	-91.93	20.40	22	17.88	-571.99
	21.24	4	0.1605	-129.53	28.68	22	28.11	-807.02
Salicylic acid	5.72	3	0.1857	-30.24	1.41	4.7	1.60	-162.86
	10.62	5	0.1791	-65.07	14.09	21.7	12.35	-363.42
	15.52	3	0.1824	-125.46	16.62	13.2	18.81	-687.94
	21.24	4	0.1816	-200.33	31.14	15.5	30.52	-1103.13
Sodium carbonate	15.52	3	0.5954	-9.08	2.82	31.0	3.19	-15.26
	21.24	4	0.5944	-12.95	2.34	18.1	2.29	-21.79
Sodium salicylate	10.62	4	0.4180	-39.81	9.22	23.2	9.03	-108.97
	15.52	15	0.4223	-61.98	20.89	33.7	10.57	-160.37
	21.24	4	0.4152	-107.55	17.94	16.7	17.58	-273.10
Sulfinpyrazone (Anturane)	21.24	3	0.1897	-9.90	ND	ND	ND	-52.19
	26.15	3	0.1428	-22.10	4.88	22.1	5.53	-154.73

\*VSC indicates volume specific chargeability; MSC, mass specific chargeability; SD, standard deviation; CV, coefficient of variation; CI, confidence interval; n, number of replicates; NF, National Formulary; and ND, nondetectable at the resolution measured.



For example, the first compound on Table 2 is spray-dried lactose. This compound was tested at 4 air speeds, starting at the highest and going down to the lowest velocity that still generated a detectable signal. For convenience, the data are presented in ascending order of air velocities. The number of replicates, presented in the next column, was in the range of 3 to 15 for all the 11 compounds and for spray-dried lactose was either 4 or 5. The average of the powder sample weight (keeping the 0.5 cc volume constant) is specified in the next column in grams. The average chargeability of spray-dried lactose after 5 replicated tests at 5.7 m/s air velocity was 24.28 mV. Because the sample volume was kept constant, this value is reported as 24.28 mV/0.5 cc. Each value of chargeability was corrected for the zero offset of the signal by adding 5.74 mV to each individual chargeability. The next column shows the standard deviation calculated from the zero-corrected data. The coefficient of variation (CV) or relative standard deviation (RSD) is presented in percentage form in the next column as well as the 95% confidence interval. Finally, the last column presents the calculated average of the mass specific chargeability (MSC), which was obtained after each individual test.

These values of chargeability are very difficult to compare with others available in the literature because the conditions of the experiments were not the same. Some similarities between tests can be found, but the dominant phenomena (ie, interactions between particles and the surface of the container) are different. For example, Reis et al<sup>20</sup> reported a negative charge when testing microcrystalline cellulose (Avicel PH101, FMC Corp., Philadelphia, PA) as received after being stored in polyethylene bags; they measured the charge using a Faraday well technique. In contrast, Watano et al<sup>21</sup> reported that Avicel PH101 exhibited a positive charge, measured by an electrostatic field sensor, when tested dried or as received in a stainless steel fluidized bed. When Murtomaa et al<sup>22</sup> tested Avicel PH200, as received, in an acrylic fluidized bed column (35% RH and 27°C) using a sensor ring, the powder exhibited a positive charge before and after fluidization.

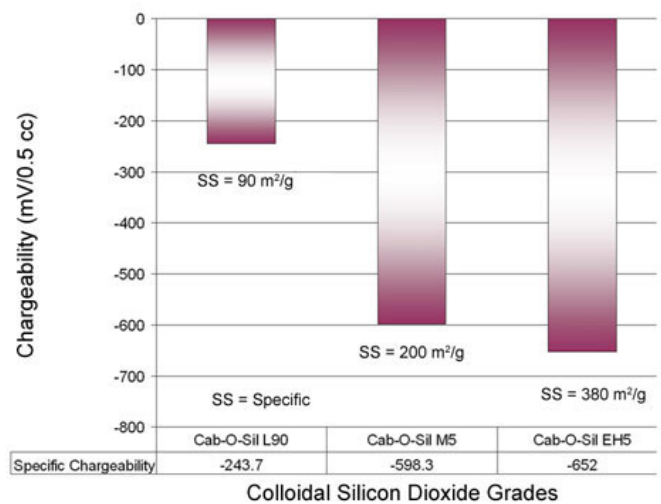
Preliminary experiments using the first generation Purdue chargeability instrument reported a positive charge for lactose after being equilibrated at 25% RH.<sup>23</sup> Watano et al,<sup>21</sup> using an electrostatic field strength sensor, reported that lactose (Pharmatose 200M, DMW, International, Veghel, The Netherlands) exhibited a positive charge during a stainless steel fluidized bed test. Bennett et al<sup>24</sup> tested crystalline and spray-dried lactose samples neutralized with a radioactive source in a stainless steel cyclone, obtaining a negative charge in both cases. Murtomaa et al<sup>22</sup> reported that lactose monohydrate (Pharmatose 80M, De Melkindustrie Veghel [DMV], Veghel, The Netherlands) exhibited a negative charge when tested as received in a fluidized bed glass column. It is clear that the chargeability values measured are very dependent on the technique used.

### The Dependence of Chargeability on Particle Size Distribution

Three different grades of Cab-O-Sil (Cabot Corp., Tuscola, IL) and 4 different grades of Avicel were tested for chargeability in our improved linear velocity/ring probe instrument. Figure 4 contains chargeability data for 3 different grades of Cab-O-Sil (ie, L90, M5, and EH5). The largest particles are L90 with a specific surface area of 90 m<sup>2</sup>/g. The M5 are medium-size particles with a specific surface area of 200m<sup>2</sup>/g, and the EH5 powder has the smallest particle sizes with a specific surface area of 390 m<sup>2</sup>/g.

Note from Figure 4 that the absolute value of the volume specific chargeability (mV/0.5 cc) increased as the particle size decreased from the L90 to the M5 grade. For smaller sizes of Cab-O-Sil (ie, EH5, the chargeability appears to plateau with respect to smaller sizes). A chargeability increase with diminished particle size was not an unexpected trend since it is known that surface area plays a part in dry powder chargeability. The smaller particle size has a greater bulk specific surface area and therefore can hold a greater charge. This property makes Cab-O-Sil an excellent candidate for a charge control agent in multicomponent mixtures.

In addition to the 3 grades of Cab-O-Sil studied, 4 grades of microcrystalline cellulose (Avicel) were studied as well. The chargeability of each grade also exhibited an inverse relationship with the particle size. The smaller the particle size, the higher the absolute value of the chargeability. The chargeability values obtained were in the range 31.12 to 68.75 mV/0.5cc, with the 2 higher chargeability values taken by the 2 smaller grades (PH105 and PH101), and the 2 lower



**Figure 4.** Volume specific chargeability (mean ± 95% CI) of 3 different grades of silicon dioxide (Cab-O-Sil) tested as received from the manufacturer. SS indicates specific surface area.

chargeability values taken by the 2 bigger grades (PH102 and PH200). These values are summarized in Table 3.

Table 3 shows the chargeability data of the 16 compounds studied at the 21.2 m/s velocity and one more powder physical parameter: specific surface area. Table 3 was sorted by the volume specific chargeability from the more positive to the more negative, to show the wide range of chargeability values among these common excipients and active ingredients. In this case the active ingredients were in the middle of the range, emphasizing the possibility of using any of the excipients on the extremes of the range to minimize the mixture chargeability.

Note how the moisture content affected the chargeability of Avicel PH101. When tested as received, its chargeability was positive, but when tested dried its chargeability measured negative. This finding showed that Avicel can hold its charge when dried and release it when its moisture content increases. Lactose showed the same charge polarity when tested dried and as received. This aspect will prove to be useful for the pharmaceutical formulators (and other dry-powder mixture manufacturers as well) because they can incorporate the powder chargeability among the set of criteria to define the formulation of dry mixtures in order to optimize their blend uniformity.

#### Instrument and Methodology Characterization

The CV was used as an indicator of the precision of the methodology and instrumentation used in this study given

that only pure compounds were used. The absolute range of values for the CV was between a nondetectable value (ND) and 33.7% (Table 2), with an average value of 16.1%.

The CV of the average values of chargeability (Table 2), calculated for each air speed of 5.72, 10.62, 15.52, and 21.24 m/s were 11% (n = 15), 15% (n = 34), 19% (n = 47), and 16% (n = 42), respectively, where n is the number of tests performed at that velocity. These values are of the same order of magnitude for comparable tests such as those completed by Zhao et al<sup>25</sup> using a vertical array of 7 Faraday pail sensors (the upper 6 with open holes on top and at the bottom, and a normal Faraday pail at the bottom), where the CV values were in the range 15.5% to 56.81% with an average value of 42.39% (n = 72). Zhao et al's tests used 3 replicas to test 3 different compounds as was done in this study. Another example of the precision obtained in measuring powder chargeability is the work of Carter et al,<sup>5</sup> who obtained an average CV of 106.85% (n = 30) when testing 1 excipient and 2 active ingredients: micronized lactose, salbutamol sulfate, and beclomethasone dipropionate (BDP). Carter et al used a cyclone separator and a Faraday well and 5 determinations for each value of chargeability.

#### Industrial Application

The chargeability of pharmaceutical compounds is expected to become a standard reported property in the pharmacopeias, given the known effect of this property on the performance of dry powders in mixtures and inhalation formulations.

**Table 3.** Summary of the Chargeability Values of 16 Compounds—Excipients and Active Ingredients—Tested at an Air Velocity of 21.2 m/s

Compound		Chargeability		Specific Surface Area m <sup>2</sup> /g
Excipients	Active Ingredients	Volume Specific mV/0.5 cc	Mass Specific mV/g	
Spray-dried Lactose NF		131.2	391.2	0.245
Avicel PH 105 (a.r.)		63.3	576.7	2.731
Avicel PH 101 (a.r.)		59.8	403.0	1.122
Avicel PH 200 (a.r.)		31.6	184.0	1.106
Avicel PH 102 (a.r.)		31.1	207.6	1.069
	Sulfinpyrazone	-9.9	-52.2	1.185
Magnesium Stearate		-10.4	-138.3	8.2
Sodium Carbonate		-13.0	-21.8	1.038
	5,5 Diphenyl-Hydantoin	-22.5	-95.7	0.863
	Cimetidine	-27.0	-115.0	0.67
Compactrol		-40.2	-85.4	3.15
	Sodium Salicylate	-107.6	-273.1	0.125
Avicel PH 101		-129.5	-807.0	1.122
	Salicylic Acid	-200.3	-1,103.1	0.256
Cab-O-Sil, I90		-243.7	-10 161.5	90
Cab-O-Sil, M5		-598.3	-34 582.0	200
Cab-O-Sil, EH5		-652.0	-32 357.0	380

a.r. indicates as received.

The present work could be the starting database of a multi-institutional effort to classify all the common excipients used today in pharmaceutical formulations using this inexpensive and portable instrument.

## CONCLUSIONS

The results showed that there are common excipients, such as colloidal silicon dioxide, that have the potential to be used as charge control agents and that these can be identified by this instrument and methodology. The sensitivity of the Purdue instrument allows the measurement of chargeability of different grades (with different particle size distributions) of the same compound, which has the potential to enhance the formulation optimization process, especially when the excipient options are limited or the available amounts of new active compounds is small.

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## REFERENCES

1. Bailey AG, Hashish AH, Williams TJ. Drug delivery by inhalation of charged particles. *J Electrostatics*. 1998;44:3–10.
2. Lucas P, Anderson K, Potter UJ, Staniforth JN. Enhancement of small particle size dry powder aerosol formulations using an ultra low density additive. *Pharm Res*. 1999;16:1643–1647.
3. Zeng XM, Martin GP, Marriot C. *Particulate Interactions in Dry Powder Formulations for Inhalations*. New York, NY: Taylor and Francis; 2001.
4. Staniforth JN, Rees JE. Electrostatic charge interactions in ordered powder mixes. *J Pharm Pharmacol*. 1982;34:69–76.
5. Carter PA, Rowley G, Fletcher EJ, Hill EA. An experimental investigation of triboelectrification in cohesive and non-cohesive pharmaceutical powders. *Drug Dev Ind Pharm*. 1992;18:1505–1526.
6. Rogers B. Difficulties associated with compounding metered-dose inhalers and dry powder inhalers [Powerpoint presentation]. *U.S. FDA, Center for Drug Evaluation and Research, Office of New Drug Chemistry, Pharmacy Compounding Advisory Committee*. Available at: [http://www.fda.gov/ohrms/dockets/ac/00/slides/3634s1\\_07\\_rogers.ppt](http://www.fda.gov/ohrms/dockets/ac/00/slides/3634s1_07_rogers.ppt). Accessed: July 19, 2003.
7. Wade EA, Weller PJ, eds. *Handbook of Pharmaceutical Excipients*. 2nd ed. Washington, DC: American Pharmaceutical Association; 1994.
8. Cabot Corporation. Cab-O-Sil untreated fumed silica properties and functions [catalog no. TD-100]. Tuscola, IL: Cabot Corporation; 1993.
9. Bavin PMG, Post A, Zarembo JE. Cimetidine. In: Florey K, ed. *Analytical Profiles of Drug Substances*. vol. 13. Orlando, FL: Academic Press; 1984.
10. Kibbe AH, ed. *Handbook of Pharmaceutical Excipients*. 3rd ed. Washington, DC: Pharmaceutical Press; 2000.
11. Pujara CP. *Determination of Factors That Affect the Generation of Airborne Particles From Bulk Pharmaceutical Powders* [thesis]. West Lafayette, IN: Industrial and Physical Pharmacy, Purdue University; 1997.
12. Abounassif MA, Mian MS, Mian AA. Salicylic acid. In: Brittain H, ed. *Analytical Profiles of Drug Substances*. vol. 23. Orlando, FL: Academic Press; 1994.
13. Sodium Salicylate MSDS. Available at: [www.skylighter.com/msds/sodium\\_salicylate.txt](http://www.skylighter.com/msds/sodium_salicylate.txt). Accessed: July 19, 2003.
14. Monograph 8541. Sodium Carbonate. In: Budavary S, ed. *The Merck Index*. 11th ed. Whitehouse Station, NJ: Merck & Co; 1989.
15. Ghosh R. *Pharmaceutical Powder Chargeability and Dustiness Characterization* [thesis]. West Lafayette, IN: Purdue University; 1997.
16. Gajewski JB, Szaynok A. Charge measurement of dust particles in motion. *J Electrostatics*. 1981;10:229–234.
17. USP. *US Pharmacopeia National Formulary*. Rockville, MD: USP; 1999.
18. Eilbeck J, Rowley G, Carter PA, Fletcher EJ. Effect of contamination of pharmaceutical equipment on powder triboelectrification. *Int J Pharm*. 2000;195:7–11.
19. Murtomaa M, Harjunen P, Mellin V, Lehto V-P, Laine E. Effect of amorphicity on the triboelectrification of lactose powder. *J Electrostatics*. 2002;56:103–110.
20. Reis GE, Bierly JN, Schwartz JB. Characterizing electrostatic charge in pharmaceutical powders. *Am J Pharm*. 1984;156:100–105.
21. Watano S, Suzuki T, Taira T, Miyanami K. Continuous monitoring and mechanism of electrostatic charge of powder in fluidized bed process. *Chem Pharm Bull (Tokyo)*. 1998;46:1438–1443.
22. Murtomaa M, Rasanen E, Rantanen J, et al. Electrostatic measurements on a miniaturized fluidized bed. *J Electrostatics*. 2003;57:91–106.
23. Swaminathan V, Kildsig DO. Effect of particle morphology on the physical stability of pharmaceutical powder mixtures: effect of surface roughness of the carrier on the stability of ordered mixtures. *Drug Dev Ind Pharm*. 2000;26:365–373.
24. Bennett FS, Carter PA, Rowley G, Dandiker Y. Modification of electrostatic charge on inhaled carrier lactose particles by addition of fine particles. *Drug Dev Ind Pharm*. 1999;25:99–103.
25. Zhao H, Castle GSP, Inculet II. The measurement of bipolar charge in polydisperse powders using a vertical array of Faraday pail sensors. *J Electrostatics*. 2002;55:261–278.