Contribution of electrostatic interactions to the dispersion of powders for inhalation

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Abstract - The purpose of this study was to explore the relationship between the charge developed on dry particles and the dispersion. The system chosen for this study is a true pharmaceutical chemical entity for pulmonary delivery, tested in the clinic. The type of analysis used is important to assess the behavior of powders. Two polymorphs, A and B, of the same drug were used for the study. The drug was micronized and mixed with coarse carrier lactose hydrous. Both pure components and binary blends drug-lactose were used for the electrostatic characterization. The electrostatic charges developed upon drug detachment were measured by two methods: static and dynamic. The measurement of charges developed by the pure neat drug showed more electrostatic developed and exhibits faster charge decay. These results suggest that the greater electrostatic nature of drug favors the formation of agglomerates of this crystal form. The forces of adhesion of solid particles to surfaces have been addressed and the charges developed by the detachment of the drug will be discussed for each polymorph.

Introduction

The formulation of dry powder for inhalation requires micronized drug. Milling is regularly used in pharmaceutical solid processing to reduce particle size to the desired level and distribution. Intensive mechanical energy is used to generate sufficient strain on the solid particles so as to cause crystal lattice disruption, followed by crack initiation, crack propagation and fracture. This high-level energy processing could induce physical instability of the material. Charge development is one manifestation of this instability. The electrostatic charge measurements of pharmaceutical dry powders have been addressed by several investigators [1, 2, 3, 4, 5]. Electrostatic measurements on powders can be classified into two types, depending on the experimental setting: static and dynamic methods. Both types of methods provide information on the charges generated upon powder movement. The static method is considered useful for information during mixing, pouring and filling, whereas the dynamic method gives useful information during fluidization or aerosolization of powders.

The static method for evaluation of the electrostatic characteristics of dry powder inhaler formulations is the shallow Faraday well static charge detector (SFC). The dynamic

method used herein is a variation of the Faraday cage dynamic charge detectors, the capacitor interchangeable mesh (CIMFC).

The electrostatic charges produced by powders were measured using SFC and CIMFC. These apparatus are essentially capacitors, where two plates of a conductor material are isolated from one another by a dielectric. In this study the conducting material in the apparatus is brass and the dielectric materials is PTFE (CIMFC). The inner container is connected to an electrometer (Type 610C, Keithley Instruments, Cleveland, OH, USA) by a shielded co-axial cable, which measures charge. When a charged material is introduced into the well, an equal and opposite charge is induced on the inner walls of the well. The induced charge is then measured by the electrometer. The charge measured by the electrometer is based on the following equation:

$$\left[C = \frac{Q}{V} \right] \qquad (1)$$

where C is the capacitance, Q is the charge and V is the applied voltage.

The electrostatic charge measurements of powders from the different Faraday wells were used to obtain the average charge-to-mass ratio generated on the detached drug particles off the carrier. The following equation was used for this determination:

$$\left[Q_{sp} = \frac{Q}{m} \right] \qquad (2)$$

where the mean specific charge, Q_{sp}, is obtained by the charge magnitude, Q, and the mass, m, of the powder. The specific charge is determined by the charge to mass of material ratio for SFC. For the CIMFC, the total charge was measured rather than the specific charge [5].

The present study investigated the contribution to the solid-solid interactions, electrostatic, between a micronized drug, and lactose as the coarse carrier. The drug was used in two different crystal modifications. The electrostatic characterization was carried out on pure components as well as on powder blends. Static methods were used for the characterisation of pure materials, whereas dynamic methods were used for the characterisation of powder blends. This distortion of the crystal lattice is a manifestation of interactions upon actuation of the device.

Materials and Experimental Conditions

Micronized drug, polymorphs A and B; coarse carrier lactose hydrous used for the electrostatic characterization of pure components and drug-carrier powder binary blends (1-50% w/w drug:carrier). Experiments were conducted in a controlled environment of temperature (T) and relative humidity (RH). Temperature was set between 20.6°C and

22°C and the relative humidity between 24% to 30 % (Honeywell T and RH room controller; RH was also monitored with a pocket meter), unless otherwise stated. Six replicate determinations were carried out for each powder sample.

Results

Table 1 shows that the two drug polymorphs and lactose developed negative charges following flow off chutes of the materials tested. Lactose being a sugar is very rich in one functional group: hydroxyl, the location of the single ether group in the molecule makes it virtually inaccessible for surface to surface contact with other materials at the macroscopic level. The abundance of oxygen atoms throughout the lactose molecule provides a highly electronegative surface for this material at any scale. The molecular structure of possesses carboxyl and amide functional groups that could also make the drug behave as an electron acceptor.

Since two polymorphs have the same chemical structure, they will have exactly the same molecular electrostatic tendencies. Whether the two different molecular arrangements in the crystal translate into a difference in macroscopic electrostatic properties, will depend on how well electronegative groups can be hidden and exposed on one surface versus the other. Table 1 shows that the two polymorphs develop very similar charges. This indicates that the two crystal modifications have surfaces with similar average, i.e., macroscopic, electronegativities. The fact that both drug and carrier develop negative charges suggests that the drug lactose attraction will include a weakening element as to allow subsequent detachment. But since carrier and drug charges do not have the exact same magnitude, net attraction will prevail. The larger the difference in magnitude of electropositive and electronegative charges of two powders, the greater the attraction, and the charge for materials of relatively large surface area, e.g. micronized drug, registered significantly higher charge values than those of the lactose.

The large surface area of the two micronized polymorphs compared with that of lactose offers greater opportunity for particles to develop charges. Charge values about ten-fold higher were registered for the drug particles following flow on the metal surfaces than for lactose particles. This ratio is of the same magnitude as the ratio of specific surface areas. The charge value for drug particles after moving through the perspex chute was, however, just a little higher than the lactose particles. This result is quite possibly explained by the fact that perspex is itself a material rich in electronegative (ester) groups; tribocharge of two electronegative materials is hindered by the inability of one of the materials to develop a stable positive charge.

Static measurements, of the pure materials following flow on chute are useful to determine the charge of the materials but it is also likely to be limited in terms of the ability to offer differences between polymoprhs A and B, since the magnitude and polarity was similar for both. However, detailed measurements of the electrostatic charges provide useful information with respect to the behaviour of particles involved in the formation of powder ordered mixes.

Table 1 Mean specific charge for drug Ro 24-5913 and carrier lactose powders following contact with metal and PMMA surfaces (n=5).

			Perspex (PMMA)	***Stainless Steel***
Material		Polarity	Mean Specific Charge $C \times 10^9\ g^{-1} \pm SD$	
α-Lactose monohydrous (45-106 μm)		-	2.721 (0.179)	0.343 (0.101)
Micronized Drug	A	-	3.860 (0.112)	4.020 (0.320)
	B	-	3.676 (0.139)	4.141 (0.278)

Figure 1 shows the device of the CIMFC "blow-off" [6] used in this study. Independently of the polarity of the charge that develops, an increase in net charge is an indication of drug detachment.

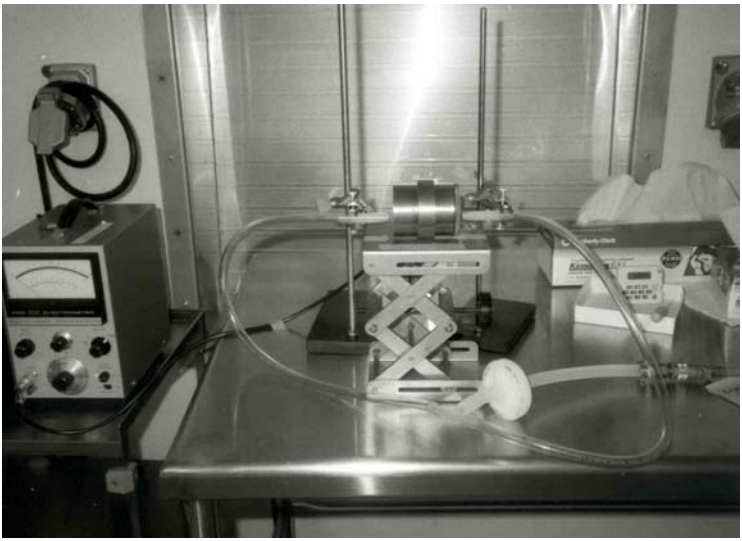

Figure 1 Photograph of the CIMFC system used for measuring charges during fluidization.

Figure 2 shows higher charges at lower drug loads. On the other hand, however, the results of centrifuge studies [7] show that the extent detachment, for both polymorphs, increases with drug load. These two events can coexist in a system where particle rearrangement brings about charge neutralization. The charging characteristics of the drug polymorphs may have changed due to the adhesion or adsorption of the different drug concentration on lactose surface forming multilayers. A monolayer is sufficient to change the work function of the surface, completely altering the electrification. Multilayers could result in modifying even further the charging characteristics on the detachment from the single or monolayer of the drug on the lactose surface. This experiment also demonstrated that on the detachment micronized materials have larger work function than lactose. When two contacting materials of different work function are separated, the charge left on the surface with greater work function is of negative polarity [8]. The surface of smaller work function becomes positively charged. Figure 2 also show that, under dynamic conditions, polymorphs A and B exhibit different electrostatic behaviour. At 5% drug load, polymorph A exhibits a sharp drop in charge, whereas polymorph B exhibits the greatest charge. In addition, polymorph B trend toward electroneutrality occurs gradually with increasing drug load. Even though the results obtained with polymorph B do not allow casting out cohesion as particles rearrange mechanism, they suggest that particle adhesion is more significant at least in relation to polymorph A.

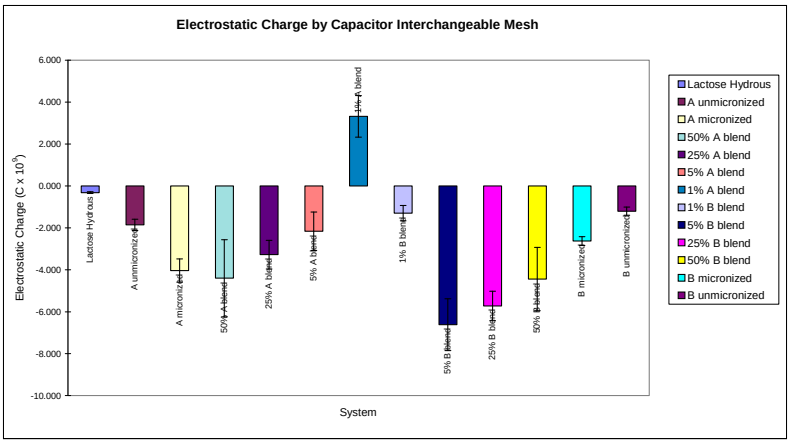

Figure 2 Graphic representation of the electrostatic measurements by capacitor interchangeable mesh (CIM). Mesh used 45-µm (n=7)

This result, and the gradual decrease in charge with increased concentration produced with polymorph B, suggests that adhesion is a more significant mechanism for rearrangement in this case. The electrostatic behaviour of polymorphs A and B is similar under static conditions, but quite different under dynamic conditions. The results obtained suggest that polymorph A has a significantly higher tendency to form drug particle agglomerates preventing good dispersion.

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