Arising of electrostatic charge in the mixing process and its influencing factors

Stefan Karner [a,*], Nora Anne Urbanetz [a,b]

[a] Institute for Process and Particle Engineering, Graz University of Technology/Austria
[b] Research Center Pharmaceutical Engineering GmbH, Graz/Austria

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ABSTRACT

The aim of this work is to improve the understanding of how triboelectric charge arises on pharmaceutical powders and of how it can be influenced and controlled especially with respect to dry powder inhaler development. In the present work the triboelectric properties of mannitol are examined because very few literature treating this new alternative carrier material for dry powder inhalers is available. To study the very complex triboelectric charging process in a simple and controlled way mixing studies are carried out. The powder samples are blended in polypropylene and stainless steel mixing containers for defined durations using a tumble blender (T2F Turbula®, Willy A. Bachofen AG — Maschinenfabrik, Switzerland) and then poured into a Faraday cup where charge measurement is performed. Several influencing factors like mixing time, particle size, mixing container size and the addition of a fines fraction to the powder are studied. In contrast to other published literature the present work focuses on the new alternative carrier material mannitol and uses statistical tools like design of experiments (DOE) to check the significance of the influence of factors and also the interactions between the influencing factors. The study reveals a direct relationship between the arising charge and the container size as well as the fines fraction and an indirect relationship between the arising charge and the particle size. Further also three different charge dissipation scenarios are investigated. It is shown that charge dissipation to the atmosphere is negligible within an hour. Keeping the powder inside the mixing container allowing charge dissipation via the container walls is more effective. Additional grounding of the mixing container does not result in a significant enhancement of the dissipation process. This is because charge transport from the powder bulk to the mixing container walls is limited.

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1. Introduction

Drug delivery to the lungs via Dry Powder Inhalers (DPIs) has become more and more important in the last decades. In order to be deposited in the deeper lung, it is essential that the drug particles of DPIs have an aerodynamic diameter between 0.5 μm and 5 μm [14]. Unfortunately such fine powders are very cohesive resulting in poor flowability and dosing behavior. One possibility to improve these properties is to mix the small drug particles with larger carrier particles. These carrier particles are usually made of lactose or glucose and have a particle size between 50 μm and 200 μm. An alternative carrier material which is still under investigation is mannitol [28]. Mixing, flowability, dosage uniformity as well as the very important drug detachment of the active from the carrier surface of ordered mixtures upon inhalation are governed by the interparticle interaction between drug and carrier which mainly arises through Van der Waals and electrostatic forces. This may result in various problems with respect to mixing homogeneity, dosing and lung deposition. Nevertheless charging of particles may also be exploited to enhance mixing

uniformity of powder blends or may be advantageously used for dry powder coating of tablets for example [15,18]. In addition to this the triboelectric charge carried by aerosolized powders may influence the release of the formulation from the inhaler and the deposition behavior of the particles in the throat and lung [29]. Telko et al. mentioned that a controlled electrostatic charge on inhalation powders could be exploited for targeting different lung physiologies.

Electrostatic charge is generated when two different materials are brought into contact and then separated [16]. Since drug as well as carrier particles consist of insulating material, they are unable to dissipate and therefore accumulate charge in any process where the powder comes into contact with surfaces. In which way sign and magnitude of the charge is influenced is still poorly understood and therefore difficult to predict. This problem gets even more complex when two or more materials and more than one varying influencing factor is involved. Especially the arising of charge in metal/insulator contact and insulator/insulator contact is very complex [33]. Unfortunately particularly this case appears in many pharmaceutical processes and also in DPI-technology. Different models to describe charge generation and accumulation like the ion transfer model [7], the surface state model (electron transfer model) of [4] and the two step model (electron transfer model) of [33] have been presented. Further [6] presented a semi-quantitative triboelectric series to estimate how

* Corresponding author. Tel.: +43 316 873 7494; fax: +43 316 873 107494.
E-mail address: stefan.karner@tugraz.at (S. Karner).

different materials will charge when they are brought into contact. Nevertheless only a small number of scientists published literature dealing with electrostatic charge on pharmaceutical powders until now.

As mentioned above the sign and magnitude of the arising charge depend on many factors such as particle size and shape [3], surface roughness [8,30], nature and work functions [2], impurities [9,10,22], amorphicity [23], contact material [11], relative humidity [20] and the energy of contact [31,32]. A summary of these influences can be found at [19].

The best way to get reproducible basic data concerning the complex arising of electrostatic charge is to focus on a simple and controlled process. Maybe the most important and common powder handling process in pharmaceutical industry is mixing. Therefore the present work focuses on the arising of triboelectric charge in the powder mixing process and the factors impacting charge acquisition of mannitol as carrier for DPI´s.

Naturally, mixing studies have been performed before by other scientists like [11–13,35]. [11] laid their attention on the dependence of the electrostatic charge on different mixing container materials and blends of different APIs and α-lactose monohydrate. They further tested the influence of relative humidity.

[12] first measured the arising netcharge in a tumble-blender for different size fractions of dicalcium phosphate dihydrate. Then they checked the efficacy of hold time after mixing and equipment grounding for charge dissipation using different grades and size fractions of microcrystalline cellulose and binary mixtures of API and excipient. [13] tried to correlate the triboelectric charging data of mixtures of different APIs with their dielectric properties.

[35] measured the arising netcharge in stainless steel containers mounted on a tumble blender and a horizontally oscillating blender for adipic acid, glycine and MCC as a function of the mixing time. They further checked the influence of the particle size fraction, the mixing speed and the relative humidity.

Beside the above mentioned investigations on mixing there is more literature available concerning the electrostatic charging behavior of pharmaceutical powders when subjected to other unit operations. But these shall not be mentioned here because this work focuses on the mixing process.

It has to be pointed out that most of the above mentioned publications just focused on the influencing factors one by one and in doing so neglect that there might be interactions among them. For this reason the present paper utilizes statistical tools like design of experiments (DOE) in order to check the significance of the factors and interactions of more than one factor.

Since triboelectric studies dealing with lactose have already been carried out in the past by [3,9,10,21,26,5,11,23–25,29] and not much literature regarding the electrostatic properties of mannitol is available the focus of the present work lies on the charging behavior of this alternative carrier material. The authors are aware that there is also literature available dealing with the electrostatic properties of mannitol [1,27]. Therefore the focus of this work was laid on other factors and investigation principles.

In this study three important factors are chosen to be analyzed using statistical design of experiments (DOE), first the particle size as it had shown to have a strong impact on the arising of charge in other materials in previous studies [26,35]. As the second factor the size of the mixing container is chosen because the area of the inner surface of the container and also the filler loading might influence the charge exchanged between the powder and the vessel. The third influencing factor is the amount of mannitol fines (the percentage of a 0 μm–40 μm mannitol fraction) in a blend with coarser mannitol particles. This is relevant for the DPI technology because it is a common practice to add carrier fines to a DPI formulation in order to increase the respirable fraction [34]. Further also detailed studies on the influence of the mixing time and the particle size are performed.

All measurements are carried out in polypropylene and stainless steel mixing containers using a tumble blender (T2F Turbula®, Willy A. Bachofen AG-Maschinenfabrik, Switzerland). In addition to the charging experiments also charge dissipation of charged powders in stainless steel containers are checked. Three scenarios are tested. Charge dissipation to the atmosphere is checked by leaving the charged powder in the faraday cup. Charge backflow to the mixing container is tested by leaving the powder in the mixing container after blending. And further the possibility to enhance this charge backflow by grounding the mixing containers is checked.

Although mannitol is an alternative to lactose in this paper just the properties of mannitol are investigated and no quantitative comparisons between mannitol and lactose are carried out. This is because comparisons between substances are difficult due to probable differences of other influencing factors like particle roughness, particle shape and amorphicity of both substances as well as the relative humidity of the surrounding environment beside the factors under investigation. For the same reasons also no quantitative comparisons to results reported in literature dealing with mannitol are undertaken. Only slight divergences in the particle properties or measurement principles can generate big differences in the results since the electrostatic charging process is extremely sensitive to a multitude of factors.

2. Materials and methods

2.1. Materials

Crystalline mannitol was donated by Roquette Frères (160 °C, Roquette Frères, Lestrem, France). As mixing containers 60 ml and 125 ml polypropylene jars are used. The 60 ml jar has an internal diameter of approximately 38 mm and an inner height of 53 mm. The 125 ml jar has an internal diameter of approximately 50 mm and an inner height of 64 mm. Further also stainless steel containers are used. Unfortunately they were not available in the same size as the polypropylene containers. Consequently the difference in size was balanced by adjusting the sample size for the stainless steel containers. Containers with a volume of 25 ml (inner diameter: 31 mm; inner height: 33 mm) and 75 ml (inner diameter: 49 mm; inner height: 40 mm) are used.

For conditioning, the powder samples are stored inside a climate box (see Section 2.2). The constant relative humidity inside this box is generated using saturated salt solution of potassium carbonate (43% at room temperature; [17]).

2.2. Sample preparation

Mannitol is size fractionated by sieving. It is mechanically sieved into size fractions of 0 μm–40 μm, 40 μm–63 μm, 63 μm–80 μm, 80 μm–100 μm, 100 μm–125 μm, 125 μm–160 μm using a sieve shaker (Analysette®, Fritsch, Germany).

In order to gain correct and reproducible experimental results it is of main importance that the powder samples are electrically discharged and equilibrated at a defined and constant relative humidity before performing the experiments. This is carried out by storing the powder samples in thin layers in earthed metal containers inside a climate box (proprietary construction) at constant relative humidity for at least 72 h. Sample size was set to 10 g for the polypropylene containers and 5 g for the stainless steel containers.

Discharging the insulating polypropylene mixing containers is difficult but important for correct measurement results. Therefore the containers are rinsed with deionized water first and then with ethanol to remove charges from their surface. After drying they are also stored open inside the climate box on an earthed metal plate for 72 h. Even though the charge transport on the surface of the polypropylene is very slow this should remove the residual charge from the containers. After this procedure the containers are only handled extreme carefully wearing insulating gloves and just as much as