An overview of the state of the art on mitigating electrostatic interference during aerodynamic testing

Yang Chen[1], Johan Rene Keegstra[2]

on behalf of the Electrostatic Sub-Team of the European Pharmaceutical Aerosol Group (EPAG)

[1]Respiratory Technology, Woolcock Institute of Medical Research, NSW 2037, Australia.

[2]Sandoz International GmbH, Industriestrasse 25, 83607 Holzkirchen, Germany

Summary

Background: In the pharmaceutical industry, electrostatic phenomena have been a topic of debate and research for many years. It has an impact on formulation performance, especially with powders. In most aerosol formation processes, like emission of droplets from a metered dose inhaler or particles from a dry powder inhaler, electrostatic changing occurs through either contact or friction between different particulates and material surfaces, as well as induction charging. Those electrostatic charges are omnipresent, very difficult to control, almost impossible to eliminate and it can significantly influence particle behavior.

Materials and Methods: A survey was developed based on the knowledge derived from literature and from expert opinions of the EPAG (electrostatic sub group) members. It consisted of two standardised questionnaires: 1) the effectiveness of different measures and, 2) methods used for minimising electrostatic interference during aerosol testing. A personal email invitation was send to representatives from 7 organisations. The survey asked participants to rank the measures used to reduce electrostatic according to their experience and knowledge, following a score system.

Results: The findings from this preliminary survey showed a lack of information and consensus on how to measure and minimise electrostatics during aerosol analysis, with the majority of the measures currently available not extensively used by pharmaceutical organisations.

Conclusions: How to measure and minimise electrostatics during aerodynamic testing of pharmaceutical is an important issue. Further extensive data will need to be collected to achieve a full overview of this problem and how it should be approached and standardised in the future.

Introduction: In the pharmaceutical industry, electrostatic phenomena have been a topic of debate and research for many years. It has a vast impact on formulation performance, especially where powders are used [1-4]. In most aerosol formation processes, like emission of droplets from a metered dose inhaler or particles from a dry powder inhaler, electrostatic changing occurs through either contact or friction between different particulates and material surfaces, as well as induction charging from a nearby electric field [5-7]. Those electrostatic charges are omnipresent, very difficult to control and almost impossible to eliminate and, at high charge magnitude, it can significantly influence particle behavior such as deposition rates and patterns [2].

During 1940s to 1980s, extensive theoretical studies demonstrated that deposition of particle is significantly increased when particles are electrostatically charged [8-10]. These findings were then proven using physical, animal and human lung models, raising an interest is the possibility to use such phenomena to improve pulmonary drug delivery [11-13]. However, during routine aerosol performance evaluations, electrostatic charges can be a nuisance especially for aerodynamic testing. In 2004, Saini *et al* demonstrated that aerosols with net neutral charge were deposited in the lower stage of an Andersen cascade impactor, whereas particles with a net positive or negative charge were deposited in the upper stages. Therefore, if not carefully controlled, electrostatic charges carried by aerosols could interfere with the measurement of the aerodynamic particle size distribution, biasing results [14]. Different measures and methods have been utilised during aerosol studies to minimize the interference of electrostatic charges on aerosol performances including control of the testing environmental conditions, equipment use and antistatic techniques. However, there are mostly used 'anecdotally', many lacking evidence and effectiveness, with no standard empirical protocols for aerodynamic testing available for the control and minimization of electrostatics. Therefore, the objective of this study was to generate a survey analysis on how and which are the techniques used in practice to minimize electrostatic interference during the aerosol testing and assess their effectiveness *in vitro*.

Method: A survey was developed based on the knowledge derived from literature and from the expert opinions of the EPAG (electrostatic sub group) members. It consisted of two standardised questionnaires on: 1) the effectiveness of different measures and, 2) methods used for minimising electrostatic interference during aerosol testing. A personal email invitation was sent to representatives from 7 organisations (6 pharmaceutical industries and one academic research institute). The survey requested the participants to rank the measures used to reduce electrostatic according to their experience and knowledge, following a score system (0-5) showed in Figure 1. In total, 7 complete responses were received, anonimised and basic quantitate and qualitative analyses were performed.

Rank the measures to reduced electrostatic interference
5. Proven effective (firm data evidence)
4. Known to be effective (limited data evidence)
3. Known to be effective (qualitative evidence only)
2. Theoretically effective (no data evidence)
1. Not effective (does not work)
0. Not applicable

Rank the methods of measure
4. Proven effective (data evidence)
3. Known to be effective (qualitative evidence only)
2. Theoretically effective (no data evidence)
1. Non-effective
0. Not applicable

Figure 1: Rankings score used in the survey for measures and methods used to reduce electrostatic interference in aerosol testing.

Results: Figure 2 has shown the results of questionnaires regarding the measures taken by the responders to minimise electrostatic interference during aerodynamic testing. Results from the participant organisations were blinded and presented by a unique identification number. The y-axis shows the ranking of the different measures based on the average of the score obtained from the survey responses, listed in descending order from top to bottom The numbers on x-axis represents the responders that ranked the effectiveness of those measures. 4 out of 7 organisations have indicated that temperature and humidity control is proven to be effective in controlling electrostatics during aerosol analysis, consequently this was ranked with the highest score at an average of 4.1 out of 5. This is consistent with previous findings where relative humidity has been shown to significant influence aerosol electrostatic charges [15]. Other methods commonly used to mitigate electrostatic charge did show variable responses regarding their effectiveness in aerodynamic testing, such as: 1) apply resting time between shots, 2) use of gloves and wristband, 3) grounding the equipment and equilibration before aerodynamic testing. Inconsistent use of antistatic equipment such as antistatic floor, mat and clothing, electrostatic gun and eliminator etc., were observed to be used between the 7 organisations, with an average of 50% indicating the measures were not consistently used during aerodynamic testing (Figure 2). 1 out of 7 organisations ranked the assembly of equipment and use of antistatic boots as not effective in controlling aerosol electrostatics, and only 1 organisation responding that the use of electrostatic balance, automation testing and antistatic boots cover were only effective theoretically (Figure 2).

Results of this first part of the survey on the effectiveness of different measures used during aerodynamic testing to minimise electrostatic interference, although small in number, gives an indication of the fact that no standard procedures are currently used during pharmaceutical aerosol analysis. Furthermore, the measures used are not scientifically proven for their effectiveness.

The second questionnaire included in the survey was to assess the effectiveness of different methods used during aerodynamic testing for minimise electrostatic interference and results are shown in Figure 3. Four out of seven organisations indicated that using accurate methods and ensuring results reproducibility were proven to be effective in minimising electrostatic interference during aerosol performance tests.

The measure of the presence of static electricity distribution was found to be the lowest ranked in the survey, with six out of seven organisations responding ‘not applicable’ (Figure 3). Mass balance comparison between testing batches was ranked with an effectiveness score at an average of 2.86 out of 5, while the majority of the organisations during aerodynamic testing did not practice total mass balance determination (including device recovery and stages). At the same time, marketed and in-house built equipment such the Electrical Low Pressure Impactor (ELPI, Dekati, Finland) [16] and the electrical Next Generation Impactor [17], respectively, were shown not to be extensively used during aerosol analysis, consequently the result presented in this survey could be biased and more investigations are needed.

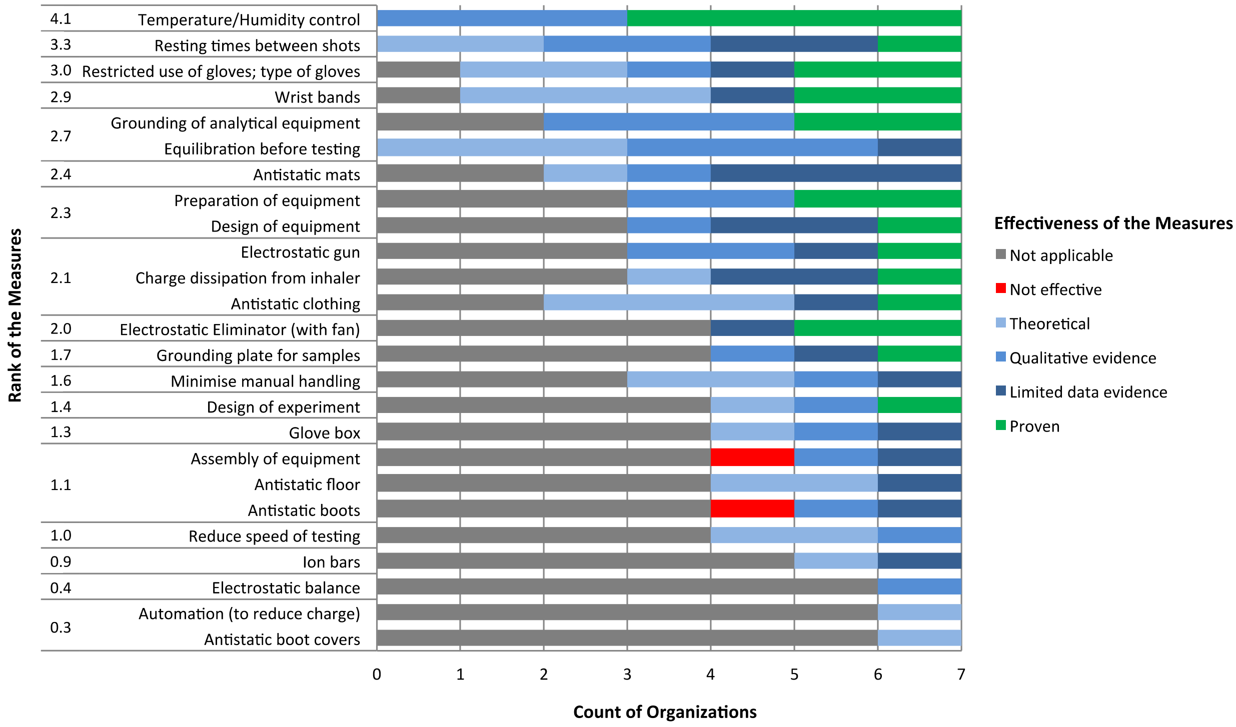

Figure 2: Rank-ordered survey responses from 7 organisations on the effectiveness of different measures used during the aerodynamic testing for reducing electrostatic interference.

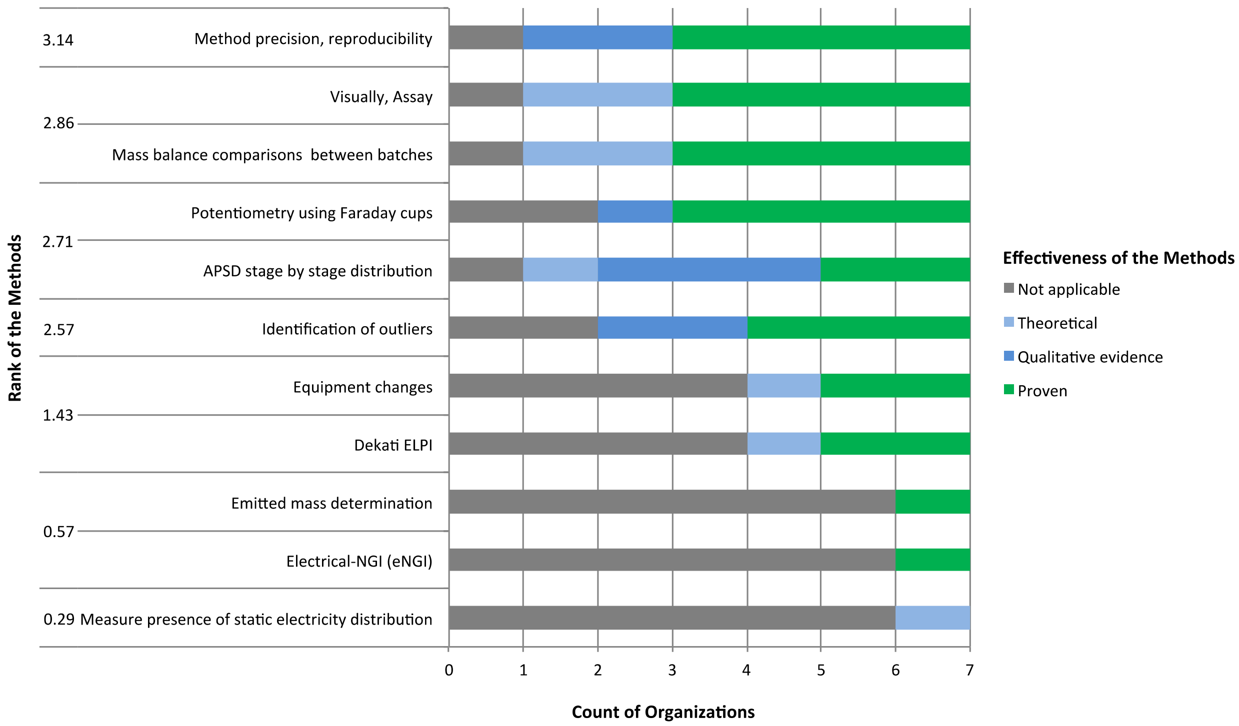

Figure 3: Rank-ordered survey responses from 7 organisations on the effectiveness of the methods used during aerodynamic testing for reducing electrostatic interference.

Conclusions: The findings from this preliminary survey showed a lack of information and consensus on how to measure and minimise electrostatics during aerosol analysis, with the majority of the measures currently available not extensively used by pharmaceutical organisations. Furthermore, most of the methods used for controlling aerosol electrostatic charges were based on theoretical predictions and no standard protocol for aerodynamic testing with consideration of electrostatic charge interference existed.

For the next stage of this work, the EPAG Electrostatic Sub-committee is planning to expand this survey to include a larger number of pharmaceutical organisations and academic research institutes to generate a larger sample survey on how electrostatic charges are controlled during aerosol analysis. The results of the survey will contribute to the improvements of current aerosol testing technology and provide better aerosol aerodynamic testing outcomes.

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