

A QbD approach to optimization of Cascade Impaction methods for measuring Aerodynamic Droplet Size Distribution for Nasal pMDI products

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INTRODUCTION

There is a need to control droplet size distribution (DSD) in nasal pharmaceutical products. Both the European Medicines Agency (EMA) ⁽¹⁾ and the US Food and Drug Administration (FDA) ⁽²⁾, provide guidance to quantify the fine material of nasal products based on in-vitro tests. A range of non-impactor analytical techniques have been evaluated but laser diffraction (LD) is the analytical technique typically used within the industry⁽³⁾. LD has significant disadvantages in that it cannot distinguish the API from other components of the formulation and it measures geometric DSD rather than the aerodynamic DSD. Methodology has recently been reviewed for measuring the Fine Particle Mass of nasal pharmaceutical products, in particular the proportion of the product with a diameter less than 10 micron⁽⁴⁾. Several Nasal Induction Ports (NIPs) were evaluated to interface between nasal pharmaceutical products and cascade impactors. This is particularly important for nasal aqueous spray products where there is an interest in how much drug will pass through the nasal cavity and enter the human lung. The big differences between nasal aqueous sprays and nasal pMDI products are that nasal pMDI products typically have much smaller diameter droplets (a significant proportion less than 10 micron) and they travel at a much higher velocity. This publication will consider a Quality by Design (QbD) approach^(5,6), to developing robust Cascade Impaction (CI) for methodology nasal pMDIs.



Figure 1: Andersen Cascade Impactor with 1 litre glass induction port

METHODS

An example of a typical experimental setup for cascade impaction of nasal pMDI products is shown in Figure 1, showing an Andersen Cascade Impactor (ACI) with a 1 litre glass induction port. Testing was performed with an air flow rate of 28.3 l/min.

A QbD approach can be adopted for assessing the critical parameters which affect CI measurements, as shown in Figure 2. Each parameter is assessed and assigned as a Control Factor, an Experimental Factor or a Noise factor⁽⁶⁾. A feature of CI analytical methodology is that a large number of the variables can be considered to be either Control Factors or Noise Factors and there are very few factors which can be experimentally varied over a range of values so that the effect of small changes be assessed for influence on CI data.

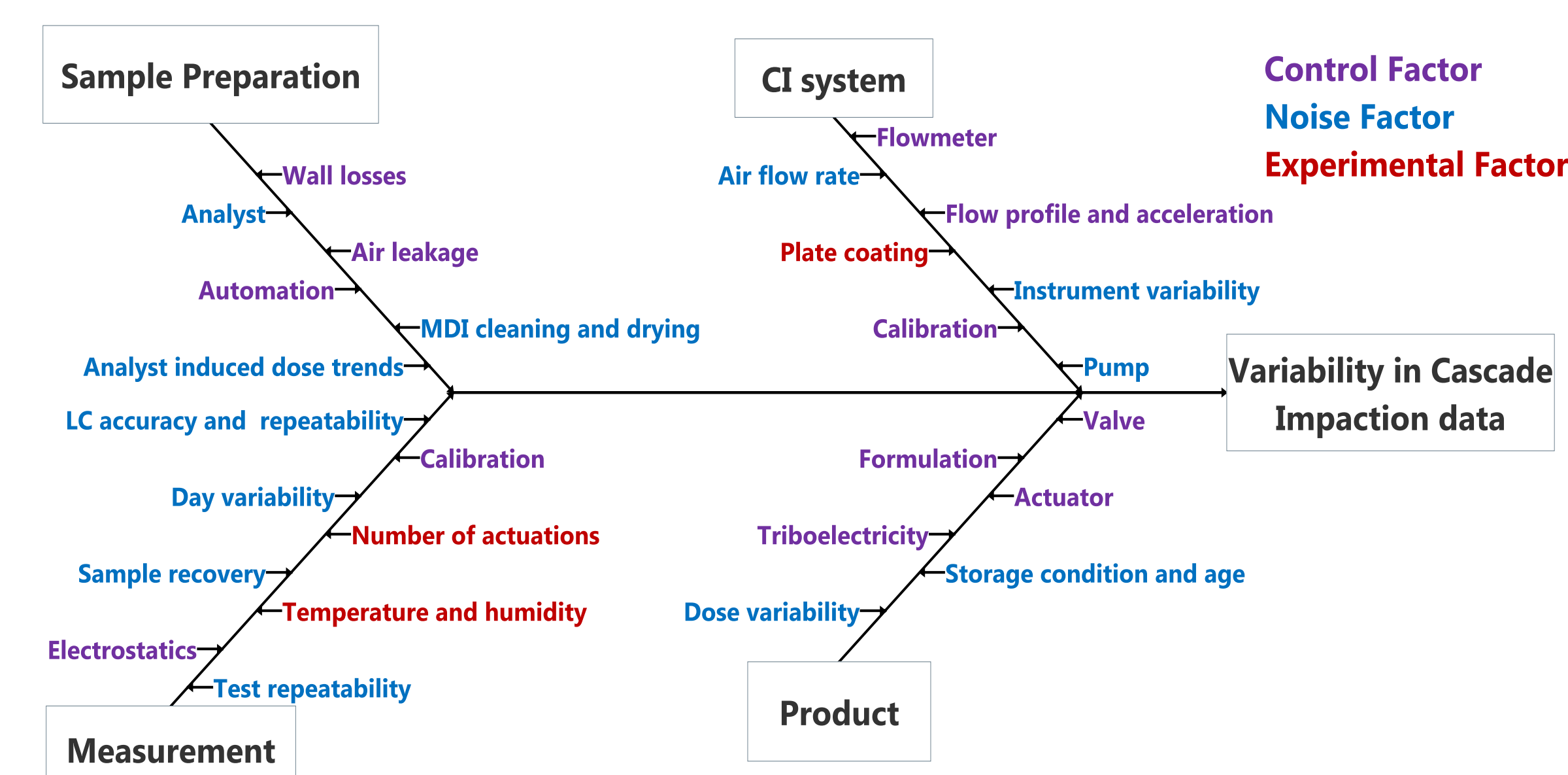


Figure 2: Fishbone diagram of sources of variability for CI data

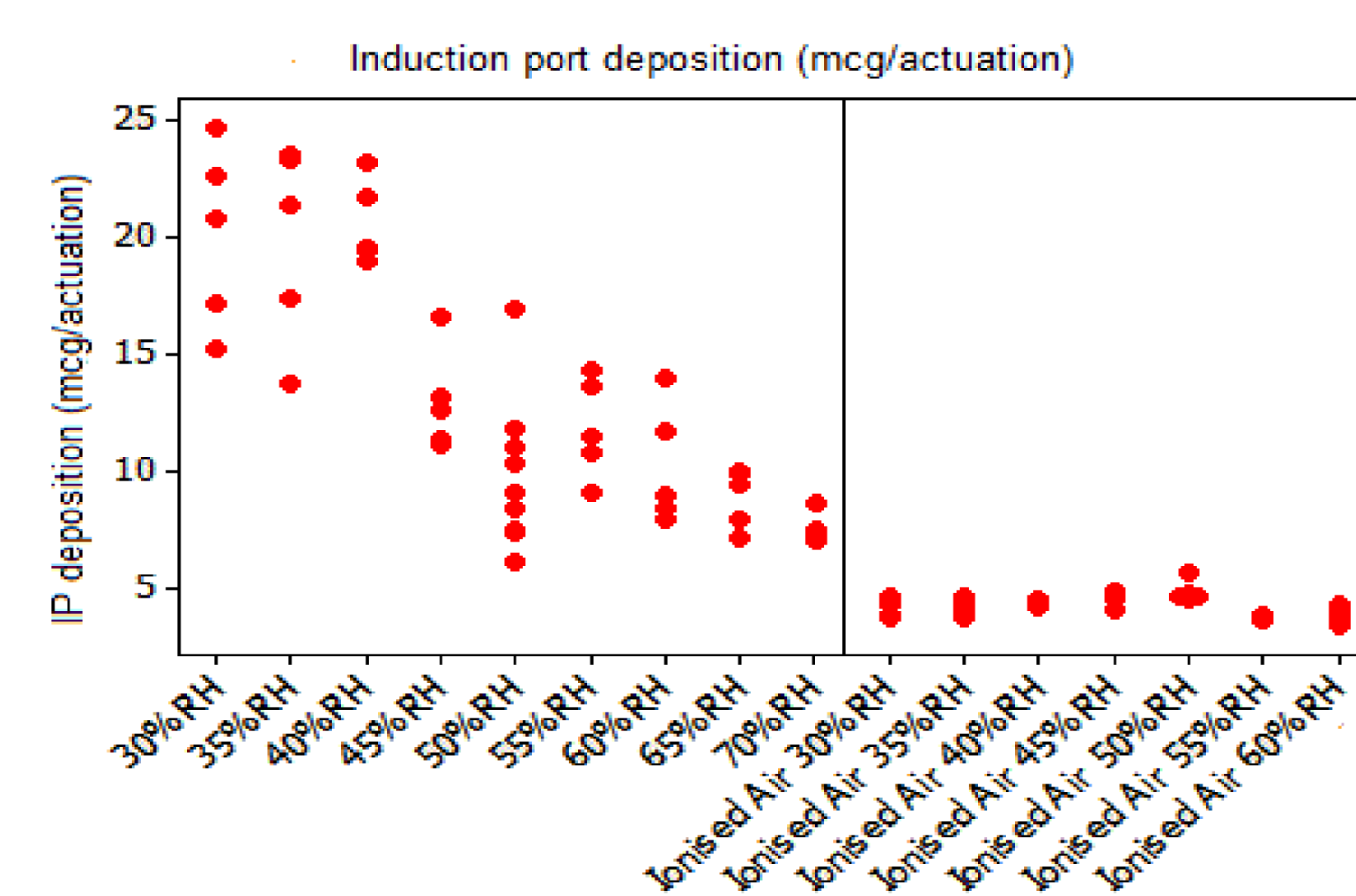


Figure 3: Effect of Relative Humidity (%) and electrostatic control on deposition in the glass induction port

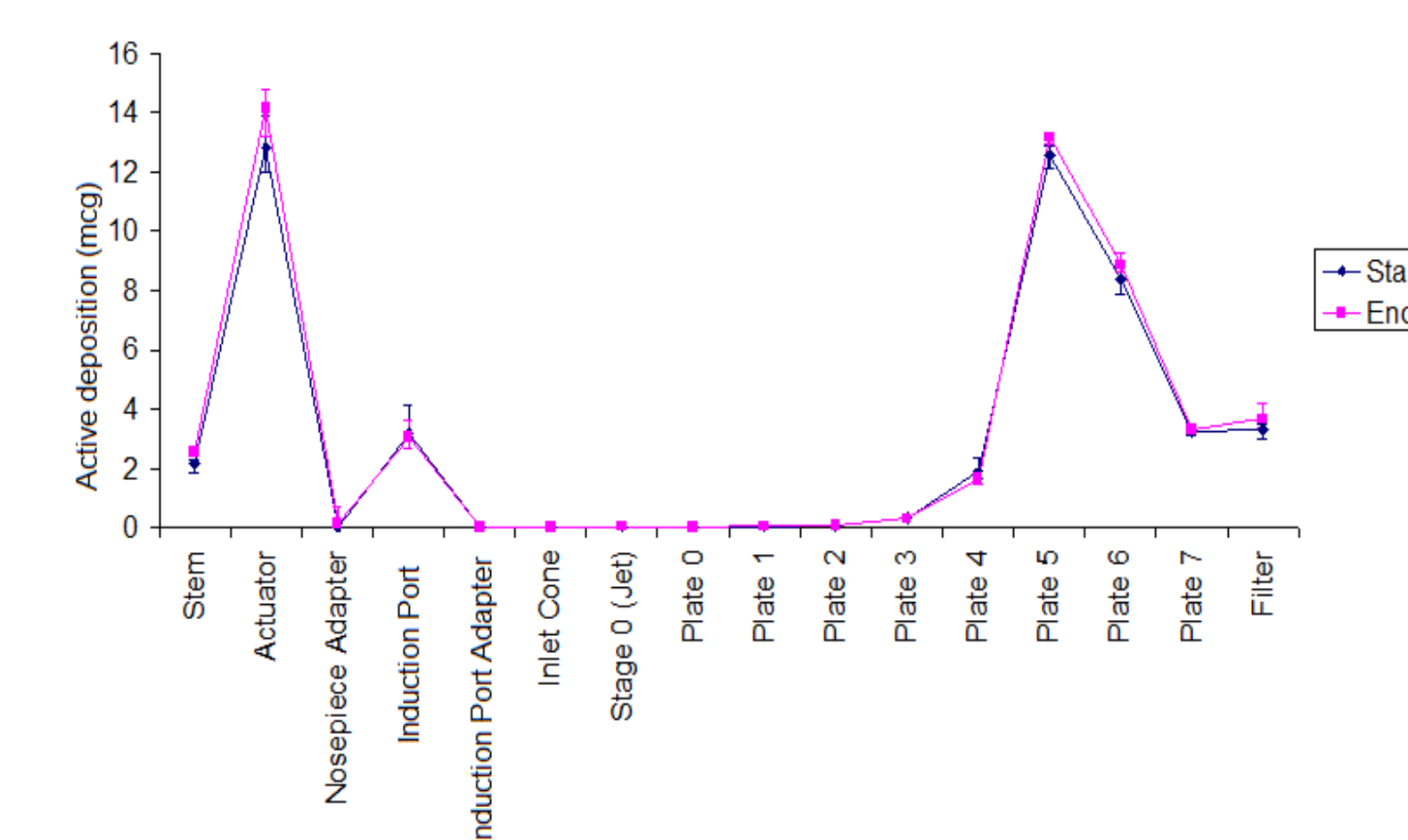


Figure 4: Typical start and end of life ACI deposition profiles for a pMDI nasal product after implementation of electrostatic control

RESULTS

During early phase experimentation it was noted that drug deposition on the glass induction port had high day to day variability and this was investigated in combination with the variable factors Relative Humidity (RH) and Electrostatic Control. RH was controlled by performing the testing in a humidity and temperature controlled cabinet (temperature controlled between 20 and 25°C and humidity controlled over the range 30 to 70%RH). The air in the cabinet was also controlled for electrostatics by introducing a Copley Scientific Ltd ESE1000 electrostatic eliminator

Figure 3 shows the very obvious effect RH has on the deposition on the glass induction port when electrostatics were not controlled. However, when the electrostatic eliminator was introduced the glass induction port deposition was low and almost completely independent of RH. Figure 4 shows the typical ACI profile for a nasal pMDI product after controls have been put in place to control variability of CI data. It is clear the ACI test is showing a large proportion of droplets with a diameter less than 10 micron when a 1L glass induction port is used. It should be noted that the measured DSD is much smaller than the DSD of the formulation at point of impaction in the nasal cavity since there is much more time for evaporation of the formulation.

The other consideration is that the velocity of droplets at the point of impaction in the nasal cavity is high and therefore this small measured DSD does not lead to significant breakthrough into the lung. This has been confirmed by scintigraphy studies which demonstrate that 98.4% of the active from a nasal pMDI is retained within the nasal cavity ⁽⁷⁾.

CONCLUSIONS

Cascade Impaction is a notoriously difficult methodology to optimize because of the numerous factors which affect data quality and the potential interactions between these parameters. A QbD approach is useful to ensure that the critical parameters are assessed and whilst most of the parameters are assigned as Control or Noise Factors there is benefit from a structured approach to method optimization and validation.

In the case of nasal pMDI products, some of the most critical parameters are controlling the relative humidity and electrostatic properties of the laboratory air so as to reduce variability in deposition on the glass induction port. Once the variability associated with the test is more clearly controlled and understood it is possible to evaluate the variability associated with the product and the method can be made suitable as a QC test. Although the test method shows a DSD with a considerable proportion of droplets below 10 micron, scintigraphy has shown this does not result in significant breakthrough from the nasal cavity into the lung.

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