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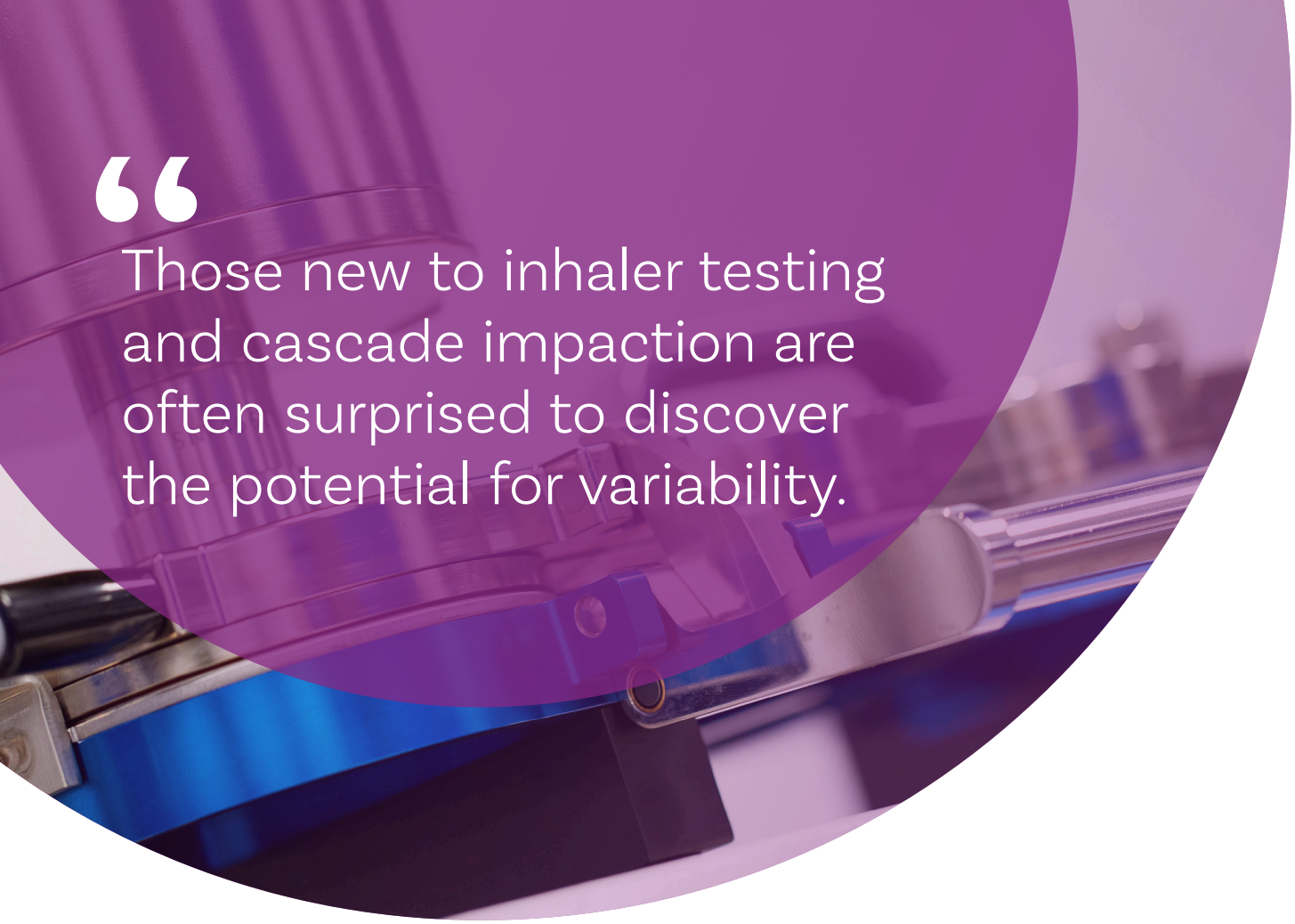
Establishing a robust environment for inhaler testing

Exploring the effects of temperature, humidity, and electrostatics.

White paper | March 2023



> Those new to inhaler testing and cascade impaction are often surprised to discover the potential for variability.

Experienced users on the other hand are all too aware of the effort required to develop and maintain a robust orally inhaled product (OIP) test set-up and use it repeatably.

Recognising its reliance on cascade impaction, the inhalation community has invested significant resource over the years in learning how to minimise variability and establish good practice[1-3]. There is much advice to draw on but at the same time the problems are far from solved. Solutions for reducing variability continue to evolve with every step forward increasing the integrity of the data relied upon to develop efficacious OIPs and safeguard their consistent manufacture.

This white paper focuses on just one potential source of variability - the test environment.

We will examine how the poor control of **temperature**, **relative humidity (RH)**, and **electrostatics** can influence inhaler testing. We consider how these variables affect the performance of OIPs thereby influencing both aerodynamic particle size distribution (APSD) measurement by cascade impaction and delivered dose uniformity (DDU) testing. Separately, we assess their impact on the performance of cascade impactors, concluding with a discussion of solutions that can help. The aim is to increase awareness of the various ways that the test environment may be influencing results and to provide practical suggestions for improvement.

A costly problem: Understanding how variability impacts the bottom line

We use analytical techniques to either detect difference or confirm comparability. In product development, the focus is typically to detect difference, to determine whether a change delivers improvement we can build on, while in Quality Control (QC) the goal is to confirm comparability. The variability of the test method directly affects its utility in both instances with greater variability obscuring trends and sub-optimally supporting decision-making.

A failure to adequately control variability therefore has significant practical and economic implications. It increases the likelihood of an erroneous out-of-specification (OOS) or out-of-trend (OOT) result, the chance and/or frequency that testing will indicate that a product doesn't meet a manufacturing specification, or isn't comparable to the products historical performance, when, in fact, it does. Both OOT and OOS results require significant investigation, including repeat testing, and can be a major drain on resources and morale. Alternatively, viewed from an R&D perspective, greater variability can result in a technique simply lacking the analytical discrimination needed to evaluate a change, since subtle differentiation becomes impossible. Here too there is potential to erode productivity, and, crucially, to lengthen time to market.

"Minimising variability improves the utility of a test method and can deliver value by helping to boost productivity and accelerate time to market.

Why is inhaler testing prone to variability?

There are two distinct answers to this question. Firstly, unlike with other drug products, such as tablets, the dose delivered by an OIP is influenced by interactions between the product – both device and formulation – and the user.

Testing an OIP involves actuation to release an aerosolised dose into the test apparatus. Dose delivery is a dynamic process and can therefore vary. For instance, with a passive dry powder inhaler (DPI), dispersion is influenced by the flow rate profile applied to the device during dose release while for a pressurised metered dose inhaler (MDI) actuation force, displacement and duration are factors. This potential for variability is a consideration in **all** inhaler testing.

Secondly, however, the technique of cascade impaction is itself prone to variability. Cascade impaction has unique attractions for inhaler testing. It measures APSD - a highly relevant particle size metric for characterising airborne particles - specifically for the drug substance, as opposed to the overall formulation. These valuable attributes more than offset the practical challenges of the technique which include complexity and poor amenability to end-to-end automation; cascade impaction remains a substantially manual activity in most labs.

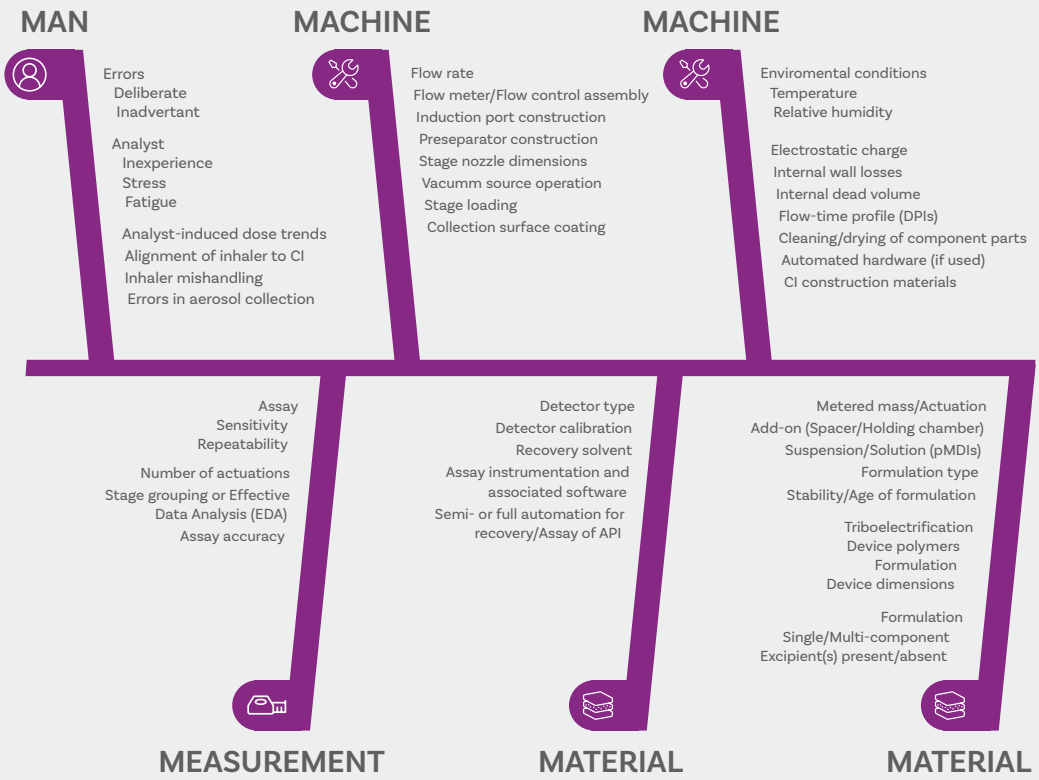


Figure 1: An Ishikawa or fishbone plot summarising potential sources of variability or uncertainty associated with a cascade impactor measurement[1].

The sources of variability associated with cascade impaction are summarised in **Figure 1** which was produced by a working group of the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) formed specifically to investigate this issue. It classifies sources of variability as relating to:

MAN
the technique or practice of the operator

MEASUREMENT
the method applied

MACHINE
the cascade impactor and associated ancillaries

MATERIAL
the product itself

Here, our focus is the test environment - temperature, RH, and electrostatics - so let's locate these on the fishbone plot. Environmental conditions and electrostatic charge are both listed under **MACHINE**; triboelectrification, a mechanism of electrostatic generation, is listed under **MATERIAL**. This confirms that both the product and the cascade impactor should be considered as we examine the impacts of a changing test environment.

> *"All OIP testing – APSD measurement and DDU testing - is subject to variability associated with the dynamic nature of inhaled drug delivery but cascade impaction itself is also prone to variability due to changes in environmental conditions, intensifying requirements for robust control.*

A note about mass balance (MB) and APSD

Sources of variability in cascade impaction are often discussed with reference to two independent aspects of measurement: the mass balance (MB) and APSD. MB figures indicate the extent of drug recovery, relative to label claim or average delivered dose, with acceptability criteria defined by the regulators. Repeatable APSD data on the other hand are indicative of consistent aerodynamic performance within the impactor.

A source of variability may impact APSD alone or both MB and APSD. For example, higher electrostatic charge may increase inter-stage losses in the impactor (MB) and distort the collection efficiency of different stages (APSD). On the other hand, droplet evaporation in a nebuliser measurement may shift APSD but have little impact on MB - all the drug could still be recovered.

Exploring the potential for change in an uncontrolled test environment

When considering the need for environmental control it is helpful to examine the scope for variability in the absence of control. To answer this question, we need some understanding of the magnitude of likely changes in the test environment.

The extent of uncontrolled variation in ambient lab temperature depends on factors such as building properties, season, and geographical location. A diurnal swing in temperature of 5 to 15°C is a reasonable starting assumption[4] with seasonal variation dependent on latitude. In the northern US for example, winter temperatures drop below freezing while summers can reach 30°C[5].

RH is the amount of water vapour present in the air relative to saturation. Saturation, the maximum amount of water vapour air can hold, increases with temperature making RH and temperature interconnected variables. Geography is again a defining factor when it comes to RH variation in the external environment with parts of India seeing values range between 40 and 80% across the year[6]. Here in the UK, natural variability is substantially less - typically between 60 – 80%[7] – but may be extended in the lab by heating and air-conditioning systems.

The potential for electrostatic variability in the absence of control is unpredictable but there is an important link to highlight between RH and electrostatics. At lower RH the effects of electrostatics tend to be more pronounced since water in the air helps to dissipate accumulated charge.

“In summary, in the absence of control RH may swing by ~30%, conservatively, and temperature by 10 – 15°C within the lab environment.

Exploring the impact of temperature variability

Changes in ambient temperature have been directly linked with changes in delivered droplet size

Against a backdrop of scoped potential for variability we can examine associated impacts focusing first on temperature and beginning with effects on OIP performance which tend to be device-specific.

For nebulisers, changes in ambient temperature have been directly linked with changes in delivered droplet size[8,9]. For example, in a design of experiments (DoE) study an ambient temperature rise from 18 to 28°C was linked with a change in MMAD of ~0.2 µm, around 5%[9]. A rationale is the influence of temperature on formulation properties such as viscosity and surface tension that define atomisation behaviour[8].

Studies of the impact of MDI device and ambient temperature during use similarly suggest a link with particle size[10,11]. In a study of four commercial MDIs, fine particle fraction was observed to decrease by as much as 70% when device and ambient temperature were simultaneously lowered with increases of 25% observed at the upper limit of the temperature range of study[10]. This range was wide, from -12 to 41.7°C, but significant changes in particle size have also been associated with more modest changes in in-use temperature, from 5 to 40°C and differentiated for suspension- (Ventolin®) and solution-based (Atrovent®) products[11].

Turning to the effect of temperature on cascade impactor performance, compendial methods highlight the risk of droplet evaporation within the impactor - specifically for nebulisers[12,13] - and an associated requirement for cooling. The Next Generation Impactor (NGI), the impactor of choice for nebulisers due to calibrated performance at 15L/min, is particularly prone to this effect because of its relatively high thermal mass. The previously cited DoE study captures this effect with a modest change from 18°C to 23°C associated with a reduction in MMAD from ~3.4 µm to just above 3.2 µm[9] in NGI measurements of a nebuliser aerosol.

No other OIPs are subject to the requirement for impactor cooling but there is scope for comparable effects with other device types such as aqueous droplet inhalers (ADIs) or soft mist inhalers which can be considered as 'metered-dose nebulisers'. With these products, droplets are similarly emitted at 100% humidity creating analogous potential for drier/warmer air in the impactor to promote evaporation. With MDIs, aerosolisation is a somewhat different propellant-driven process, but here too there are reports of impactor conditions affecting measured particle size. In the aforementioned study of Ventolin and Atrovent, a change in impactor temperature from 25 to 5°C was associated with an increase in MMAD of 38.14 and 73.75% respectively and a corresponding reduction in FPF of ~36% for both products[11].

In general, it is therefore reasonable to conclude that consistency in ambient temperature may be broadly beneficial for both device and impactor performance.

A note about air density

Air density, a function of ambient temperature and RH, affects the aerodynamic forces that shape the aerosolisation behaviour of OIPs, thereby influencing drug delivery performance. For example, low air density at high altitude or in hypobaric chambers has been linked with less effective DPI performance[14]. Variability in environmental conditions and by extension air density may be problematic for this reason.

In the impactor any potential effect of air density is mitigated by controlling inlet volumetric air flow rate, a defining parameter for cascade impactor performance. High quality, modern flow meters measure volumetric flow rate under ambient conditions thereby consistently providing a relevant value for cascade impactor calibration and accurate measurement; older models may require a simple manual correction to achieve the same effect.

Exploring the impact of relative humidity (RH) variability

Focusing specifically on product-related effects, the susceptibility of DPI formulations to moisture is widely recognised and studied routinely, particularly within the context of stability and packaging selection[14-16]. There is potential for RH to impact DPI testing by influencing behaviour within the impactor or indirectly, by influencing electrostatics.

For nebulisers and MDIs, there is evidence that the dynamic droplet formation processes associated with drug delivery may be directly influenced by changes in RH. For example, in a study of nebuliser performance, an increase in ambient RH from 30 to 50% was associated with a change in MMAD in the order of 8.6%, with a further increase, from 50 to 70% producing an additional increase of 10.5%[17]. The magnitude of this effect was found to be nebuliser-specific with alternative technology exhibiting more robust performance. A study comparing MDI performance following actuation into a chamber at less than 10% and >98% RH similarly illustrated a link between high RH and larger droplet size[18].

RH can also affect both product and cascade impactor performance by influencing air density and triboelectric effects at the point of test. At higher RH, moisture in the air naturally earths any developing static charge, conducting it away from OIPs and instrument surfaces. At RH values in the range 40 – 60% static may develop but leakage to ground will be appreciable[19]; RH levels greater than 55% typically prevent any significant charge build-up. This provides a rationale for the routinely observed suggestion to maintain an RH of 40 – 60% for OIP testing.

> *“Focusing specifically on product-related effects, the susceptibility of DPI formulations to moisture is widely recognised and studied routinely*

Exploring the impact of electrostatics

Electrostatic effects are complex and unpredictable, not just in inhaled drug delivery but more generally across the pharmaceutical and other industries and it is only relatively recently that we have been able to make meaningful measures of charge. Both static techniques, such as Faraday wells/pails, aerosol electrometers, and dynamic methods based on the mobility of electrons are now increasingly being used to implement studies that advance understanding [20-23].

The acquisition of charge by OIP particles is predominantly attributable to triboelectrification, a process in which uncharged bodies become charged via a process of contact and subsequent separation[20,22,24]. OIP operation presents ideal conditions for triboelectrification though it may also occur during manufacture, via drug substance micronisation for example. Shaking prior to actuation, release of the dose through an intricate metering valve, and/or highly energetic dose dispersion and aerosolisation exemplify the microprocesses that result in charge acquisition. Contact and friction between solid OIP particles and/or disruption of the liquid surface in solution and suspension formulations impart charge which may or may not subsequently dissipate. All OIPs are therefore susceptible to electrostatic charging though DPIs and MDIs especially so. The routine use of valved holding chambers (VHCs) and spacers with MDIs is also a complicating factor since these are typically manufactured from insulating plastics that readily accumulate charge, promoting dose deposition and compromising dose delivery[25]. Spacer coatings developed to mitigate this effect are becoming an increasingly routine feature of more modern designs.

The magnitude and polarity – negative or positive – of electrostatic charges depend on a wide range of formulation and device properties, from drug load and crystal structure to the choice and physical properties of excipients (e.g. particle size distribution and morphology), to the material of construction used to make capsules and key device components[20,22,25]. For MDIs the impact of propellant is especially noteworthy within the context of ongoing efforts towards reformulation for lighter environmental impact. Changing propellant alters electrostatic behaviour directly, and often indirectly too, by necessitating a change in materials of construction.

When it comes to considering the effects of electrostatics we can differentiate two forces. Space charge forces are repulsive and associated with interaction between particles charged with the same polarity in the aerosol cloud. In contrast, image charge forces are attractive and typically associated with induced charge of opposite polarity on a neutral surface [22,23]. Both have potential to affect particle movement and deposition, *in vivo* and *in vitro*.

For example, in the body higher image charge forces may promote deposition, particularly in narrower airways because of the strong dependence of electrostatic charge on the distance between charged objects (Coulomb's Law)[22]. In a cascade impactor set-up these same forces may influence particle collection on non-conducting or insulating surfaces such as plastic induction ports or throat models, if used. Space charge forces, on the other hand, may promote dispersion. Via these and other mechanisms, electrostatics can affect both DDU testing and APSD measurement.

Though the study of electrostatic effects is still in its infancy the following examples provide some illustration of just what electrostatics can mean in practice:

- Increased levels of charge on a plastic throat model, induced by rubbing with a nitrile glove, were shown to increase deposition for a range of commercial MDIs and a soft mist inhaler; low RH, ~15% exacerbated the observed effect[26].
- The charge accumulated by a range of commercial MDIs was shown to be sufficient to influence both total and regional drug deposition *in vivo* when assessed against results from modelling studies. There are indications that lower charge may be advantageous for penetration to the lung while higher surface charge is associated with increased deposition in the upper airways[23].
- CFD studies have shown that charge levels typical of those accumulated by commercial MDIs are sufficient to change the collection efficiency of plates 4 through 7 on the ACI[24] a finding reinforced by experimental studies showing a clear link between electrostatic charge and deposition behaviour in an ACI[27].

The multiple, complex, confounding impacts of electrostatics are widely recognised as evidenced by a survey carried out by the electrostatic sub-group of EPAG (European Pharmaceutical Aerosol Group)[28]. There is also some consensus about the best way to tackle them with robust temperature and RH control identified as the most popular, proven strategy for mitigation by participants in the preceding study[28].

Electrostatics in action

The figure below shows results from DDU testing for three different types of MDI aluminium canister (H&T Presspart): plain, plasma-treated and PTFE coated. DDU over the entire contents was carried out in each case, necessitating 200 actuations for each cannister. Testing was carried out using an automated shake and fire system (**Vertus® Plus**) to ensure exemplary repeatability and as a result, the effect of progressive static build-up can be seen clearly, and indeed differentiated for the three cannister types.

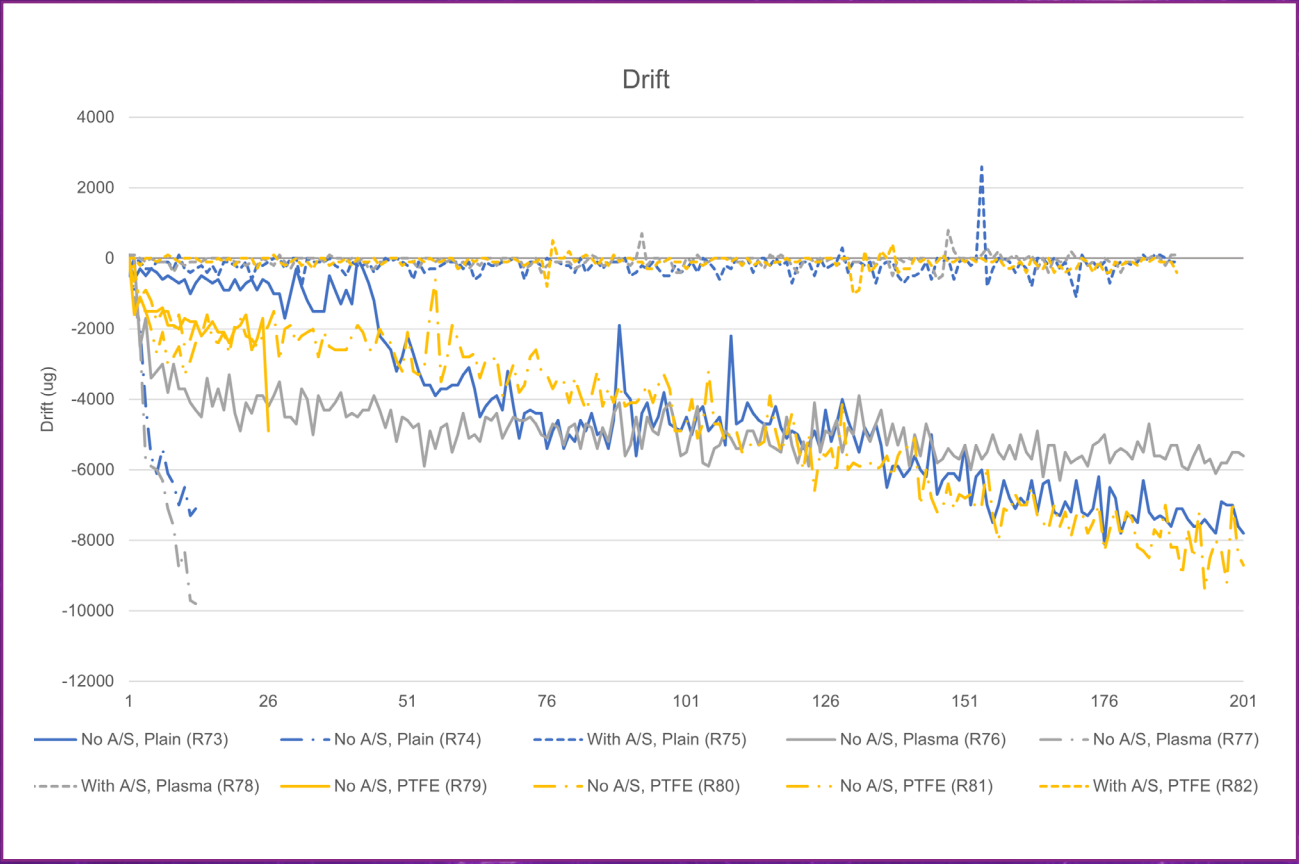


Figure 2: The drift data shows that the A/S device substantially reduces electrostatic effects (Smith, A., & Copley, M. Investigating the Impact of Electrostatics on Delivered Dose Uniformity for pMDIs. Published at RDD 2022).

The recorded parameter here is drift – the change in shot weight from a baseline recorded 1s after dose delivery to a stabilised value. In the absence of an anti-static device, drift is appreciable for all three types of cannister. Duplicate testing with an anti-static (A/S) device in place eliminates drift which can therefore be securely linked with the build-up of static over sequential actuations.

Taking control of the test environment

The preceding discussions provide ample evidence of the need to take control of the test environment to mitigate variability. In this last section we therefore conclude with an overview of the solutions available to achieve consistency in a cost-efficient way.

Reducing electrostatic effects

Electrostatic mitigation calls for the careful consideration of every aspect of measurement and the judicial deployment of appropriate practice and technology, from start to finish. Simple, routinely used strategies include[2,28]:

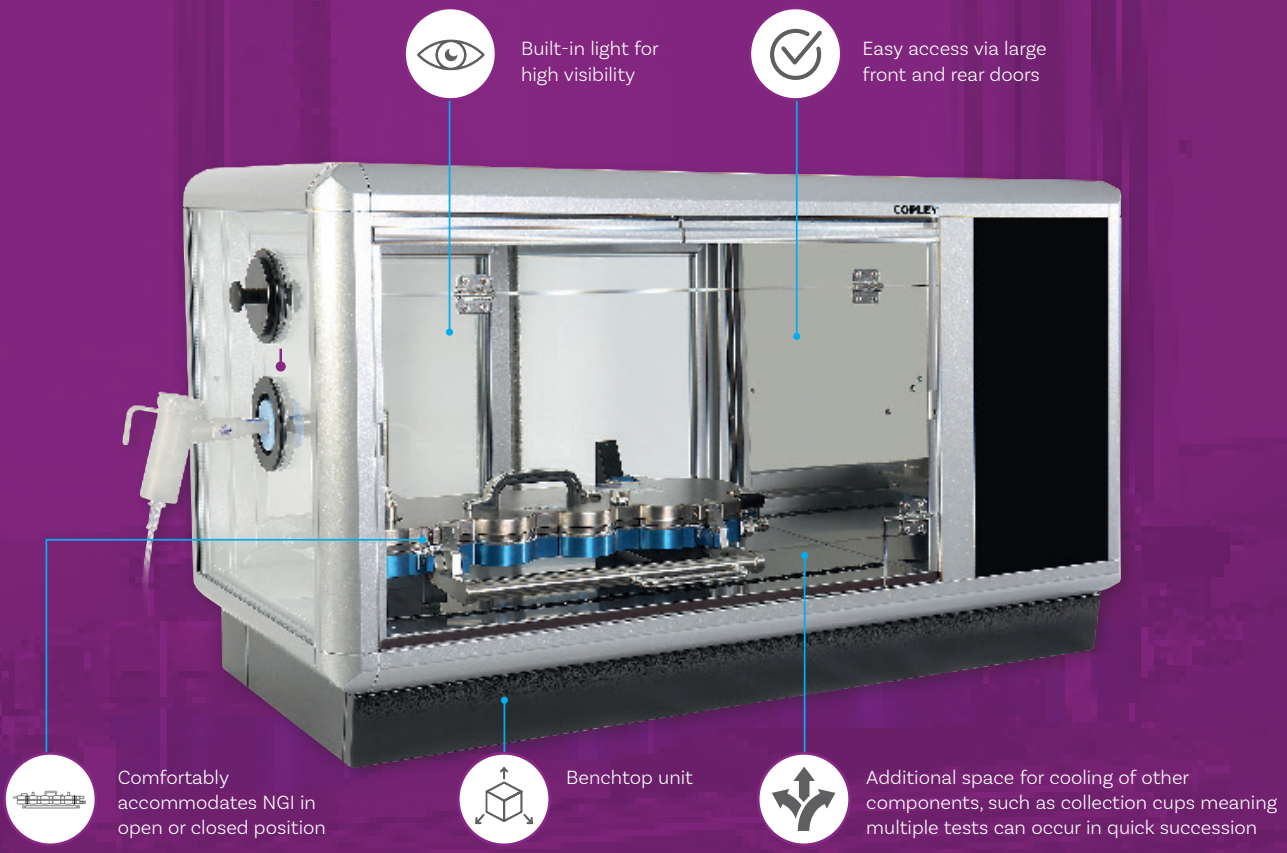
- Grounding of equipment and operators; anti-static wristbands are frequently used to minimise charge accumulation
- Restricting the use of gloves and/or specifying the types of gloves that may be worn
- Careful choice of protective lab equipment - anti-static shoes, clothing and/or mats are all commonplace
- The use of electrostatic eliminators and guns, and ionisation bars.

We offer several products that support the implementation of these strategies including an **Anti-Static Grounding Kit**, for individual operator use, and an **Electrostatic Eliminator**, a compact benchtop unit that efficiently neutralises static across a broad working area. Our **Digital Static Meter** is a useful, handheld tool for checking the effectiveness of any electrostatic mitigation steps that measures both intensity and polarity.

Controlling impactor temperature

When it comes to controlling impactor temperature, we need to align with compendial requirements for nebulisers which state that 'evaporation can be minimised by cooling the impactor to a temperature of about 5°C[12]. This temperature is not consistent with equilibration at a well-controlled ambient lab temperature but rather calls for refrigeration. One option is to put the impactor in a standard lab refrigerator for an extended period (typically 90 minutes), taking care that experiments are carried out before any appreciable warming of the instrument. An alternative is the **NGI Cooler™** which is designed specifically to address this issue.

NGI Cooler™



The NGI Cooler is a temperature controlled, well-lit cabinet for nebuliser testing in accordance with USP <1601> and EP 2.9.44[12,13]. It can be used as a benchtop unit or mounted on an optional stand to comfortably accommodate and access the NGI – open or closed – along with key components such as collection cups, to streamline sequential testing.

Key features include:

Temperature control between 0 and 10°C to and accuracy of +/-1.5°C.

Double-glazed, highly energy efficient construction.

Twin side access ports for connection to the nebuliser and other items that may be needed to complete the test set-up such as a mixing inlet.

Comprehensive control of the test environment

For robust control of ambient temperature and RH, full climate control may be the first thought and, if well-implemented should deliver a consistent and comfortable working environment.

However, for many, the associated costs are prohibitive because of the initial capital investment and/or ongoing running costs. The security, reliability and cost of energy supplies may be particularly problematic if the prevailing geography imposes a heavy working load on the climate control system.

The alternative is to use individual climate-controlled chambers, a solution that combines greater flexibility with low upfront and running costs. This approach is highly effective in providing uniform control of the immediate test area, efficiently mitigating the impact of, for example, heat release by in-use equipment, drafts, windows, air-conditioning vents. For example, we have recently introduced **EnviroMate™** a compact, movable benchtop unit that has the distinction of being designed specifically for inhaler testing.

Key features include:

- Accurate temperature (+/-2°C) and RH (+/-5%) control with efficient air circulation through the full chamber volume to ensure uniform conditions throughout.
- An integrated anti-static system to minimise static effects within the working environment.
- Ability to accommodate all types of cascade impactor including preseparator and mixing inlet as required.
- No requirement for desiccant or refrigerant.
- Dedicated side ports for easy connection to externally located ancillaries (including the **NGI Cooler™**, **Breathing Simulator BRS 200i**) required to complete the test set-up.

> *“By simultaneously controlling temperature, RH and electrostatics, solutions such as the EnviroMate™ can be an extremely cost-efficient option for driving down variability associated with the test environment.*

EnviroMate™

Sensitive temperature and relative humidity sensor ensures accurate performance
Adjacent holder for BAC 100i/ TPK 100i Temperature and Relative Humidity Sensor included

Anti-static system minimises electrostatic-induced variability

Internal light maximises visibility

Easy-to-remove water supply/waste reservoirs

Temperature and relative humidity parameters are easily set and clearly visible to users

Large, slot-sealed entry ports enable easy handling of test equipment

A large, hinged door provides easy access

Access ports and built-in quick-release connectors accommodate a wide range of ancillaries, such as flow controllers and vacuum pumps

EnviroMate is a cost-effective, compact, benchtop solution that offers considerable value for scientists faced with:

- variable laboratory conditions or inadequate climate control
- OINDPs with high sensitivity to temperature, humidity and/or electrostatic charge
- poor reproducibility and unexplained out-of-specification (OOS) results
- achieving better environmental control, in a cost-effective manner, without investing in a dedicated climatically-controlled laboratory for testing

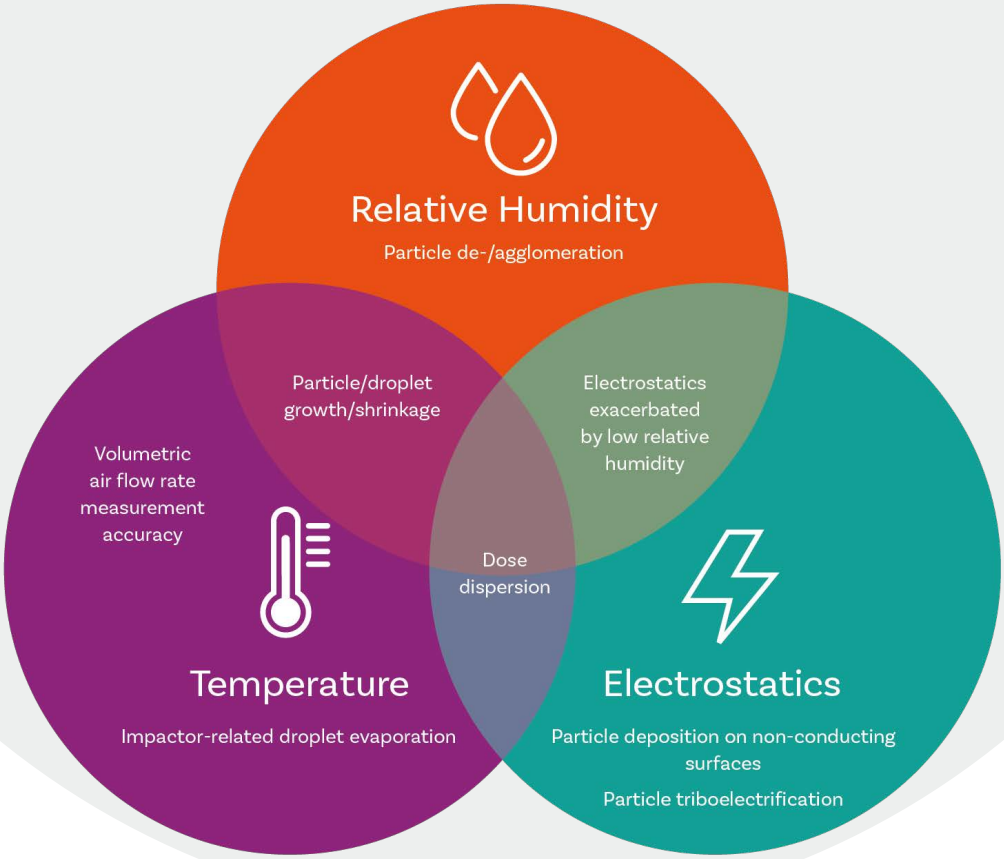


Figure 3: Environmental factors can influence inhaler testing by multiple, complex and interconnected ways making environmental control essential for all types of OIPs.

In Summary: Key points to understand about the impact of environmental variability in the test environment and how to tackle it.

- Variability in the test environment – temperature, RH, and electrostatics – can influence the performance of OIPs and separately, in the absence of appropriate control, particle behaviour within a cascade impactor. It can therefore affect both DDU testing and APSD measurement.
- Variability associated with realistic diurnal and seasonal fluctuations in temperature and RH is sufficient to erode the value and integrity of OIP data.
- The effects of temperature, RH and, especially electrostatics, are complex, and intimately interwoven making a comprehensive strategy for environmental control essential.
- Off-the-shelf solutions designed specifically to improve the quality of inhaler test data are an excellent starting point when it comes to tackling variability associated with the environment, typically providing a cost-effective route to substantially enhanced performance.

Would you like to speak to someone about environmental control for inhaler testing?

Contact us: sales@copleyscientific.co.uk | +44 (0)115 961 6229

References

[1] Bonam, M. Christopher, D. Cipolla, D. Donovan, B. Goodwin, D. Holmes, S. Lyapustina, S. Mitchell, J. Nichols, S. Pettersson, G. Quale, C. Rao, N. Singh, D. Tougas, T. Van Oort, M. Walther, B. and Wyka, B. 'Minimizing Variability of Cascade Impaction Measurements in Inhalers and Nebulizers' AAPS Pharm Sci Tech AAPS, 2008

[2] Stein, R. 'CI testing of passive DPIs: Best practices and relevance to patient use – an IPAC-RS viewpoint' Presentation at RDD 2018.

[3] 'Considerations for the Development and Practice of Cascade Impaction Testing Including a Mass Balance Failure Investigation Tree'. A report issued by the PQRI Particle Size Distribution Mass Balance Working Group, 2002

[4] Means, T. 'Understanding Diurnal Temperature Range' July 24th 2019. Available to view at:
https://www.thoughtco.com/diurnal-temperature-range-3444244

[5] 'Climate and average weather in United States of America' Available to view at:
https://weather-and-climate.com/average-monthly-Rainfall-Temperature-Sunshine-in-United-States-of-America

[6] 'Relative humidity data of Delhi' Available to view at:
https://www.indianclimate.com/relative-humidity-data.php?request=5DWH4PLGSL

[7] 'Average humidity in London' Available to view at:
https://weather-and-climate.com/average-monthly-Humidity-perc,London,United-Kingdom

[8] Steckel, H. and Eskander, F. 'Factors affecting aerosol performance during nebulization with jet and ultrasonic nebulizers' Eur J Pharm Sci. 2003 Aug; 19(5) 443-55

[9] Schuschnig, U. Hug, M. Klopfer, E. Knoch, M. and Keller, M. 'The Next Generation Impactor: Effects of Environmental Conditions and Impactor Temperature on Particle Size Measurement of an Aqueous Aerosol' Poster presented at RDD Europe 2007.

[10] Morin, C.M.D. Ivey, J.W. Titosky, J.T.F. Suderman, J.D. Olfert, J.S. Vehring, R and Finlay, W.H. 'Performance of pressurized metered-dose inhalers at extreme temperatures' J Pharm Sci 2014 Nov; 103 (11) 3553:3559.

[11] Zhang, R. Song, X. Zhan, S. Hu, J. and Tan, W 'Investigation of influence factors on particle size measurement with pMDI' Biomedical Research 2017; 28 (21): 9582 - 9588

[12]USP <1601> Products for nebulization – Characterization tests

[13] Ph. Eur. 2.9.44 Preparations for nebulisation: characterisation

[14] Ruzycki, C.A. Tavernini, S. Martin, A.R. and Finlay, W.H. 'Characterization of dry powder inhaler performance through experimental methods' Advanced Drug Delivery Reviews 189 (2022) 114518

[15] Bhope, S. Gondhale, P. Kulkarni, S. Musmade, B. Kolsure, P. Dhavale, S. Padmanabhan, S. 'Effect of temperature and moisture on the uniformity of delivered dose, emitted dose and fine particle fraction for three different DPI formulations in different packs.' J Appl Biotechnol Bioeng. 2020;7(4):161-167.

[16] Pleasants, R.A. 'Dry Powder Inhalers and Humidity: Another Factor to Consider to Ensure Adequate Lung Delivery.' Annals of the American Thoracic Society, Vol 14, Issue 10, 2017

[17] Williams, K. 'The influence of ambient relative humidity during cooled NGI testing' Patient Centricity Event. Poster presented at DDL21, Edinburgh, 2010

[18] Martin, A.R. and Finlay, W.H. 'The effect of humidity on the size of particles delivered from metered dose inhalers' Aerosol Science and Technology 39; 283 - 289, 2005.

[19] 'Why does low humidity cause static electricity?' Blog posted 18/02/2019, available to view at:
https://www.condair.com/humidifiernews/blog-overview/why-does-low-humidity-cause-static-electricity

[20] Thielman, F. 'Electrostatic properties of inhalable drug products' Poster presented at DDL22, Edinburgh, 2011.

References

[21] Chen, Y. Traini, D. Fletcher, D.F. Chan, H-K, Lewis, D. Church, T. and Young, P.M. 'The Effect of Active Pharmaceutical Ingredients on Electrostatic Charges from Pressurized Metered Dose Inhalers.' In Respiratory Drug Delivery 2014. Volume 3. Edited by: Dalby, R.N. Byron, P.R. Peart, J. Suman, J.D. Farr, S.J. Young, P.M. and Traini, D.

[22] Kwok P.C.L and Chan H-K: Electrostatics of Pharmaceutical Inhalation Aerosols Journal of Pharmacy and Pharmacology 2009 61 (12):1587-1599

[23] Peart, J. Prapaporn, K. and Orban, J.C. 'Relevance of Electrostatics in Respiratory Drug Delivery' Business briefing: Pharma Generics 2003.

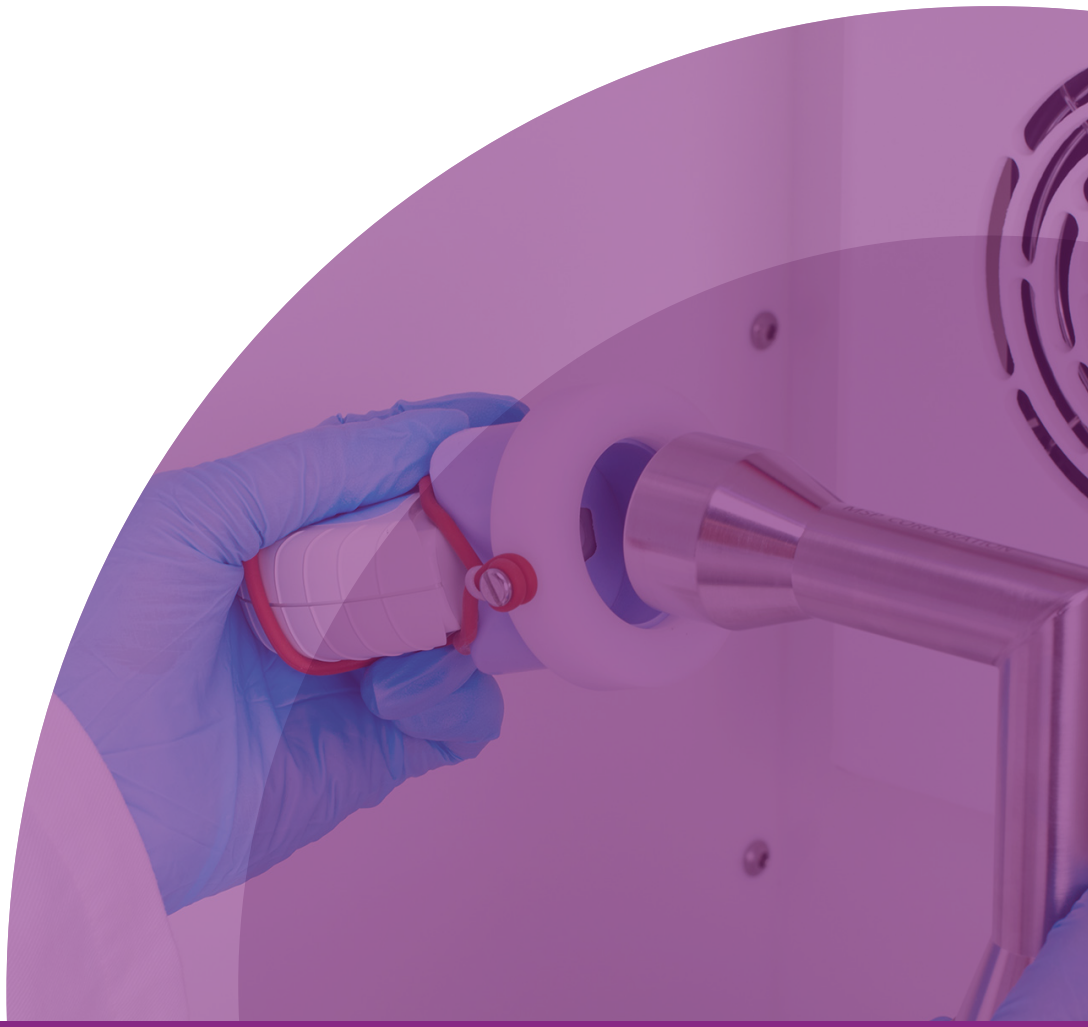
[24] Doub, W. Stein, S. Mitchell, J. and Goodey, A.P. 'Addressing the Need for Controls on Partic;e Bounce and re-entrainment in the Cascade Impactor and for the Mitigation of Electrostatic Charge for Aerodynamic Particle Size Assessment of Orally Inhaled Products: an Assessment by the International Consortium on Regulation and Science (IPAC-RS). AAPS PharmSciTech 2020 21:239

[25] Mitchell, J.P. Coppolo, D. P. and Nagel, M.W. 'Electrostatics and inhaled medications: Influence on delivery via pressurized metered-dose inhalers and add-on devices' Respiratory Care 52 (3) 283 – 300 (2007)

[26] Huynh, B.K. Wei, X. Byron, P.R. and Hindle, M. 'Evaluating pharmaceutical aerosol deposition in electrostatically charged plastic mouth-throat models.' RDD Europe 2017

[27] Mohan, M. Peart, P. and Byron, P.R. 'Influence of Polarity of Electrostatic Charge upon Deposition within an Andersen Cascade Impactor' Respiratory Drug Delivery 2012, Vol 3, 2012, 893 - 898

[28] Chen, Y. and Keegstra, J.R. 'An Overview of the State of the Art on Mitigating Electrostatic Interference During Aerodynamic Testing' Poster presented at DDL26, Edinburgh, 2015.



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