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Pharmacopeial methodologies for determining aerodynamic mass distributions of ultra-high dose inhaler medicines

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ABSTRACT

Three different impactor methodologies, the Andersen cascade impactor (ACI), next-generation impactor (NGI) and multistage-liquid impinger (MSLI) were studied to determine their performance when testing ultra-high dose dry powder formulations. Cumulative doses of spray-dried mannitol (Aridol™) were delivered to each impactor at a flow rate of 60 L min^{-1} (up to a max dose of 800 mg delivering 20 sequential 40 mg capsules). In general, total drug collected in both the ACI and NGI falls below the range 85–115% of label claim criteria recommended by the United States of America Food and Drug Administration (FDA) at nominal mannitol doses exceeding 20 mg and 200 mg, respectively. In comparison analysis of the MSLI data, over a 5–800 mg cumulative dosing range, indicated that the percentage of nominal dose recovered from the MSLI was within the ±15% limits set in this study. Furthermore all samples, apart from the 5 mg and 10 mg analysis were within 5% of the nominal cumulative dose. While the MSLI is not routinely used for regulatory submission, the use of this impinger when studying ultra-high dose formulations should be considered as a complementary and comparative source of aerosol deposition data.

1. Introduction

Dry powder inhalers (DPIs) pose significant advantages over nebulizers and pressurised metered dose inhalers (pMDIs), since they are generally cheaper to manufacture, have improved patient compliance, greater stability and can be used to deliver higher doses than pMDIs over short timescales than nebulizers. Many respiratory medicines have relatively low dose formulations (for example β2-agonists DPIs range from 6 to 500 μg dose^{-1} and corticosteroid DPIs from 50 to 500 μg dose^{-1} [1]). In addition, these devices can be used to what is usually classified as high dose regimes (such as sodium cromoglycate and nedocromil sodium at up to 4 mg dose^{-1} [2], and zanamivir at 10 mg dose^{-1} [3]). However, recent developments in the field have seen the emergence of 'ultra-high dose' DPI medicines for the treatment of asthma, chronic obstructive pulmonary disease, cystic fibrosis and infectious diseases (such as tuberculosis and pneumonia) where doses range from 40 mg to 800 mg per treatment [1,4–7].

Aridol™ and Bronchitol™, produced by Pharmaxis Ltd. (Sydney, Australia) are two examples of ultra-high dose medicines, used in the diagnosis of asthma and the treatment of cystic fibrosis and bronchiectasis [1,6]. Specifically, Aridol is a bronchial challenge diagnostic kit consisting of a micron-sized dry powder mannitol filled in hard gelatin capsules, which can be aerosolised through a conventional DPI device. The diagnostic kit contains 1× 5 mg, 1× 10 mg, 1× 20 mg and 15× 40 mg. The patient is exposed to cumulative dosing up to 635 mg, and their forced expiratory volume monitored to determine the severity of asthma.

Pharmacopeial methodologies [8,9] and US federal guidelines [10] exist for the testing of DPI products. These guidelines include methodologies for the testing of aerosol performance and particle size distribution using *in vitro* cascade impactor methodologies such as the Andersen cascade impactor (ACI) [11] and next-generation impactor (NGI) [12]. Excluding the NGI, many of these methods would have originally been developed to test environmental particulates and/or used for low dose medicaments. Subsequently, both the United States and European Pharmacopeia state that the plates should be coated with silicone oil or equivalent [8,9] to avoid particle bounce effects when using DPI based formulations.

The use of silicone oil to reduce particle bounce and inter-stage loss appears to be critical to the successful characterisation of aerodynamic mass distributions in many impactors. The phenomenon of particle bounce and stage overloading has been well observed [13]. Previous studies have shown the degree of particle bounce to be drug and dose specific. For example, Hindle et al., have shown drug specific bounce effects with terbutaline sulphate and cromolyn sodium powders delivered to a Marple–Miller impactor, and

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reported that bounce effects were avoided with cumulative dosing up to 40 mg cromolyn sodium when the plates were coated [14]. Dunbar et al., reported bounce effects when 5–10 mg of large porous particles were delivered to an ACI at 60 L min^{-1}. They also noted that bounce effect could be reduced, but not eliminated, with reduction in the jet velocity along with plate coating [15]. Nasr et al. showed that even low dose pMDI formulations, containing 100 μg albuterol, had appreciable plate deposition differences if Marple–Miller or ACI impactor plates were not coated [16]. More recently, Kamiya et al., evaluated ACI and NGI stage-deposition efficiencies at 90 L min^{-1} with a high dose (5 mg of zanamivir) formulation and concluded that the NGI was within the pharmacopeial guidelines for impactor losses (<5%) when coated, while the ACI failed regardless of plate coating.

While these previous studies have demonstrated the variability in impactor efficiency with respect to both low and high dose medicaments, to the authors' knowledge, no study has been conducted to evaluate ultra-high dose formulations (for example cumulative dosing up to 800 mg). The United States of America Food and Drug Administration (FDA) recommends that the total mass of drug collected on all stages of the cascade impactor and accessories (i.e. throat and mouthpiece adaptor) be between 85% and 115% of the label claim [10]. As such, the authors aim to evaluate three impactor methodologies: the ACI, NGI and multistage-liquid impinger (MSLI), for the study of the deposition and performance of cumulative doses of mannitol for inhalation and whether each methodology can satisfy the FDA recommendations for ultra-high doses. It is hypothesised that due to factors such as particle bounce and stage overloading, the ACI and NGI will be inappropriate for testing ultra-high doses.

2. Materials and methods

2.1. Materials

Commercial 5 mg, 10 mg, 20 mg and 40 mg mannitol Aridol capsules (mannitol production batch number M08-060) were supplied by Pharmaxis Ltd. (Sydney, NSW, Australia). Samples were provided in sealed blister packs and contained spray dried mannitol of inhalable size with no excipient. Water was purified by reverse osmosis (MilliQ, Molsheim, France). All solvents were analytical grade and were supplied by Sigma-Aldrich (Sydney, NSW, Australia). Silicone oil (Q7-9120, 12,500 Centistokes) was supplied by DOW Corning (Sydney, NSW, Australia).

2.2. Particle size analysis

The volumetric particle size distribution of the mannitol samples was measured using laser diffraction (Malvern 2000, Malvern Instruments, Worcestershire, UK). Mannitol was dispersed in chloroform and sonicated for 5 minutes prior to analysis. An aliquot of the suspension was then transferred to the small volume dispersion unit (Hydro SM, Malvern, Worcestershire, UK) of the Malvern particle sizer, operating at a pump speed of 2000 RPM until an obscuration between 15% and 30% was achieved. Particle size was measured using a refractive index of 1.52 for mannitol and 1.44 for chloroform, determined using a refractometer (Thermo Spectronic 334610, Thermo Fisher Scientific, Waltham, MA, USA).

2.3. Scanning electron microscopy

The morphology of the mannitol particles was investigated using scanning electron microscopy (SEM) at 10 keV (FESEM JEOL 6000, JEOL, Japan). Samples were deposited on carbon sticky tabs, mounted on SEM stubs and sputter coated with a 15–20 nm layer of gold prior to imaging.

2.4. Content uniformity

Content uniformity analysis of each capsule formulation was conducted. Five capsules of each lower dose formulation or 10 capsules of the 40 mg formulation were washed into separate volumetric flasks with water and analysed using the high performance liquid chromatography (HPLC) method described in Section 2.6 [8].

2.5. In vitro aerosol performance analysis

The aerosol size distribution of different cumulative doses of mannitol was assessed using three cascade impactor methodologies: the ACI, NGI and MSLI. These three impactors are specified in the USP Chapter <601> and Ph. Eur. Chapter 2.9.18 for their use in measuring the mass distribution of pharmaceutical aerosols by aerodynamic diameter.

At 60 L min^{-1} the three impactors have a range of cut-off diameters as shown in Table 1, with particles captured on any specific stage having an aerodynamic diameter less than preceding stage, assuming ideal collection behaviour on each stage.

All three impactors had a USP/Ph Eur stainless-steel induction port (throat) (and mouthpiece adapter) connected to the impactor. As the formulation contains no excipients, no pre-separator stage was utilised for any of the impactors.

Each impactor flow rate was set to 60 L min^{-1} using a Rotary vane pump and solenoid valve timer (Erweka GmbH, Germany) and a calibrated flow meter (TSI 3063, TSI instruments Ltd., Buckinghamshire, UK).

Prior to measurement the ACI and NGI impactor plates were coated with silicone oil, as outlined in the pharmacopeial specifications for DPIs. Specifically, each plate was submerged in a 10% (v/v) silicone/hexane solution before placing in a fume-hood to air-dry for 10 minutes. This procedure was not repeated for the MSLI since it is technically a wet impinger and does not have plates or

Table 1
Effective cut-off diameters for the three impactors at 60 L min^{-1}.

ACI[a]	Aerodynamic cut-off diameter (μm)	NGI[b]	Aerodynamic cut-off diameter (μm)	MSLI[b]	Aerodynamic cut-off diameter (μm)
Stage −1	9.0	Stage 1	8.1	Stage 1	13
Stage 0	5.8	Stage 2	4.5	Stage 2	6.8
Stage 1	4.7	Stage 3	2.9	Stage 3	3.1
Stage 2	3.3	Stage 4	1.7	Stage 4	1.7
Stage 3	2.1	Stage 5	1.0	Filter	<1.7
Stage 4	1.1	Stage 6	0.6	–	–
Stage 5	0.7	Stage 7	0.3	–	–
Stage 6	0.4	MOC	<0.3	–	–
Filter	<0.4	–	–	–	–

Aerodynamic cut-off diameter *s* obtained from the following sources.
[a] USP Pharmacopeial Forum volume 28, number 2, pp. 601–603.
[b] [8].

collection cups. The MSLI stages were prepared by adding 20 mL of purified water to each compartment.

Cumulative doses ranging from 5 mg to 800 mg were chosen with a dosing order that followed the guidelines specified for Aridol (i.e. 1× 5 mg, 1× 10 mg, 1× 20 mg or 1× 40 mg with doses higher than 40 mg being made up of multiple 40 mg capsules).

For each analysis, a capsule was removed from its blister and inserted into a Cyclohaler® DPI. The capsule was pierced using the actuator of the device and placed in the USP/Ph. Eur. throat of the impactor under study and tested for 4 s at 60 L min^{-1}. This process was repeated until the cumulative dose required was achieved. After actuation, the device, capsules, throat and all sample impactor stages were washed into separate volumetrics using MilliQ water, before analysis by HPLC.

2.6. High performance liquid chromatography

The concentration of mannitol from content uniformity and impactor/impinger studies was quantified using HPLC coupled with refractive index detection. The system set-up was as follows: LC20AT pump, SIL20AHT autosampler, CBM-Lite system controller with a PC-computer running LC solution v1.22 software and a RID-10A refractive index detector (Shimadzu, Sydney, NSW, Australia). A 8 mm Resolve C18 Radial Pack chromatography Cartridge (Waters Asia Ltd., Singapore) was used for separation at a flow rate of 1 mL min^{-1}. Purified water was used as the mobile phase and sample diluent.

3. Results and discussion

3.1. Physical characterisation

The laser diffractometry-measured particle size distribution of the mannitol powder is shown in Fig. 1. Analysis of the size data indicated 90% of particles had a volume equivalent diameter $\leq 6.82 \pm 0.37$ μm and 50% of particles $\leq 3.91 \pm 0.15$ μm ($n = 3$) suggesting the powder would be suitable for inhalation purposes [17]. A representative SEM image of the mannitol particles is shown in Fig. 2. The particles displayed sizes consistent with the size distribution measured by laser diffraction. Furthermore, the particles appeared to be spherical in nature with a surface made up of many crystalline units, since the glass transition temperature of amorphous mannitol has been reported as 16 °C [18].

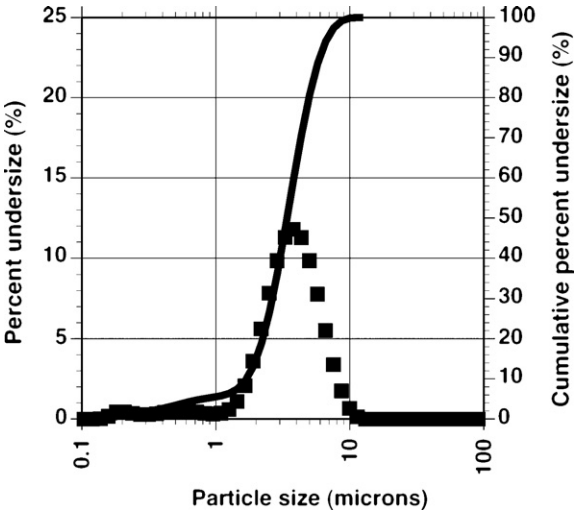

Fig. 1. Mean particle size distribution of mannitol powder measured with laser diffraction ($n = 3$).

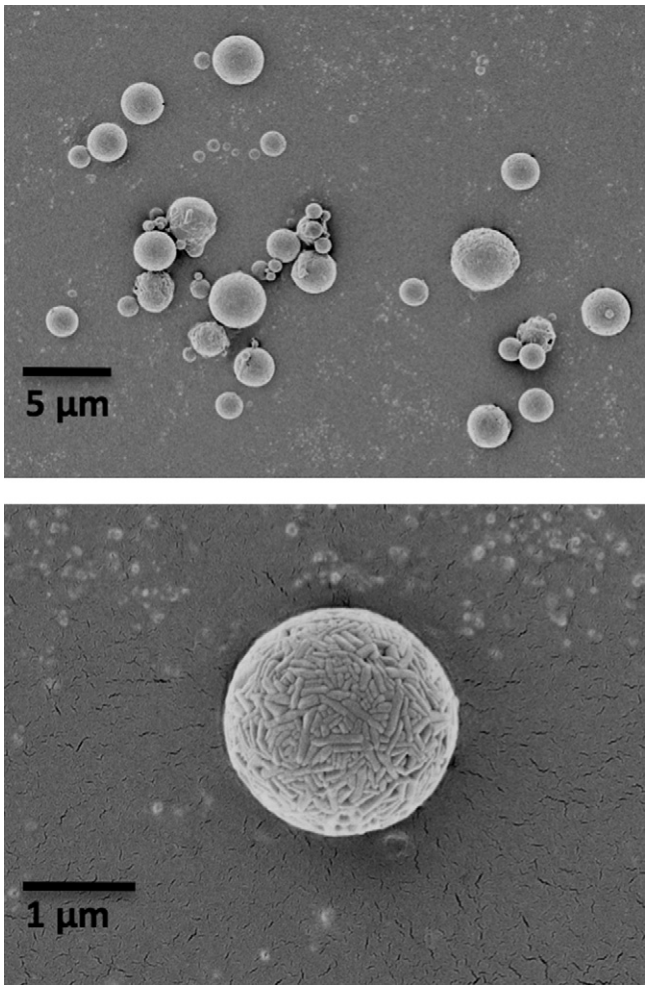

Fig. 2. SEM images of mannitol powder.

3.2. In vitro aerosol assessment

Content uniformity data (Table 2) indicated that all capsule masses were within product specifications for Aridol (±15% of nominal dose), with a relative standard deviation (RSD) ≤5.1%.

The drug mass from each stage of the cascade impactor, throat, adaptor, device, capsule(s) and filter (where present) was determined. In addition, the fine particle dose (FPD) (≤5 μm), fine particle fraction (FPF), mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were calculated from regression of log-linear plots of stage-size verses cumulative stage-deposition [19]. This normalised the data set against variations in impactor cut-off diameters.

The percentage drug recovered from the total of all stages, throat, adaptor, device, capsule(s) and filter (where present) was calculated and plotted against the predicted cumulative nominal dose (Fig. 3). An upper and lower limit of 115% and 85% of the nominal dose were chosen as an indication of impactor system suitability based on the FDA recommendation for DPI systems as previously

Table 2
Capsule content uniformity data for mannitol capsule fill weight.

Nominal dose	5 mg	10 mg	20 mg	40 mg
Mean content	5.0 mg[a]	9.3 mg[a]	18.1 mg[a]	37.5 mg[b]
Standard deviation	0.1 mg	0.5 mg	0.6 mg	1.4 mg
RSD	1.4%	5.1%	3.2%	3.8%

[a] $n = 5$.
[b] $n = 10$.

outlined [10]. Since the content uniformity indicated that fill mass was within ±15% label claim (Table 2), it may be assumed that significant deviation outside these limits will be due to a reduction in impactor efficiency and inter-stage drug losses.

Analysis of the percentage recovery for cumulative dosing to the ACI (Fig. 3A) suggested that less than 85% of the nominal dose was collected for formulations greater than 20 mg. Visual observation of the inter-stage casing showed powder was deposited on the underside, around the jet chamfer, and on the inner walls of the ACI (Fig. 4). The likely reason for such observations is due to a combination of particle bounce, as reported previously [14–16,20], and plate 'saturation' at the impaction zone.

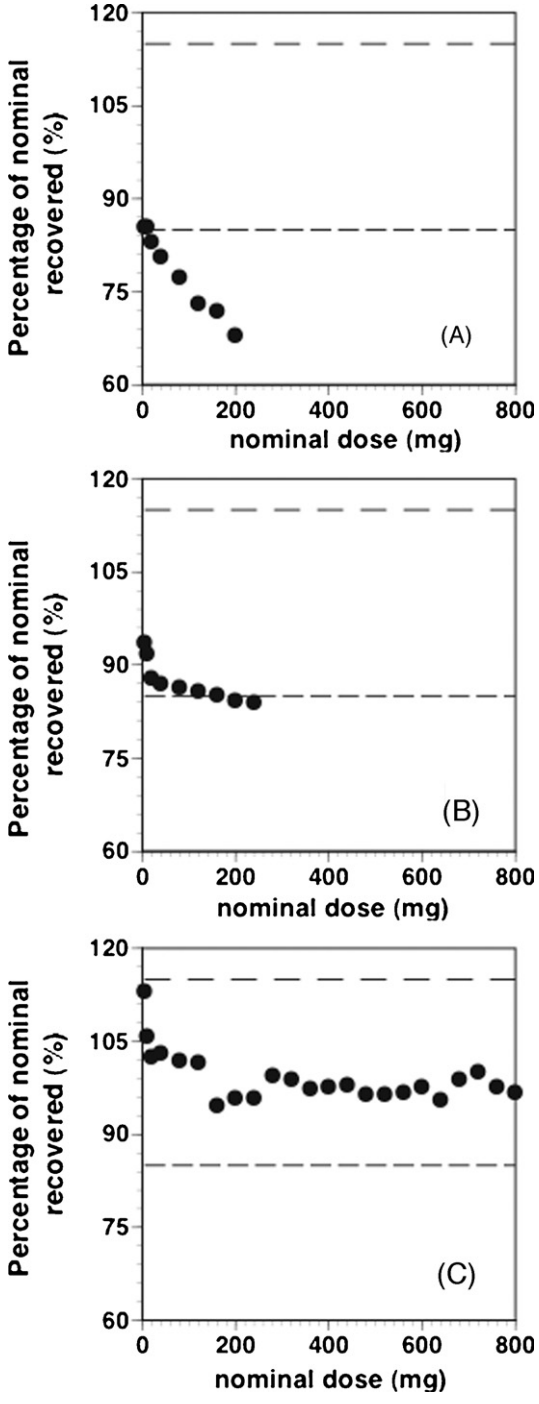

Fig. 3. Total percent mannitol recovered as a function of nominal cumulative dose (A) ACI, (B) NGI and (C) MSLI. Dotted lines represent the 15% limits.

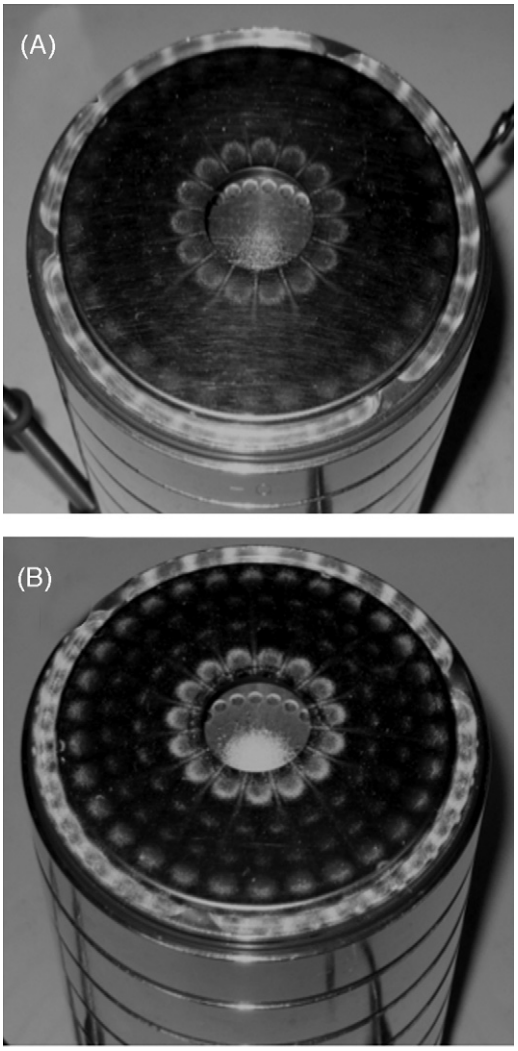

Fig. 4. Photographs of stage 1 of the ACI with (A) 40 mg and (B) 200 mg cumulative dosing showing powder loss on the inter-stage casing.

In comparison, analysis of the NGI data set indicated cumulative doses of ≥200 mg had losses greater than 15% of the nominal dose (Fig. 3B). Based on the recovered mass, all formulations had exceeded the 5% inter-stage loss limit specified in the pharmacopoeias [9] (only 94% mannitol was recovered for the 5 mg formulation). Such inter-stage losses are higher than that reported previously [20] and are most likely due to the difference in the drugs used. Mannitol is highly crystalline, spherical (Fig. 2) and delivered as a drug only formulation. In comparison, the study conducted by Kamyia et al. [20] used a zanamivir-lactose carrier formulation, in which the drug particles are likely to be hygroscopic and plate like [21]. Subsequently, plate deposition in the zanamivir system is likely to be more efficient due to drug–plate contact geometry and higher adhesion.

Analysis of the MSLI data, over a 5–800 mg cumulative dosing range, indicated that the percentage of nominal dose recovered from the MSLI, USP/Ph Eur throat and device components was within the ±15% limits set in the study (Fig. 3C). Furthermore all samples, apart from the 5 mg and 10 mg analysis were within 5% of the nominal cumulative dose. The overall mean percentage nominal dose was 99.4 ± 4.1% indicating that the methodology was suitable for evaluating ultra-high dose formulations such as Aridol.

The FPF, GSD and MMAD across all data sets are shown in Table 3. Regression analysis of the GSD and MMAD values for each impactor,

Table 3
Mean deposition data for mannitol over the dose ranges studied in different impactor models.

	ACI	NGI	MSLI
Dose range studied	5–200 mg	5–240 mg	5–800 mg
GSD[a]	1.67 ± 0.02	1.80 ± 0.14	1.84 ± 0.02
MMAD ($d_{(a)0.5}$) (μm)	3.53 ± 0.13	3.29 ± 0.54	3.81 ± 0.15
FPF (%)[b]	35.7 ± 1.83	33.5 ± 4.58	38.3 ± 3.00

[a] $GSD = [d_{(a)0.84}/d_{(a)0.16}]^{0.5}$.
[b] Percentage mass of particles with an aerodynamic diameter <5 μm based on the nominal fill weight.

as a function of cumulative dose, as previously outlined, showed no clear trend ($R^2 < 0.5$). Interestingly, the intra-variation of GSD and MMAD between impactors also indicated no significant differences (ANOVA analysis of 5–200 mg cumulative doses; $p < 0.05$). Such observations are expected if the mechanism of particle bounce is uniform across all plates, since the geometric standard deviation and median will remain constant.

No relationship between FPF and cumulative dose was observed for the ACI and NGI, where R^2 values of 0.36 and 0.02 were observed, respectively. This observation is counterintuitive, since inter-stage wall losses increase, as a function of dose and thus, the FPF based on the nominal cumulative dose should alter accordingly. Such observations are likely due to the inherent high variability in FPF, where relative standard deviations of 5% and 14% were observed for the ACI and NGI, respectively. As expected, no variation was seen in these parameters for the MSLI.

It is important to note that a limitation of this study is in the cumulative nature of analysis. For example an 800 mg bolus dose may produce significantly different results than 20× 40 mg doses. However, to date, no commercially available device is capable to deliver such high powder loads. Pharmacopeial conventions outline that the use of the smallest single bolus dose is sufficient in determining aerodynamic particle size distributions, making the cumulative high dose testing performed in this study seemingly unnecessary [8,9]. However the emergence of ultra-high doses medication, such as Pumactant (with a single bolus dose of up to 250 mg) highlights the need for the evaluation of impactor performance in these DPI medicines [22].

4. Conclusions

Previous studies have indicated cascade impactors such as the NGI are suitable for the measurement of high dose formulations (~5 mg). However, for ultra-high dose formulations conventional plate and cup-based impactors may not be suitable, even with coating. This study has suggested that both the ACI and NGI falls below the ±15% variation of label claim recommended by the FDA at mannitol doses exceeding 20 mg and 200 mg, respectively. In comparison the MSLI is capable of measuring cumulative doses up to, at least 800 mg. The liquid-based particle collection medium in the MSLI allows more efficient particle entrapment with minimal inter-stage losses. While the MSLI is not routinely used for regulatory submission, the use of this impinger apparatus when studying ultra-high dose formulations should be considered as a complimentary and comparative source of aerosol deposition data.

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