

Chapter 2

Current Approaches to APSD Measurements of OIPs Based on Inertial Impaction

Jolyon P. Mitchell and Daryl L. Roberts

Abstract The AIM and EDA concepts are founded on the principles of inertial impaction of aerosol particles under laminar flow conditions. This chapter examines the current CI systems that are recognized by the pharmaceutical compendia, providing a summary of the key parameters that affect the size-resolving capability of each system. The potential for bias introduced through the assumption that individual stage collection efficiency curves are step functions at the calibration size is explored, with attention given to the effect of removing stages in order to achieve an AIM-based configuration. Non-sizing accessories, such as the induction port (IP) entry and preseparator (PS), are discussed and the chapter concludes with consideration of how add-on devices, such as spacers and VHCs that are commonly used in conjunction with MDIs, should be evaluated.

2.1 Introduction

Aerosols produced by all types of OIP comprise either solid particles or liquid droplets suspended in air that the patient receiving therapy is intended to inhale. If suspended particles are present, each droplet itself will strictly be inhomogeneous, if one or more particles are incorporated within each droplet. For simplicity, the term “particles” will be used from now onwards to include droplets as well as solid particles. Aerosols are by definition semistable phenomena, in that the size distribution of particles continually changes with time due to several physical processes happening simultaneously [1]. The most important of these processes affecting the

J.P. Mitchell (✉)

Trudell Medical International, 725 Third Street, London, ON N5V 5G4, Canada
e-mail: jmitchell@trudellmed.com

D.L. Roberts

MSP Corporation, 5910 Rice Creek Pkwy, Ste 300, Shoreview, MN 55126, USA
e-mail: droberts@mspcorp.com

size range of OIP-produced aerosols (0.5- to 10- μm aerodynamic diameter) are as follows (in no particular order of priority) [2]:

1. Gravitational sedimentation
2. Turbulent deposition to adjacent surfaces
3. Particle–particle agglomeration (if the particle concentration is sufficiently high)
4. Flash evaporation of highly volatile propellants associated with the aerosol formation process with MDIs
5. Evaporation/condensation of associated low-volatility substances (e.g., ethanol cosolvent incorporated with some MDI formulations as well as ambient moisture, if present)
6. Molecular (Brownian) diffusion

The latter process is only significant with the finest particles < ca. 0.5- μm physical (geometric) diameter. The influence of these processes on CI-measured APSDs is reviewed in Chap. 9 (Sect. 9.4) in the context of evaluating how resulting changes in APSD may or may not be detected by the efficient data analysis (EDA) metrics.

This book is concerned with the CI method that determines the aerodynamic rather than physical (e.g., geometric) size of such particles, as would be measured by means of a microscopy-based technique [1]. As a general rule, particles in the size range from about 0.5 to 10 μm in aerodynamic diameter will deposit somewhere in the human respiratory tract (HRT) and larger particles in the upper airways (oropharyngeal region), with finer particles penetrating progressively further into the 23 generations of the airways of the lungs before the finest ultimately reach the alveolar sacs in which gas exchange takes place.

Detailed descriptions of aerosol mechanics associated with transport through the HRT can be found in the books by Hinds [1] and Finlay [2]. The explanation given here is intended to provide the basics in order to understand the capability and limitations of the inertial impaction method for size-characterizing aerosols emitted from OIPs.

Particle motion throughout the airways of the respiratory tract is assumed to take place following Stokes's law, in that the relative velocity of the gas at the surface of the particle is zero. Under Stokesian motion in a stagnant support gas, the force (F_d) acting on a particle in a fluid (air) comprises both form and frictional components, such that

$$F_d = 3\pi\eta_a v_t d_p \quad (2.1)$$

where η_a is the air viscosity which is a function of the temperature of the air, v_t is particle terminal velocity, and d_p is the particle volume-equivalent diameter [i.e., the diameter of a spherical particle of the same volume and the same as the physical (geometric) diameter for particles possessing spherical geometry]. Particles rapidly reach their setting velocity (v_t) when released from rest, and the drag force (F_d) is balanced by the gravitational force F_g , where $F_g = mg$, so that

$$v_t = \frac{\rho_p d_p^2 g}{18\eta} \quad (2.2)$$

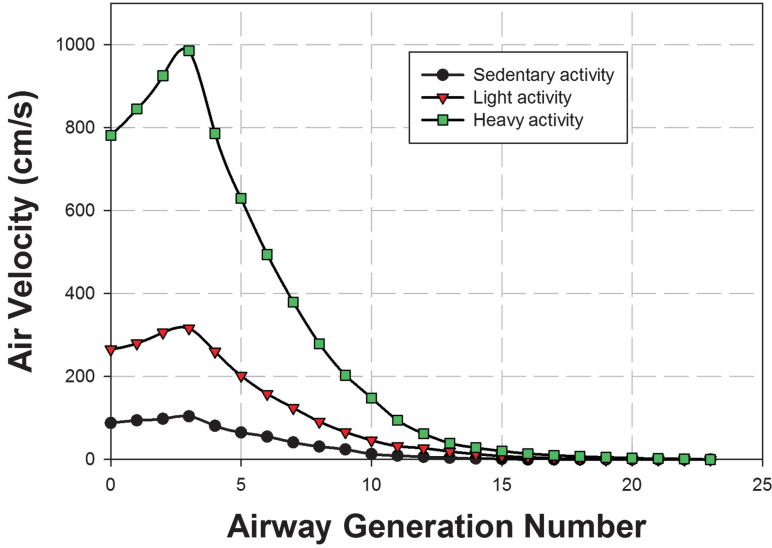


Fig. 2.1 Particle velocity-airway generation profiles in the HRT for three levels of adult physical activity; sedentary is defined as $V_t=500$ mL, 14 breaths/min, and PIFR = 14 L/min; light activity is $V_t=1,291$ mL, 15.5 breaths/min, and PIFR = 40 L/min; heavy activity is $V_t=2,449$ mL, 40 breaths/min, and PIFR = 120 L/min (*adapted from* [3])

Moving from the stagnant environment in which Stokes's law is defined to consider particle motion in the flow through the respiratory tract, an interesting feature is the steady decrease in velocity with increasing airway generation number beyond generation 3 (Fig. 2.1) [3]. In contrast, CIs size particles by increasing the velocity of air from stage to stage, as the aerosol passes through the apparatus. Furthermore, their diameters may decrease slightly during passage, due to the continuous evaporation of any volatile liquid species present, whereas in the HRT, some drug particles may grow due to the presence of near-saturation relative humidity conditions in their immediate surroundings. Hence, although the physical principles of impaction apply equally to the CI as to the lung, these aerosol measurement devices do not in any sense “simulate” the lung, as will be discussed further below.

Aerodynamic diameter (d_{ae}) represents the size scale that takes into account the effect of both particle density and shape on mobility in any flow field, such as in the respiratory tract, and is related to d_p , which is the diameter of a spherical particle (dynamic shape factor, χ , of unity and density of 10^3 kg/m³) through the expression

$$d_{ae} = \left[\frac{\rho_p}{\rho_0 \chi} \right]^{1/2} d_p C_c \quad (2.3)$$

where ρ_p is the particle density (kg/m³). C_c is the Cunningham slip correction factor, which reflects reduction in F_d due to “slip” of the particle by adjacent gas molecules. For particles with $d_{ae} < 1.0$ μ m, C_c can be described in terms of the particle Knudsen

number (Kn_p) in which the size of the particle in terms of d_p is related to the mean free path length of a molecule of the surrounding air (λ), where [1]

$$\text{Kn}_p = 2\lambda / d_p \quad (2.4)$$

and

$$C_c = 1 + 0.5\text{Kn}_p \left[2.34 + 1.05 \exp(-0.195\text{Kn}_p) \right] \quad (2.5)$$

The value of C_c asymptotically approaches unity for particle sizes larger than a few micrometers and can generally be ignored unless the mass-weighted APSD (either differential or cumulative plot of API mass versus d_{ac} [1]) contains an appreciable proportion of particles $< 0.5 \mu\text{m}$.

The multistage CI links the determination of mass of API in the OIP aerosol with d_{ac} and has been therefore accepted by both the compendial [4, 5] and regulatory [6, 7] authorities as the apparatus of choice for sizing these aerosols. Alternative aerodynamic particle size characterization techniques, such as particle time of flight (TOF) in accelerating motion, can size aerosols based on the d_{ac} scale more rapidly than the CI method [8]. However, such near real-time methods do not, at the present time, provide traceability to the mass of API(s) in the formulation through the use of well-defined and widely accepted analytical assay principles (i.e., high-performance liquid chromatography combined with a quantitative spectroscopic detection method, usually UV/visible light absorption or fluorescence that is API specific) [9]. This latter attribute is regarded as being of critical importance by the major regulatory agencies [6, 7]. The foci of this chapter, and the book as a whole, are therefore on OIP aerosol particle sizing by CI-based methods.

2.2 The CI Is Not an In Vitro Analog of the Human Respiratory Tract

It has often, but erroneously, been promoted that multistage CI-derived APSD data can directly indicate the fate of the particles in the human respiratory tract (Fig. 2.2).

If this situation was totally true, such data would be ideal for estimating the likelihood of clinical response in studies of the efficacy and safety of OIPs. However, it is important at the outset to realize that the CI is fundamentally not a lung simulator, as more mechanisms governing particle deposition are at play in the HRT. The difference between the two becomes readily apparent when overlaying the collection efficiency curves of the ACI, chosen as a representative multistage CI, with the corresponding empirical/theoretical particle collection efficiency curves associated with the morphological regions within the respiratory tract (Fig. 2.3).

The relatively poor size selectivity of the HRT has been recognized for many years by the community of aerosol scientists involved with environmental protection [11], where three subfractions covering inhalable particles are currently

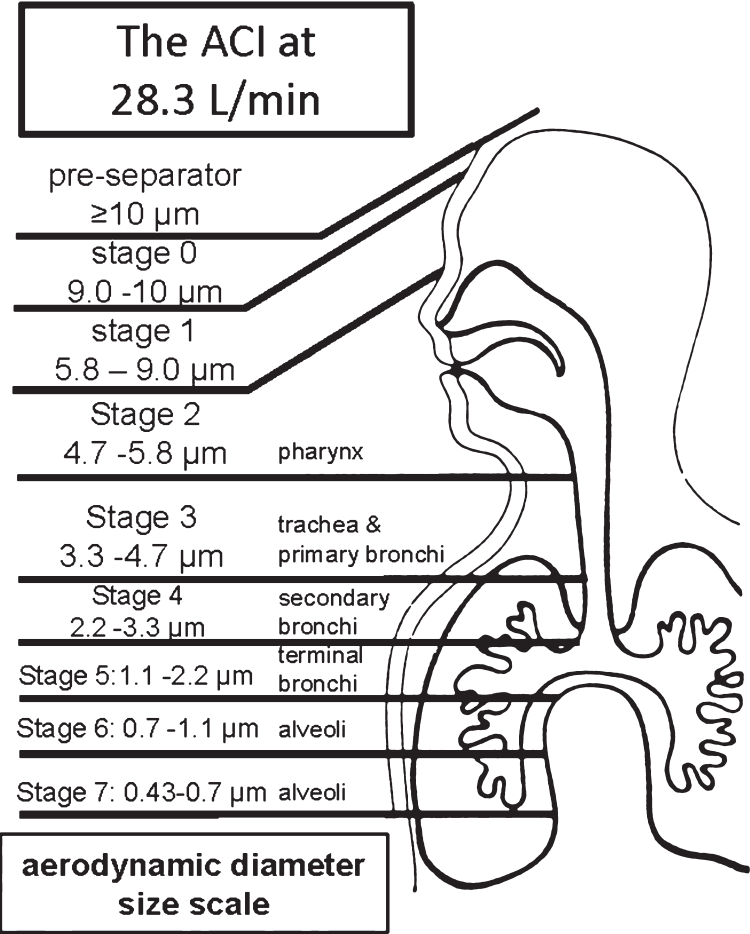


Fig. 2.2 A postulated, but unfounded, relationship of the ACI to particle deposition in the human respiratory tract (*adapted from the operators' manual for the ACI*)

recognized: (1) PM_{10} , suspended coarse particles with $d_{ac} < 10 \mu\text{m}$; (2) $PM_{2.5}$, suspended fine particles with $d_{ac} < 2.5 \mu\text{m}$, analogous to the majority of the fine particles from OIPs; and (3) $PM_{1.0}$, suspended ultrafine particles with $d_{ac} < 1.0 \mu\text{m}$ (approximately equivalent to extrafines from OIPs).

The US FDA, in its 1998 draft Guidance for Industry document relating to Chemistry, Manufacturing and Controls for OIPs [7], recommended treating cascade impaction data as follows: “Data from full resolution CI measurements may also be presented in terms of the percentage of the mass found on the various stages and accessories relative to the label claim. Acceptance criteria may be proposed in terms of appropriate groupings of stages and/or accessories. However, if this approach is

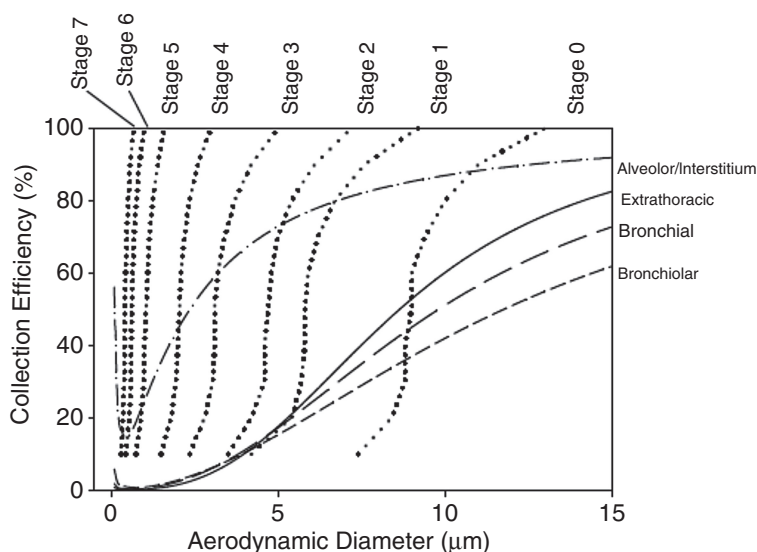


Fig. 2.3 Collection efficiencies of the ACI stages ($Q=28.3$ LPM) and of morphological regions of the lung (PIFR = 28.3 LPM; $V=2$ L; healthy male) (from [10]—used with permission)

used, at a minimum there should be three to four groupings to ensure future batch-to-batch consistency of the particle size distribution.” Currently, these specifications often require that the ratio of the upper to lower allowed mass of API on stage groupings be 1.5:1 or 2:1. However, these ratios are based neither on drug class specific nor on mechanism of action, or on clinical factors, such as patient age and disease modality.

In relation to single clinical dose testing, the corresponding European regulatory guidance [6], which is harmonized with equivalent Health Canada (HC) guidance [12], focuses on the determination of fine particle mass with $d_{ae} < 5 \mu\text{m}$ and only refers to pooling of mass on stages in the context of limited analytical sensitivity for the API. For APSD determination, the EMA and HC guidance documents state: “individual stage particle size distribution data should be provided for the batches used in these studies, as well as data on batches representative of the commercial process.”

From the perspective of product QC, however, OIP performance metrics based on stage groupings or even stage-by-stage data are confounded with respect to changes in APSD, for example, because mass transferred from one group to an adjacent group in direction of either increasing or decreasing aerodynamic size is inevitably associated with a compensating decline in the mass associated with the group from which the mass was transferred (Fig. 2.4). In Chaps. 7 and 8, it will be demonstrated that a suboptimal performance of these metrics for product quality control (QC) purposes exists compared to the capability of the EDA method.

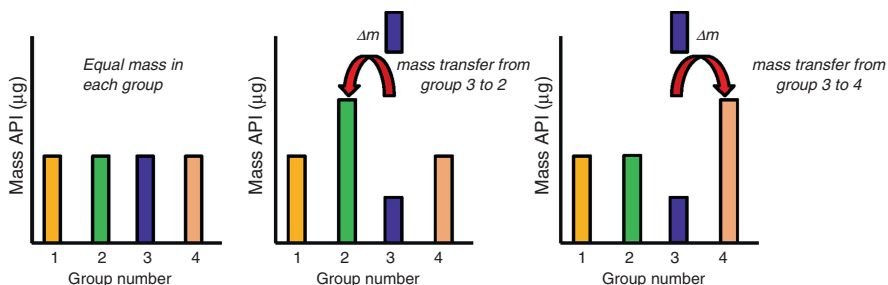


Fig. 2.4 API mass transfer from one stage grouping to its neighbor results in an equal and opposite change to both groupings

2.3 Capability of the Cascade Impaction Method

The multistage CI is fundamentally a particle size-fractionating instrument, making use of differences in particle inertia in (ideally) a laminar flow field to result in either collection on a solid substrate or impingement into a liquid. CIs are designed to operate at a constant flow rate. This limitation therefore becomes an issue in connection with DPI testing, in which it is necessary to approximate an idealized inspiratory maneuver in order to aerosolize and disperse the aliquot of dry powder either from a reservoir or from a punctured retaining capsule/blister. A compromise is reached in the compendial DPI testing procedures, in that although the CI is operated from zero flow at start of sample, sufficient volume of air is drawn through the system (typically 4 L), so that the finest suspended particles have time to pass through the entire apparatus, enabling the CI to properly size fractionate the emitted dose. This requirement places a limit on the lowest sample volume it is reasonable to use, because below this volume there will be insufficient time for the aerosol to pass entirely through the CI system to be fractionated. This minimum volume is based on the magnitude of the internal dead volume of the CI together with the preseparator (PS), if used, and induction port (IP). Recent work undertaken by the European Pharmaceutical Aerosol Group (EPAG), in which this sample volume has been intentionally reduced to be close to the dead volume of the system (ca. 2 L), has confirmed that the APSD is significantly affected in the case of the NGI under such circumstances [13]. In the NGI, operated at 60 L/min, $FPF_{0.94-4.46\mu m}$ was shown to be systematically reduced with decreasing sample volume, reflecting the fact that the finer particles have had insufficient time to move through the CI to the stages at which they would normally be collected. In contrast, the ACI appeared not to be as sensitive as the NGI, with $FPF_{0.76-6.18\mu m}$ remaining nearly independent of sample volume. The underlying reason for this anomalous behavior is not obvious, but it is believed to be likely related to flow maldistribution in the ACI. Given this situation, it is good sampling practice to ensure that the sample volume exceeds the dead volume by at least a factor of two.

The use of CIs in conjunction with breathing simulators is at first sight at odds with the constant flow rate limitation. However, as will be discussed in Chap. 12, various groups have found ways to effect such an interface, enabling the OIP to be operated either through a half cycle (i.e., inspiration only) for DPIs or in conjunction with a continuously varying flow rate cycle associated with mimicking tidal respiration. At the same time, the CI is simultaneously sampling the resulting aerosol at a fixed flow rate. In general, these arrangements are complex [9] and have therefore thus far not been incorporated into the compendial methods. There are also limited validation data available, so that caution is urged before implementing such an approach.

A further limitation of the CI technique is its relatively limited size-resolving capability compared with that obtainable by optical particle detection methods, such as TOF, OPC, LD, PDPA, and even microscopy image analysis [8]. The resolution of a CI is restricted by the finite size range within which a given stage operates, as will be seen in the next section of this chapter. The NGI, designed to optimize resolution, is capable of providing an APSD with at most five measurements of mass within the important range from 0.5- to 5.0- μm aerodynamic diameter [14]. Attempts to develop a CI with greater than this size resolution will fail because the resulting APSDs will inevitably contain intrinsic bias brought about through substantial overlap of the collection efficiency-size profiles of adjacent stages.

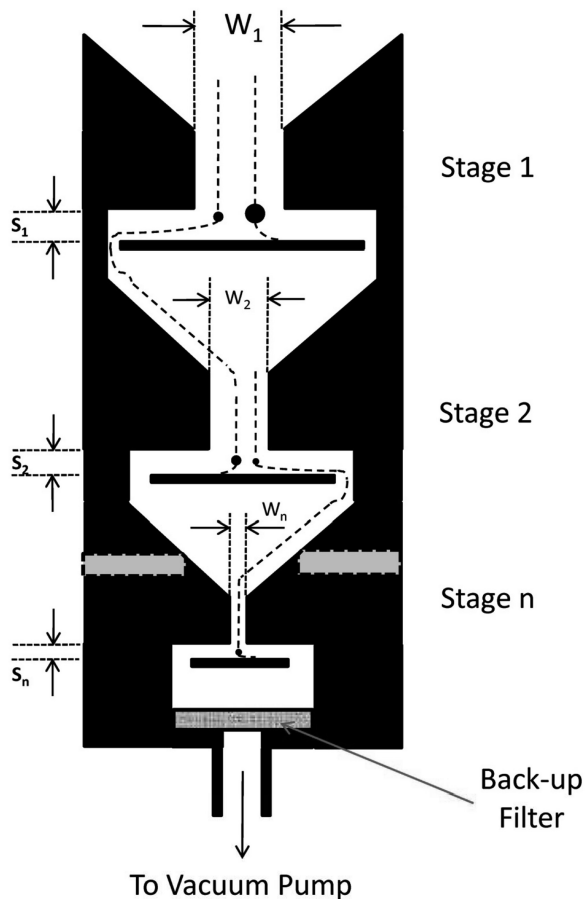
2.4 Fundamentals of Inertial Size Fractionation Affecting Multistage CI Performance

The principles of multistage CIs in the context of in vitro testing of OINDPs were reviewed in 2003 by Mitchell and Nagel [9]. Little of a fundamental nature in terms of the underlying theory has changed since this date, although there has been a concerted effort to acquire a more robust understanding of the processes associated with calibration and validation of full-resolution cascade impaction systems [14, 15].

Key aspects of cascade impaction theory are presented in this chapter to familiarize the reader with sufficient background information to understand the advantages and, perhaps more importantly, the limitations of the AIM-based techniques that are introduced in Chap. 5.

A typical CI used for OIP testing comprises several stages (Fig. 2.5), each of which functions as a size fractionator of the incoming aerosol in a gas stream moving at constant velocity [proportional to volumetric flow rate (Q)]. In concept, a single-stage impactor comprises a jet or nozzle plate containing one or more circular or slot-shaped orifices located a fixed distance from a collection surface that is usually horizontal. The stage functions by classifying incoming particles of various sizes (d_{ae}) on the basis of their differing inertia, the magnitude of which reflects the resistance to a change in direction of the laminar flow streamlines.

Fig. 2.5 Idealized n -stage cascade impactor



As the incoming flow passes through the nozzle plate, the streamlines diverge on approach to the collection surface, whereas the finite inertia of the particles causes them to cross the streamlines, if sufficiently large. The dimensionless Stokes number (St), which is the ratio of the stopping distance of a particle to a characteristic dimension, in this case the nozzle diameter, W (or average diameter, for a multiorifice stage), describes the process. It will be seen later that the square root of St defines a critical particle size in terms of aerodynamic diameter that will succeed in leaving the airstream and reaching the collection surface for a particular stage geometry (Fig. 2.6).

The modern theory underlying impactor function has been developed over the past 35 years based firstly upon solving the Navier–Stokes equations for steady, incompressible, and isothermal conditions that define the gas flow field having viscosity, η , and density, ρ_g , modeling the simplified geometry of a single-stage “ideal” impactor. This operation is undertaken in the absence of particles.

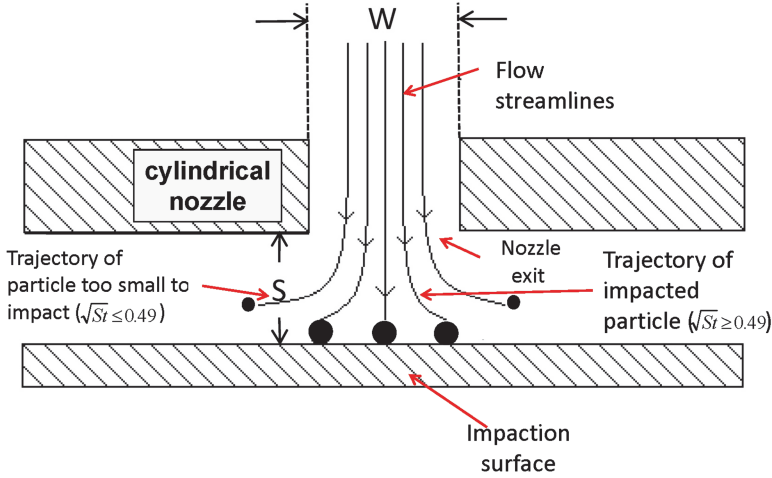


Fig. 2.6 Hypothetical single-stage impactor showing trajectories of particles that are collected and those that miss the collection substrate

Subsequently, Newton's equation of motion is used to model the passage of different-sized particles through the ideal impactor. The process may ultimately be extended to evaluate the particle transport and size fractionation through impactor stages having various nozzle dimensions (diameter, W , and length, L) as well as several nozzle-to-collection surface distances (S) [16]. Flow is normally assumed to be laminar within the stages of the CI. However, if gas flow and particle transport through the induction port inlet are also being modeled, an appropriate model of turbulence such as the low Reynolds number (LRN) $\kappa\omega$ approach can be introduced, based on its ability to accurately predict pressure drop, velocity profiles, and shear stress for transitional and turbulent flows [17].

Returning to the idealized single-nozzle (jet) impactor (Fig. 2.5), St is related to W through the expression

$$St = \frac{\rho_p C_c d_p^2 U}{18\eta W} \quad (2.6)$$

in a self-consistent set of units, based on d_p . U is the linear velocity of the particle, which can be considered the same as the surrounding local air velocity when the flow rate through the impactor is constant. The Cunningham slip correction factor, C_c , that takes into account the faster settling of particles whose size is close to that of the mean free path of the surrounding gas is defined by (2.4) and (2.5).

The particle collection efficiency (E) of an ideal impactor stage, expressed as a percentage, will increase in a stepwise manner between limits of 0–100%. In practice, for a well-designed stage, E is a monotonic sigmoidal function of either St or d_p that increases steeply from $E \approx 0\%$ to $>95\%$, reaching its maximum steepness

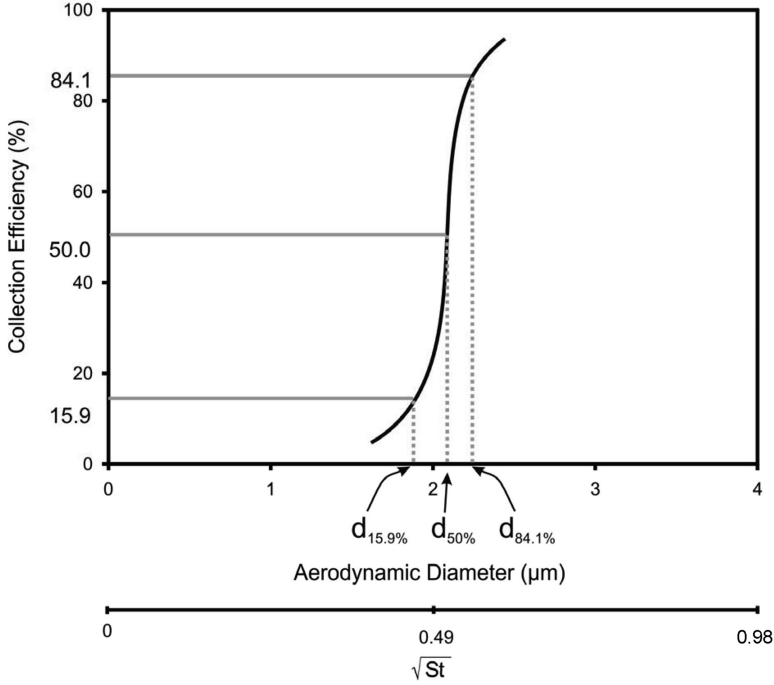


Fig. 2.7 Hypothetic single stage impactor collection efficiency curve

when E is 50% (Fig. 2.7). At this location, defined as the cut size ($d_{p,50}$) or effective cutoff diameter,

$$\sqrt{C_{c,50}} d_{p,50} = \left[\frac{9\eta n W}{\rho_0 U} \right]^{1/2} \sqrt{St_{50}} \quad (2.7)$$

or in terms of volumetric flow rate (Q),

$$\sqrt{C_{c,50}} d_{p,50} = \left[\frac{9\pi\mu n W^3}{4\rho_0 Q} \right]^{1/2} \sqrt{St_{50}} \quad (2.8)$$

for a multiorifice stage comprising n circular nozzles. Equations (2.7) and (2.8) can be written in terms of the more usually encountered aerodynamic diameter scale ($d_{ae,50}$), substituting (2.3) for d_p .

The assumption is often made that the mass of particles larger than d_{50} (the size corresponding to E_{50}) that penetrate the stage is exactly compensated by the mass associated with particles finer than this size that are collected. Thus, the cut size can be defined as a single-valued constant for a given stage at a fixed flow rate. Particles with $d_{ae} \geq d_{50}$ are assumed to be fully collected, whereas all particles finer than d_{50} are

Table 2.1 Values of d_{50} (μm) and GSD_{stage} for the NGI size-fractionating stages at flow rates associated with its archival calibration

$Q=$	15 L/min		30 L/min		60 L/min		100 L/min	
Stage	d_{50}	GSD_{stage}	d_{50}	GSD_{stage}	d_{50}	GSD_{stage}	d_{50}	GSD_{stage}
1 ^a	14.1	1.39	11.7	1.34	8.06	1.33	6.12	1.35
2	8.61	1.16	6.40	1.19	4.46	1.21	3.42	1.26
3	5.39	1.15	3.99	1.21	2.82	1.24	2.18	1.27
4	3.30	1.12	2.30	1.11	1.66	1.17	1.31	1.22
5	2.08	1.14	1.36	1.11	0.94	1.17	0.72	1.20
6	1.36	1.13	0.83	1.14	0.55	1.15	0.40	1.28
7	0.98	1.12	0.54	1.17	0.34	1.20	0.24	1.38

^aPreceded by USP/Ph.Eur. induction port—values are slightly different if a preseparator is also used

deemed to have penetrated the stage. The sharpness of a given CI stage efficiency curve is defined in terms of the geometric standard deviation (GSD_{stage}) by analogy with the properties of the lognormal distribution function:

$$GSD_{\text{stage}} = \sqrt{\frac{d_{84.1}}{d_{15.9}}} \quad (2.9)$$

A stage having its GSD_{stage} at unity corresponds to the ideal size separator. In practice, however, GSD_{stage} is ideally <1.2 . GSD_{stage} values in excess of this limit do occur with compendial CIs, particularly for those stages that size fractionate particles larger than about $5 \mu\text{m}$ aerodynamic diameter where gravitational settling contributes significantly to the size-separation process. Values of d_{50} and GSD_{stage} can be determined by calibration of the impactor with uniform-sized particles of known mean values of d_{ae} ; however, the process is both time-consuming and highly exacting [18–20]. A further refinement of the calibration process is to undertake a so-called archival calibration of a single CI whose stage dimensions (principally nozzle diameters) have been intentionally manufactured to be as close as possible to their nominal values. This procedure avoids the need to calibrate each and every CI at the time of manufacture and also after use for validation purposes. Such a calibration was undertaken for the first time early in the development for the NGI at volumetric flow rates of 100, 60, and 30 L/min [21] and later extended to 15 L/min to enable this CI to be used for the measurement of nebulizing systems [22]. Values of d_{50} and GSD_{stage} from these archival calibrations are summarized in Table 2.1.

Equivalent information is given in Table 2.2 for the ACI at 28.3 L/min that is widely used for MDI-based evaluations. However, to date, an archival calibration of the ACI has not been undertaken, so the actual values of d_{50} and GSD_{stage} are presented based on the historic data provided by Vaughan in 1989 [19]. These calibration-produced d_{50} values are compared with the corresponding nominal values that have been adopted by manufacturers of this impactor since that time. It is important to note that it is common practice to work with the nominal values of d_{50} for the stages of ACI. However, Stein and Olson, in an extensive investigation of impactors manufactured before the year 1995, reported that significant deviations in

Table 2.2 Values of d_{50} (μm) and $\text{GSD}_{\text{stage}}$ for the size-fractionating stages of the ACI at $Q=28.3$ L/min

Stage	Nominal d_{50}	Calibration d_{50}	Calibration $\text{GSD}_{\text{stage}}$
0	9.0	9.0	1.15
1	5.8	6.0	1.17
2	4.7	5.7	1.20
3	3.3	3.1	1.22
4	2.1	2.1	1.20
5	1.1	0.9	1.23
6	0.7	0.6	1.21
7	0.4	ND	ND

ND not determined

nozzle diameters from nominal were possible as the result of imperfections during manufacture as well as the expected result of wear (corrosion/plugging) in normal use [23]. Later in this chapter, the importance of having an accurate understanding of each stage collection efficiency curve profile will be explained, since an understanding of the issues involved is essential in the context of abbreviating full-resolution impactors by the process of removing intermediate stages that is at the heart of the AIM concept.

Returning to the basic impactor theory, Marple and Liu [16] and Rader and Marple [24] identified that the value of $\sqrt{St}$ at E_{50} , defined as $\sqrt{St_{50}}$, should be close to 0.49 for well-designed circular-profiled nozzles, where differences in particle inertia dominate the size-separation process. The compendial CIs include only round nozzles, although other geometries, such as a slit, are possible. However, at least two other parameters have a secondary influence on the particle size-separation performance of a CI. The ratio of nozzle-to-collection surface distance/nozzle diameter (S/W) describes the geometry of the stage. The value of $\sqrt{St_{50}}$ is unaffected by small variations in S/W if S/W is between 1.0 and 10.0. At the same time, the dimensionless flow Reynolds number (Re_f), defined as

$$\text{Re}_f = \frac{\rho_g UW}{\eta} \quad (2.10)$$

should ideally be in the range 500–3,000 to minimize the value of $\text{GSD}_{\text{stage}}$. However, this criterion may be overstringent [25], as indicated by the summary of the ACI design information presented in 1998 by Marple et al. for the ACI [26], where several stages do not meet this criterion yet function effectively as size fractionators at 28.3 L/min (Table 2.3).

The ratio of nozzle throat length (T) to W can also influence size-separation efficiency, decreasing $\sqrt{St_{50}}$ with increasing T/W [16]. However, the effect is likely to be small with commercially available impactors, where T/W is typically <10 [25].

Cross-flow, induced by air exiting the nozzles near the center of the nozzle plate and flowing outwards past other air jets located near the periphery of the nozzle cluster, can prevent the air jets near the edge of the cluster from reaching

Table 2.3 Original design characteristics of the ACI at 28.3 L/min (*From [26]—used with permission*)

Stage	0	1	2	3	4	5	6	7
d_{50}^a (μm)	9.0	5.8	4.7	3.3	2.1	1.1	0.65	0.43
Re_i	163	221	110	141	188	292	394	782
S/W^b	0.4	0.54	2.37	3.05	4.07	6.32	8.54	8.54
X_c	—	—	1.2	0.93	0.69	0.44	0.33	0.16

^aNominal cut-point sizes

^bThe nominal value of S is 1.6 mm (see Table 2.5)

the impaction plate with multinozzle designs [28]. Under these circumstances, particles that would otherwise be collected are instead captured by the cross-flow and transferred beyond the collection surface. Increased interstage losses as well as bias towards smaller sizes can therefore result with multistage impactors. The dimensionless cross-flow parameter (X_c) is defined as

$$X_c = \frac{nW}{4D_c} \quad (2.11)$$

where n is the number of nozzles per stage having nominal nozzle diameter, W , and D_c is the diameter of the overall cluster of nozzles in a multinozzle impactor stage. Values of X_c are listed in Table 2.3 for the ACI calibration by Vaughan [19].

It follows from its definition that X_c for a given stage remains unaltered if the design of the CI is fixed irrespective of design flow rate, as will be seen later is the case with any of the Marple-Miller model 150/160 variants or the NGI. This parameter should be <1.2 to avoid cross-flow-related problems that can lead to unacceptably high internal wall losses. This criterion is achieved for all of the commonly encountered CIs used with inhaler testing, with the notable exception of stage 2 of the ACI, where X_c is 1.2.

In 2000, Nichols and Smurthwaite [29] and Nichols et al. [30] extended the use of the ACI to higher flow rates primarily for the purpose of performance-testing DPIs. At 60 L/min, stage 7 is removed from the bottom of the stack and replaced by a new stage “-1” that is located immediately above stage “0.” If the ACI is to be used at 90 L/min, stage 6 is also removed and replaced by a further new stage “-2” (Table 2.4).

Stage-1 comprises 96 nozzles, each with 4.5-mm diameter, whereas stage-2 contains 95 nozzles, each with 5.5-mm diameter. Importantly, in 2004, Byron et al. published definitive data for current production ACIs, superseding performance data developed from previous versions of this CI as the result of drawing changes to make manufacture of this impactor a more robust process [31]. These changes, together with the alternative high flow rate configurations, modify the original ACI design characteristics given in Table 2.3 to those summarized in Table 2.5.

Small differences and discrepancies remain between various reports of the values of parameters in the ACI. For example, one manufacturer’s user guide establishes the d_{50} of stage 5 at 90 L/min to be 0.44 μm (BGI, Waltham, MA, USA). Although this value appears to be unsupported by a technical reference, it is rather

Table 2.4 Stage d_{50} values for the ACI with standard configuration for operation at 28.3 L/min compared with specialized configurations for use at 60 and 90 L/min (*From [27]—used with permission*)

Stage	28.3 L/min	60 L/min	90 L/min
−2	—	—	8.0
−1	—	8.6	6.5
0 ^a	9.0	6.5	5.2
1	5.8	4.4	3.5
2	4.7	3.2	2.6
3	3.3	1.9	1.7
4	2.1	1.2	1.0
5	1.1	0.55	0.22
6	0.7	0.26	—
7	0.4	—	—

^aThe version of stage 0 used at 60 and 90 L/min has external modification permitting another stage, rather than the inlet adapter cone to be fitted above it. Its internal characteristics and performance are unaltered

Table 2.5 Design characteristics of the current ACI for $Q=28.3$, 60, and 90 L/min

Stage	−2 ^a	−1 ^a	0	1	2	3	4	5	6	7
W (mm)	5.50	4.50	2.55	1.89	0.914	0.711	0.533	0.343	0.254	0.254
N	95	96	96	96	400	400	400	400	400	201
Re_f at 28.3 L/min	—	—	163	221	110	141	188	292	394	782
Re_f at 60 L/min	—	194	346	469	233	299	399	619	835	—
Re_f at 90 L/min	241	291	518	703	350	448	598	929	—	—
S/W^b at all Q	0.29	0.36	0.63	0.85	1.75	2.25	3.00	4.66	6.30	6.30
X_c at all Q	N/A	N/A	N/A	N/A	1.2	0.93	0.69	0.44	0.33	0.16

^aStage −2 and −1 data provided by Mike Smurthwaite (Westech Instrument Services, UK), 2011—other data from Byron et al. [27] (Used with permission)

^bThe nominal value of S used in the calculations of S/W is 1.6 mm, but values between 1.5 and 1.7 mm have been observed with individual CIs

close to the value predicted by extrapolation from the 60 L/min value of 0.55 μm . Indeed the values of d_{50} of stage 6 at 60 L/min and stage 5 at 90 L/min recorded in Table 2.4 are much smaller than the values predicted by extrapolating from the previous lower flow rate figures. And although the user guides of manufacturers of the ACI may cite the Vaughan calibration of the ACI at 28.3 L/min [19] as definitive, Vaughan actually reported the d_{50} for stage 2 to be 5.7 μm , rather than the generally accepted value of 4.7 μm for this particular stage.

Note also that the value of 4.7 μm for stage 2 at 28.3 L/min has recently been confirmed by Roberts, undertaking a more rigorous calibration with monodisperse standard particles akin to that used for the archival NGI calibration measurements [32]. It should also be noted that the jet-to-plate distance, S , is 1.6 mm, as reported by Roberts [14].

Table 2.6 Flow Reynolds numbers (Re_f dimensionless) associated with the four-stage MSLI at different flow rates (Q)

	Stage	1	2	3	4
	S/W	0.38	0.39	0.50	2.22
Q (L/min)	X_c	N/A	N/A	N/A	0.31
20		1,132	2,018	3,552	1,485
30		1,701	3,030	5,334	2,250
40		2,267	4,043	7,115	3,002
50		2,835	5,049	8,886	3,749
60		3,401	6,061	10,667	4,500
70		3,962	7,073	12,449	5,252

Table 2.7 Stage d_{50} values (μm) for the four-stage MSLI at $Q = 60$ L/min (From [26]—used with permission)

Stage	1	2	3	4
d_{50}	13.0	6.8	3.1	1.7

Overall, the available literature indicates that some historical differences exist between commercially available ACIs and some uncertainties exist in the performance characteristics of the basic ACI design.

In the case of the multistage liquid impinger (MSLI), cited as one of the standard apparatuses for aerodynamic assessment of OIP aerosols in the European Pharmacopoeia the values of S/W are lower than the recommended range for all except stage 4 and values of Re_f are in general much higher than their equivalents with the ACI at ca. 30 L/min. Table 2.6 summarizes the design properties of the MSLI at different flow rates [33].

Particle bounce and re-entrainment are avoided altogether because particles are captured in the impingement fluid ready for recovery and subsequent assay. However, this design results in shallower collection efficiency curves that are indicative of poorer size selectivity, and the d_{50} sizes (Table 2.7) are therefore likely to be more dependent upon small changes in either S or W compared with either the ACI or NGI systems.

The Marple-Miller series of five-stage impactors (MMI), cited in the US Pharmacopoeia, are currently available in three sizes, all based on the original work of Miller [34] and Marple et al. [35]. A low-flow rate version (model 150P) was developed in the late 1990s to permit MDIs with add-on devices intended for low-flow patients to be tested at more appropriate conditions of use (4.9 and 12 L/min) [36]. This addition enables measurements to be made by MMIs at flow rates ranging from 4.9 to 90 L/min with d_{50} values that are all located within the useful range for all types of OIP testing (Table 2.8).

Stage collection efficiency curves for all versions of this CI expressed either in terms of d_{ac} or $\sqrt{St}$ are steep and associated with GSD_{stage} values that are close to or below 1.2 (Table 2.9).

Table 2.8 Stage d_{50} values (μm) for the Marple-Miller five-stage CIs

Stage	Model and design flow rate (Q)				
	150P		150	160	
	4.9 (L/min)	12.0 (L/min)	30 (L/min)	60 (L/min)	90 (L/min)
1	10.0	10.0	10.0	10.0	8.1
2	7.2	4.7	5.0	5.0	4.0
3	4.7	3.1	2.5	2.5	2.0
4	3.1	2.0	1.25	1.25	1.0
5	0.77	0.44	0.63	0.63	0.5

Table 2.9 Design characteristics of the Marple-Miller CI variants at $Q=4.9, 12.0, 30, 60,$ and 90 L/min

Model	Parameter	Q (L/min)	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
150/160	Re_f	30, 60	3,160	1,240	1,240	1,260	1,260
		90	4,740	1,860	1,860	1,890	1,890
	S/W	30, 60, 90	1.0	1.0	1.0	1.2	2.5
	X_c	30, 60, 90	N/A	0.37	0.37	0.37	0.36
150P	Re_f	4.9	918	539	453	386	548
		12.0	1,765	1,320	1,109	945	1,342
	S/W	4.9	1.71	5.36	4.43	3.84	5.03
		12.0	1.31				
	X_c	4.9, 12.0	N/A	0.18	0.21	0.25	0.17

These CIs were first designed for OIP testing to make use of collection cups as particle collectors, with the purpose of improving productivity. However, API recovery can be more difficult than with the simpler geometry of collection plates with recovery procedures requiring more than contact with solvent to dissolve the collected particles. The model 160 (high flow) MMI is the standard configuration intended for use at 60–90 L/min. The model 150 MMI has half the number of nozzles per stage compared with the model 160 MMI, for use as an alternative to the ACI for MDI characterization at 30–60 L/min.

Although these CIs have not been as widely adopted as the ACI, NGI, or MSLI, internal losses for models 150 and 160 MMIs reported by Marple et al. were no more than 5% of the incoming aerosol at worst case ($4\text{ }\mu\text{m} < d_{ac} < 6\text{ }\mu\text{m}$), decreasing to <1% for finer particle sizes and <2% for larger particles [35]. These measurements were based on calibration with monodisperse droplets.

The model 160 MMI has subsequently been reported as having internal losses at 60 L/min with at least one DPI (Bricanyl Turbuhaler®, AstraZeneca, Sweden) that were comparable with those indicated by Marple et al. [35], provided that precautions were taken to eliminate particle bounce and re-entrainment by coating the collection surfaces with a tacky surface (silicone oil) [37]. By comparison, losses within the low-flow MMI have also been reported as being <5% of the material balance from two types of MDI-generated formulations [36].

Table 2.10 Values of X_c , S/W , Re_f , and d_{50} (μm) for the NGI size-fractionating stages at flow rates (Q) associated with its archival calibration

All flow rates								
Stage	1	2	3	4	5	6	7	MOC ^a
X_c	N/A ^b	N/A ^b	0.35	0.41	0.61	0.84	0.85	0.94
S/W	1.0	2.0	3.0	3.0	3.0	3.1	4.9	7.1
$Q = 15 \text{ L/min}$								
d_{50}	14.1	8.61	5.39	3.30	2.08	1.36	0.98	Do not use
Re_f	1,482	724	404	338	230	167	166	
$Q = 30 \text{ L/min}$								
d_{50}	11.8	6.40	3.97	2.30	1.36	0.83	0.54	0.36
Re_f	2,938	1,435	801	669	455	328	324	149
$Q = 60 \text{ L/min}$								
d_{50}	8.06	4.46	2.82	1.66	0.94	0.55	0.34	0.14
Re_f	5,876	2,870	1,602	1,339	909	757	647	298
$Q = 100 \text{ L/min}$								
d_{50}	6.12	3.42	2.18	1.31	0.72	0.40	0.24	0.07
Re_f	9,793	4,783	2,671	2,231	1,515	1,095	1,079	496

^aMOC micro-orifice collector—used as an alternative to a backup filter; note that the size corresponding to 80% collection efficiency (d_{80}) rather than d_{50} values are quoted for this equivalent to a backup filter, rather than an impaction stage

^bSingle-nozzle geometry; therefore, cross-flow parameter does not apply

In summary, there is some freedom in establishing the precise location of the collection surface beneath the nozzle plate with many impactor designs except perhaps the MSLI. This flexibility is available for the ACI and NGI, which are the apparatuses most likely these days to be used in OIP aerosol characterization. More importantly from a user's standpoint, small variations in the precise thickness (depth) of a tacky coating that could be applied under normal circumstances to the collection surfaces, to improve particle adhesion, are unlikely to affect stage performance. As will be seen in Chap. 10, the ability to mitigate bias due to particle bounce and blowoff from the collection surface is particularly important with abbreviated systems when used to characterize both MDI- and DPI-generated aerosols.

The NGI represents the state of the art for CI design. Based on their experience with the Marple-Miller series of CIs, the developers of the NGI took the opportunity to ensure that the criterion for S/W was met for all stages (Table 2.10). Likewise, the multinozzle designs of stages 3–7 and the MOC were arranged such that values of X_c were significantly <1.2 . Some values of Re_f are <500 for certain stages, particularly those that size fractionate the finer particles and when operating this CI at the lower flow rates within its range [38]. Nevertheless, all stage collection efficiency curves for this impactor throughout the original design range of operation from 30 to 100 L/min were shown to be sharply defined with minimal overlap [21]. Even at the lower flow rate extension at 15 L/min for nebulizer testing, these curves are still acceptable for size-fractionating purposes [22]. Note, however, that the MOC should be followed by a final filter or the internal filter option be used to replace the MOC when used at 15 L/min [22].

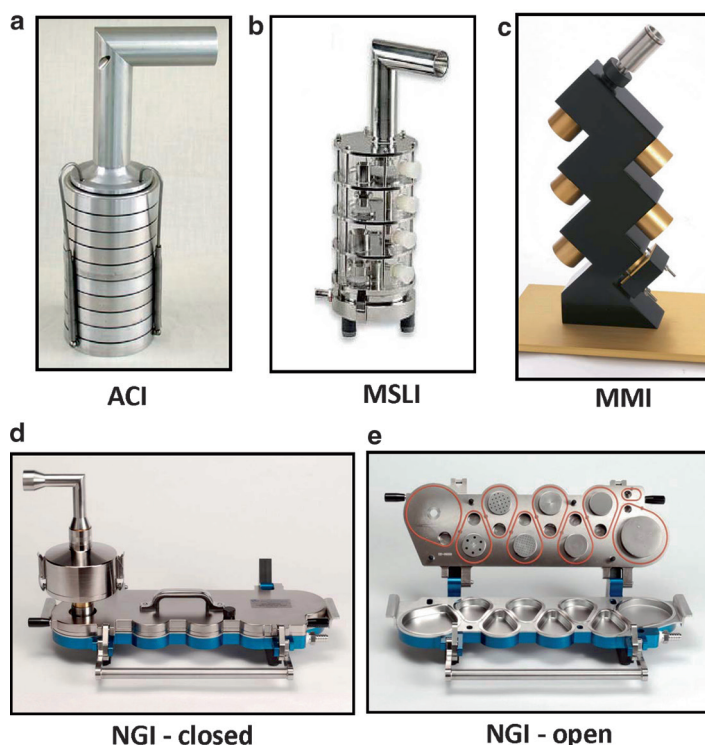


Fig. 2.8 External appearance of the (a) ACI, (b) MSLI, (c) MMI, and (d) and (e) NGI

In the designs of the ACI (Fig. 2.8a), MSLI (Fig. 2.8b), and MMI (Fig. 2.8c) systems, the individual impaction stages are connected together in a more-or-less vertical alignment. It is notable, however, that the NGI has all of its stages located adjacent to each other in the horizontal plane (Fig. 2.8d, e). This configuration was chosen primarily for ease of use for semi- or fully automated operation.

The function of a multistage CI is primarily to fractionate the incoming aerosol into progressively finer particle sizes, beginning with the coarsest particles. The linear air velocity, U , is therefore increased in a series of well-defined steps as the aerosol particles move from one stage to the next throughout the sequence. These increases are put into effect primarily by reductions in the nozzle diameter (W) from one stage to the next in the series. However, the number of nozzles per stage (n) as well as the number of stages within the CI can also be adjusted to optimize size resolution and minimize pressure drop across especially the stages that size separate the finest subfractions. It is important to note that inserting more than five stages per decade of particle size is counterproductive with this technology, because the stage(s) immediately before a given stage will interfere with efficient particle collection, due to the nonideal nature of their collection efficiency curves. This practical

restriction therefore limited the design of the NGI such that a maximum of five stages with d_{50} sizes in the range from 0.5 to 5 μm aerodynamic diameter was possible at most flow rates within the range 30–100 L/min [38].

2.5 Potential Bias Arising from the Assumption That Stage Collection Efficiency Profiles Are Each Step Functions at the d_{50} Value Appropriate to the Stage Under Consideration

In the previous section, the performance characteristics for the most widely used CIs were described on the basis of an assumption that each stage d_{50} size is truly representative of the particle aerodynamic diameter at which size fractionation takes place. Hence, APSDs are usually reported with data points for the stages on the size axis based on their d_{50} values so that in a typical data analysis method, the size of particles on each CI stage is considered to be larger than its d_{50} . With this assumption, it is possible to calculate the values of *MMAD* and *GSD* representing measures of central tendency and spread respectively of an APSD. Note that the determination of *GSD* is calculated on the basis that the APSD is both unimodal and lognormal, assumptions that are in most cases valid for OIP-generated aerosols.

In atmospheric aerosol research where CIs are also widely used, the nonideal nature of stage collection efficiency profiles has been tackled by many groups, with well-accepted methods in place, based on MPS data inversion that is predicated on knowing the functional form of the stage collection efficiency curves [39–41]. However, this approach had not been brought into the assessment of OIP aerosols until recently. It is highly germane to the abbreviation of CIs, since any overlap that might be significant in the collection efficiency profiles of adjacent stages of the full-resolution CI configuration is likely no longer present.

Roberts and Mitchell have therefore evaluated theoretically the potential impact of assuming a step function change in stage collection efficiency in both the full-resolution ACI and NGI systems [42] and have also extended the analysis to include abbreviated versions of these CIs [43]. In the analysis of the full-resolution CIs, they postulated an aerosol entering the NGI or ACI to have a lognormal distribution of particles with known *MMAD* and *GSD*, an assumption not far from the true condition for most OIPs. On this basis, the fraction of the mass that deposits on stage “*N*” is given by

$$f_N = \frac{1}{\sqrt{2\pi}} \frac{1}{\ln \sigma_g} \cdot \int_0^\infty \frac{1}{x} \exp \left[-\frac{1}{2} \frac{(\ln x - \ln[MMAD])^2}{(\ln \sigma_g)^2} \right] \cdot E_N(x) \left[(1 - E_0(x))(1 - E_1(x)) \dots (1 - E_{N-1}(x)) \right] dx \quad (2.12)$$

Table 2.11 Parameters for
ACI stage collection
efficiency curves at
 $Q = 28.3$ L/min

Stage	A (μm^{-1})	B (dimensionless)
0	-1.324	12.51
1	-1.874	11.39
2	-1.928	9.604
3	-2.808	9.329
4	-4.494	9.668
5	-8.258	8.787
6	-14.82	9.483
7	-17.76	7.725

Here, σ_g is the geometric standard deviation (GSD). The quantities $E_0 \dots E_N$ are the fractional efficiency curves of stages 0– N of the CI.

They then developed analytical forms of the real stage efficiency curves of both CIs. For the NGI, these were based on the hyperbolic tangent functional form first described by Rader et al. [40] to compute how this model aerosol distributed itself on each stage of the CI under consideration:

$$E_i(d_{pc}) = \tanh \left[\left(\frac{d_{pc}}{Y_i} \right)^{Z_i} \right] \quad (2.13)$$

in which d_{pc} is the modified particle diameter corrected for slip in accordance with the expression

$$d_{pc} = d_p \sqrt{\frac{\rho_p}{\rho_0}} \sqrt{C_c} = d_{ae} \sqrt{C_c (d_{ae})} \quad (2.14)$$

and Y_i and Z_i are best fit parameters for each impaction stage. The values of the parameters in (2.13) that fit the archival calibration data for the NGI are in the supplementary information associated with Roberts [14] and available on-line at <http://www.tandfonline.com/doi/suppl/10.1080/02786820903204060>

For the ACI at 28.3 L/min, Roberts and Mitchell used the exponential function developed by Gulak et al. [44] for the stage efficiency curves:

$$E_i(d_{ae}) = \frac{1}{1 + \exp(A_i d_{ae} + B_i)} \quad (2.15)$$

Table 2.11 lists the values of the parameters A_i and B_i that best fitted the adjusted calibration data of Vaughan for this CI.

When calculated MMAD and GSD parameters for selected APSDs were compared with those of hypothetical aerosols likely to be encountered with OIPs that entered the NGI or ACI (using CITDAS® software; version 3.00, Copley Scientific, Nottingham, UK), the differences were at most 5% for the MMAD and 11% for the

Table 2.12 Comparison of input MMAD and GSD with CITDAS[®]-generated values for both ACI and NGI (*From [42], courtesy of DL Roberts and JP Mitchell*)

Input APSD		ACI: $Q=28.3$ L/min		NGI: $Q=30.0$ L/min	
MMAD (μm)	GSD	MMAD (μm)	GSD	MMAD (μm)	GSD
1.10	2.0	1.16	1.98	1.10	2.00
2.50	2.0	2.53	1.99	2.57	2.08
4.00	2.0	3.96	1.93	4.12	2.07
5.00	2.0	4.77	1.96	5.02	2.06
4.00	1.5	4.00	1.50	4.17	1.57
4.00	1.2	3.98	1.26	4.13	1.33

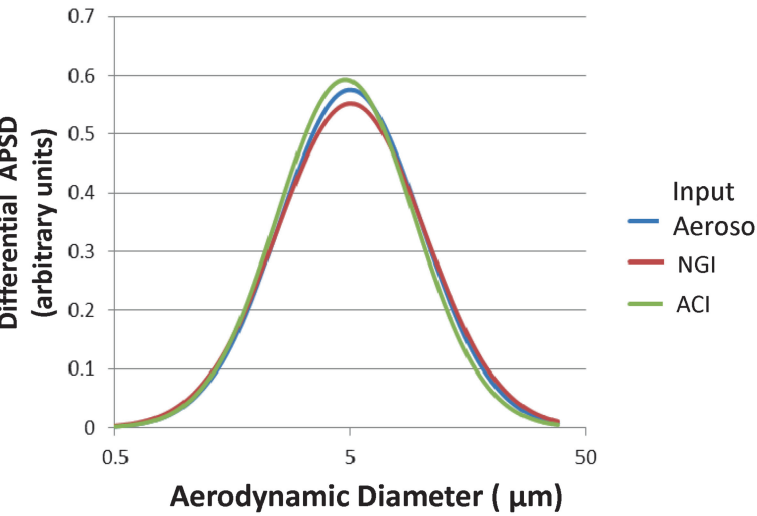
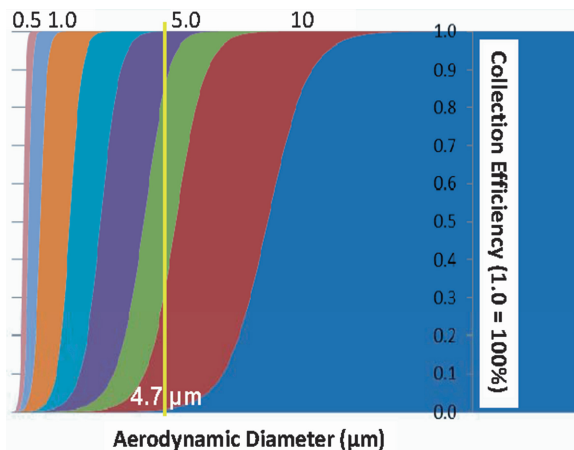


Fig. 2.9 Input and calculated APSDs from a hypothetical OIP-generated unimodal, lognormal distributed aerosol having MMAD of 5 μm and GSD of 2.0 (*From [42], courtesy of D L Roberts and J P Mitchell*)

GSD values (Table 2.12). The larger discrepancies arose as the result not so much because of the nonideal nature of stage collection efficiency curves but because of the inaccuracies of the two-point linearization of the lognormal curve fit. These divergences were more evident when the MMAD of the input aerosol was nearly identical with one of the stage d_{50} values.

The difference between the input and the calculated aerosol APSDs is illustrated in the example shown in Fig. 2.9 where the input MMAD and GSD were chosen to be 5 μm and 2.0, respectively. This example was chosen because the differences between input and calculated APSDs arose mostly as the result of overlap between neighboring CI stages. The calculated APSD from the NGI data was very close to that of the input aerosol, whereas the calculated APSD for the ACI was shifted only slightly to finer sizes, mostly as a result of the significant overlap between stage 2 and stages 1 and 3 with this CI. This finding most probably arises because of the

Fig. 2.10 Stage collection efficiency curves for the full-resolution ACI at 28.3 L/min, based on the adjusted calibration data of Vaughan [19] (From [42], courtesy of D L Roberts and J P Mitchell)



symmetry of each collection efficiency curve about the d_{50} value. Under such a condition, the mass of API that is associated with particles large enough that they should have been captured is almost counterbalanced by the mass of API contained in finer particles that should have penetrated the stage in question.

Roberts and Mitchell concluded that these differences would likely be unimportant in understanding the aerosol coming from an OIP [42]. Their assessment was based in part on recent industry guidance from the EMA, in which bounds of $\pm 15\%$ are deemed equivalent from in vitro measurements in regulatory submissions (i.e., for target dose and for comparison of CI stage deposition between reference and test OIP [44]).

In their follow-on assessment of abbreviated ACI and NGI systems, Roberts and Mitchell adapted the same approach by comparing abbreviated with full-resolution CI results calculated from hypothetical aerosols with unimodal and lognormal APSDs [43]. It is important to note that the amount of overlap from stage to neighboring stage in an abbreviated CI is greatly reduced or even abolished compared with the situation that exists in a full-resolution CI of the same design. As a result, however, even for the same input aerosol, the APSD of the aerosol approaching a given stage of an abbreviated impactor is different to that which exists when approaching the sequence of individual stages of the full-resolution system. This situation exists even if some of the stages of the abbreviated CI are identical to those of the full-resolution CI.

In the case of the ACI operated at 28.3 L/min, the problem was summarized by comparing the stage collection efficiency curves for the full-resolution CI operated at 28.3 L/min to the corresponding profiles of the remaining stages of the particular abbreviated ACI configuration investigated, in which measures of fine and extrafine particle fractions are sought by retaining just stages 2 and 5 and the final filter from the full-resolution system (the stage numbering in the abbreviated CI corresponds with that of the full-resolution impactor for simplicity). Hence, although stage 2 in the abbreviated ACI was physically the first impaction stage, its construction is that of stage 2 of a full-resolution ACI. When all the stages were present (Fig. 2.10),

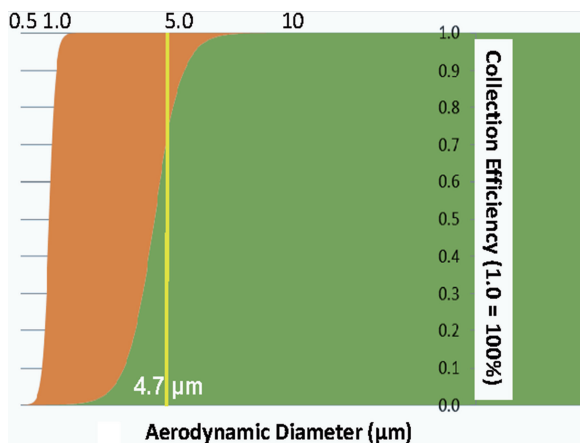


Fig. 2.11 Collection efficiency curves for the abbreviated ACI at 28.3 L/min, based on the adjusted calibration data of Vaughan [19] for stages 2 and 5 of the ACI (From [43], courtesy of D L Roberts and J P Mitchell)

overlap of the collection efficiency curves for stages 1 and 3 with that from stage 2 is prominent. Hence, a 4.7- μm aerodynamic diameter particle could potentially be captured on stage 1 or 2 or 3.

However, when only stages 2 and 5 are present, the overlap region between these two stages is absent, and a 4.7- μm -diameter particle would either be captured or pass the first stage (Fig. 2.11). Consequently, of the particles that would have a chance of collecting on stages 1 or 2 or 3 with the full-resolution ACI, a larger mass fraction is available to approach stage 2 of the abbreviated ACI configuration. In consequence, more particles can penetrate stage 2 of the abbreviated apparatus than would be the case if stage 1 is present.

It follows that summing up the masses collected on stages 0, 1, and 2 of the full-resolution system will not give the identical result as the mass collected by stage 2, in the absence of stages 0 and 1, with the abbreviated CI configuration.

The approach to develop a theoretical interpretation of the behavior above was similar to that described already for the full-resolution CIs [42]. On this occasion, though, an aerosol that is both unimodal and lognormal in terms of its APSD distribution was considered as it enters and passes through the abbreviated impactor.

To calculate how a lognormal aerosol distributes itself throughout an impactor with some stages removed, the stage efficiency functions, $E_i(x)$, in (2.15) were set equal to zero for stages of the full-resolution ACI that are removed and (2.12) applied to the remaining stages of the abbreviated ACI configuration.

Roberts and Mitchell also considered an abbreviated NGI likewise, by postulating that the user removes the airflow after stage 3 and reintroduces it just upstream of stage 6 with special cups for the NGI, as described by Svensson and Berg [45]. In this arrangement, the abbreviated NGI is much like a full-resolution NGI but with fewer stages. It is important to note that Mitchell and Roberts did not consider in

this analysis the Fast Screening Impactor (FSI, MSP Corp., St Paul, MN, USA), as this abbreviated system is based on the NGI preseparator [46] and is therefore not simply a full-resolution NGI comprising fewer stages.

Roberts and Mitchell first calculated how the lognormally distributed aerosol described above would distribute in all stages of a full-resolution ACI or NGI, accounting for the actual stage efficiency curves. They then calculated where in the appropriate abbreviated apparatus the mass actually distributes, according to the stage efficiency curves for this reduced system. Next, they compared these values to the relevant values of mass from summed stages of the full-resolution parent CI. Finally, to complete the validation, they compared the mass on the summed stages from the parent CI and the mass on the abbreviated impactor stages to the *actual* mass in the size range present in the input aerosol.

Equation (2.12) was evaluated numerically using Simpson's rule to calculate the fraction of the input aerosol that goes to a given stage of either a full-resolution or an abbreviated CI configuration. Note that numerical integration was not necessary for calculating the inlet aerosol mass in a given size range, because an analytical expression could be derived by setting the $E_i(x)$ functions in (2.13) equal to step functions at the impactor d_{50} sizes:

$$f_N = \frac{1}{2} \left\{ \operatorname{erf} \left[\frac{\ln \left(\frac{D_{50,N-1}}{\bar{D}} \right)}{\sqrt{2} \ln(\sigma_g)} \right] - \operatorname{erf} \left[\frac{\ln \left(\frac{D_{50,N}}{\bar{D}} \right)}{\sqrt{2} \ln(\sigma_g)} \right] \right\} \quad (2.16)$$

The error function (erf) given by the expression from Matthews and Walker [47] was used:

$$\operatorname{erf}(x) = \frac{2}{\sqrt{\pi}} \int_0^x \exp(-h^2) dh \quad (2.17)$$

For the incoming aerosol that is in the size range larger than the d_{50} size for the first stage, the value of $d_{50,N-1}$ is set to infinity, and it is known that $\operatorname{erf}(\infty) = 1$.

As in the investigation of the full-resolution CIs, a series of model aerosols were evaluated, having MMAD values in the range 1.0–5.0 μm and GSD values selected between 1.2 and 2.0. There was always less mass found on the first stage of the abbreviated ACI than on the corresponding sum of the stages on the full-resolution CI (see the two examples shown in Figs. 2.12 and 2.13). This bias was $\leq 5\%$ for the broadest (GSD=2.0) APSDs comprising the largest particles (MMAD=5.0 μm). However, it increased to as much as 11% for narrow (GSD=1.2) and finer (MMAD=1.0 μm) aerosols. In the context of Figs. 2.12 and 2.13, it should be noted that a ratio of mass on “AIM” to “summed stage” of unity would represent an abbreviated system without bias arising from the nonideal nature of the stage collection efficiency curves.

Similar trends were also detected with the NGI system analysis (Figs. 2.14 and 2.15). However, the bias associated with the abbreviated NGI was $\leq 2.5\%$ regardless

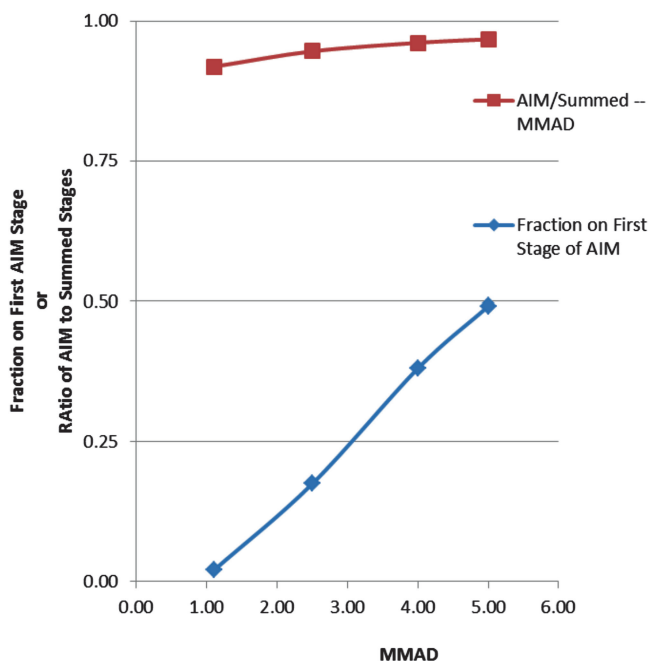


Fig. 2.12 ACI system: mass fraction on first AIM collection stage or ratio of AIM system compared with corresponding summed stages—MMAD varied in the range 1–5 μm with GSD fixed at 2.0 (From [43], courtesy of D L Roberts and J P Mitchell)

of APSD profile. Roberts and Mitchell concluded that such a small discrepancy would likely not be observable experimentally. In addition, for an aerosol with MMAD of 4.0 μm , the fraction on the first stage of the abbreviated NGI was close to 0.5 and nearly independent of the dispersity of the input aerosol (Fig. 2.15). This was not the case for the corresponding ACI data where the mass fraction on the first stage (stage 2) reduced as the dispersity of the incoming aerosol decreased (Fig. 2.12). The improved robustness of the NGI system derives from the relative sharpness of the individual NGI stage efficiency curves compared with those of the ACI and the consequent minimal overlap between neighboring stages [21]. The increase in the mass fraction collected by the first stage (stage 2) of the abbreviated ACI with the model aerosols having larger MMAD values (Fig. 2.12) and also for the corresponding situation with the NGI system (Fig. 2.14) would be a linear function of MMAD if there is no bias associated with the nonideal nature of the stage collection efficiency curves.

From this analysis of both CI systems, Roberts and Mitchell observed that bias in measures of the ratio of “AIM” to “summed stages” is systematically in one direction but can sometimes expand and on other occasions reduce the difference between the input aerosol and the abbreviated CI results in terms of mass fractions. Importantly, no cases were observed in which the abbreviated ACI deviated from

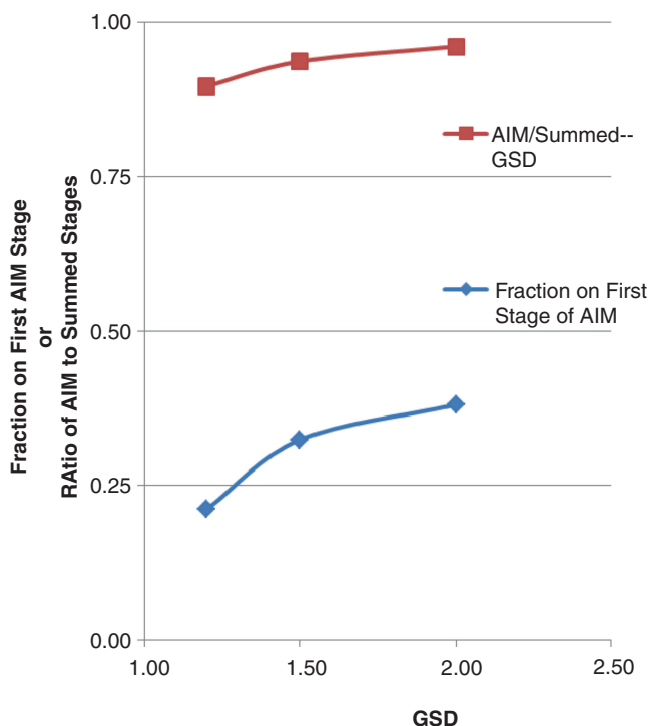


Fig. 2.13 ACI system: mass fraction on first AIM collection stage or ratio of AIM system compared with corresponding summed stages—GSD varied with MMAD fixed at $4.0\ \mu\text{m}$ (From [43], courtesy of D L Roberts and J P Mitchell)

the input aerosol by more than about 10%. However, it is believed that the potential exists for larger discrepancies to arise if the incoming aerosol is more monodisperse than those considered and also if it contains finer particles in the range of interest.

In summary, although bias from the assumption of ideal stage collection efficiency behavior appears small with both systems, it can likely be ignored for the NGI. However, account may need to be taken of this effect in the most accurate work with the ACI and particularly when comparing data from abbreviated systems developed from this CI design.

2.6 Overview of the Compendial Full-Resolution CI-Based Methods for OIP Aerosol Characterization

Currently, the requirements for OIP in vitro performance assessment throughout the product life cycle dictate the need for measurements by full-resolution multistage CI, since this type of apparatus has good compatibility for the assessment of all formats currently manufactured (Table 2.13).

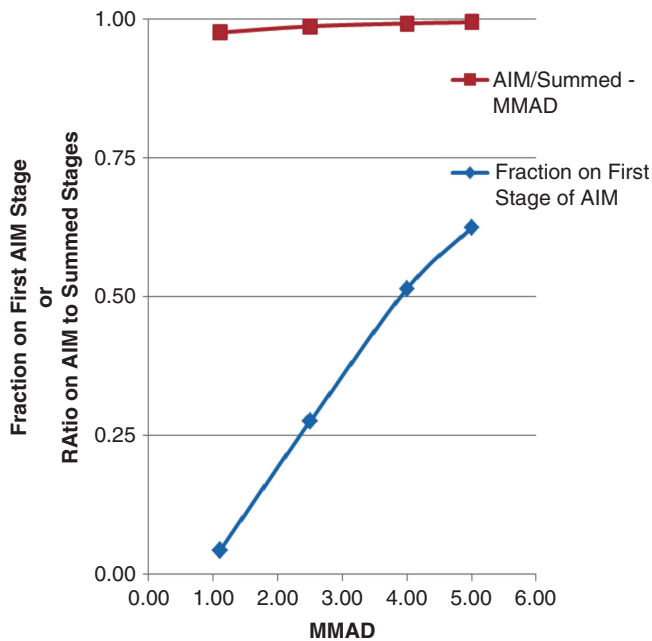


Fig. 2.14 NGI system: mass fraction on first AIM collection stage or ratio of AIM system to corresponding summed stages—MMAD varied with GSD fixed at 2.0 (From [43], courtesy of D L Roberts and J P Mitchell)

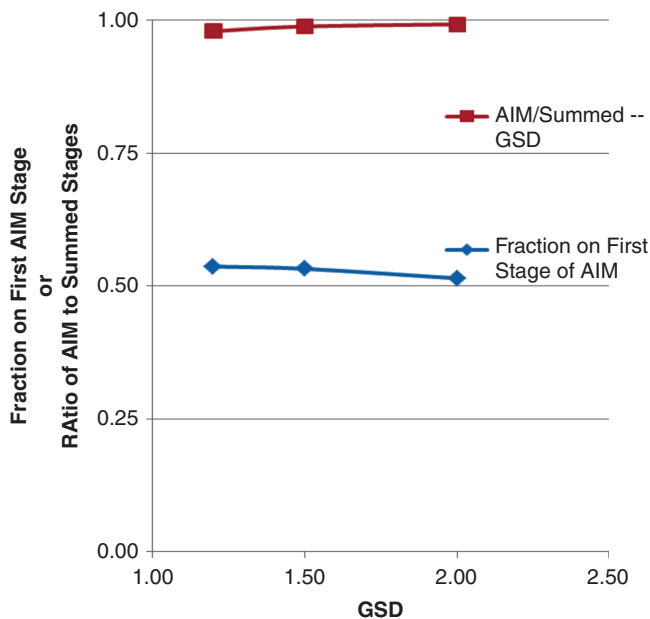


Fig. 2.15 NGI system: mass fraction on first AIM collection stage or ratio of AIM system to corresponding summed stages—GSD varied with MMAD fixed at 4.0 μm (From [43], courtesy of D L Roberts and J P Mitchell)

Table 2.13 Suitability of the cascade impactor method for the various inhaler classes

Inhaler class	Inhalation route	Suitability
MDI	Oral	Good
DPI		Good
SMI		Good
Nebulizer		Good
Nasal MDI		Fair
Aqueous nasal spray	Nasal ^a	Poor

^aNasal inhaled products are shown to illustrate relatively poor compatibility with the CI method but are outside the scope of the book

Table 2.14 Multistage CI apparatuses recognized in the European and United States Pharmacopeias as of 2011

Impactor or impinger	US Pharmacopeia	European Pharmacopoeia
Glass twin impinger (TI)	Not referenced	Apparatus A
Andersen eight-stage (ACI) nonviable impactor without preseparator	Apparatus 1 for MDIs	Apparatus D
Marple-Miller impactor model 160	Apparatus 2 for DPIs	Not referenced
ACI with preseparator	Apparatus 3 for DPIs	Apparatus D
Multistage liquid impinger (MSLI)	Apparatus 4 for DPIs	Apparatus C
Next generation pharmaceutical impactor (NGI)	Apparatus 5 for DPIs	Apparatus E
	Apparatus 6 for MDIs	

The CI method is most suitable for the assessment of aerosols from MDI, DPI, and SMI inhaler forms, although in the case of DPI testing, the compendial methods require the impactor to be started from zero flow at the beginning of the sample, simulating an inhalation maneuver, whereas it is evident from the previous sections that CIs ideally operate at a fixed flow rate. Their applicability to the assessment of nebulizing systems is slightly more problematic, in that precautions need to be taken to prevent heat transfer from the CI to the aqueous aerosols that are produced by these systems [48].

Likewise, precautions need to be taken with sprays from nasal MDIs, as these frequently comprise aqueous solutions. Aqueous nasal spray characterization is normally undertaken by laser diffractometry (LD), as the size range of the droplets, which typically lies between 20 and 300 μm diameters, is well outside the range of operation of a CI [49]. This is the primary reason why this class of inhalers is largely outside the scope of this publication. However, single-stage impactors with d_{50} close to 10 μm aerodynamic diameter have been used to identify the small subfraction of ultrafine droplets potentially capable of penetrating the nasopharynx and entering the airways of the lungs [50].

Chapter 601 of the US Pharmacopeia and the corresponding monograph 2.9.18 in the European Pharmacopoeia permit several different types of CI to be used for OIP evaluations (Table 2.14).

In a survey undertaken in 2006 by EPAG in connection with CI qualification testing, the ACI was identified as the most widely used multistage CI, with the NGI following closely in second place [51]. The MSLI came third, but this apparatus is not in use outside of European regulatory submissions. Other systems were seldom used. It should be noted that the glass TI (Apparatus A of the European Pharmacopoeia) would qualify as an abbreviated impactor method, since it size classifies the incoming aerosol into only two subfractions with its d_{50} size at $6.4\ \mu\text{m}$ aerodynamic diameter, when operated at its design flow rate of $60\ \text{L/min}$.

2.7 Preseparators and Induction Ports

Some form of inlet to the CI is required to ensure that the aerosol produced by the inhaler enters the impactor in a reproducible manner. Most OIPs are designed such that they emit their medication in the horizontal plane and entrances to impactors are typically oriented in the vertical downward direction. The solution to the problem is the induction port, which also mimics to a greater or lesser extent depending on its design, the human oropharynx. There are many designs of induction port currently in use, with their shape and capacity reflecting differing viewpoints on how inhaler aerosols should be sampled. Seven examples are illustrated in Fig. 2.16 [52]. By far the most commonly encountered is the relatively

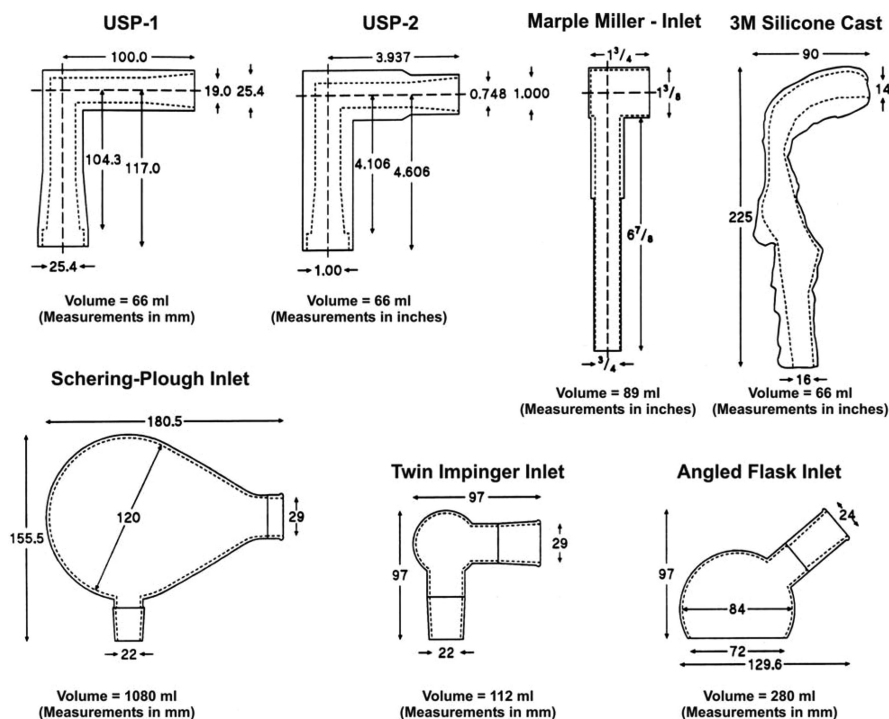


Fig. 2.16 Assortment of induction ports used in OIP testing (From [52]—used with permission)

straightforward metal right-angle bend (so-called USP/Ph.Eur. design) described in both regional pharmacopeias.

It is important to note that this inlet is not intended to be an accurate representation of the upper airway but rather a simplified arrangement that reproducibly collects incoming aerosol for the purpose of product quality assessment. Chapter 12 contains information about more anatomically appropriate inlets, including the new generation of “idealized” geometries that have been developed at the University of Alberta, Canada.

In its role as a model of the entrance to the respiratory tract, the induction port collects almost all the fast moving “ballistic” component of MDI-produced aerosols that is formed by flash evaporation of the propellant and therefore likely to deposit in the oropharynx [53]. It also serves to remove larger and often aggregated particles generated by most DPIs. The USP/Ph.Eur. design is intended to provide a common benchmark to compare different formulations by standardizing its critical dimensions (internal diameter and unobstructed path length). Unfortunately, unlike a CI stage, its collection efficiency is not easily determined, since there is significant turbulence at flow rates encountered typically for inhaler testing [54], and particles in the ballistic component from MDIs have velocities greater than that of the surrounding airflow when entering the induction port. Nevertheless, recently, Zhou et al. reported calibration data with monodisperse particles for this inlet (Fig. 2.17), from which they estimated d_{50} sizes to be 14.4- and 20.2- μm aerodynamic diameters for flow rates of 60 and 30 L/min, respectively, by fitting their experimental data to flow rate-dependent empirical relationships linking deposition fraction and d_{ac} [55].

Their term “deposition fraction” can be considered equivalent to collection efficiency. They found that d_{50} at the lowest flow rate investigated (15 L/min) could not be obtained, as the collection efficiency was found to be <50% regardless of particle size to an upper limit close to 30 μm aerodynamic diameter (Fig. 2.17). It should be noted that Zhou et al. grease coated the interior surfaces to mitigate particle bounce and re-entrainment, a practice that is possible but rarely undertaken with OIP testing.

In summary, although several attempts have been made to develop an understanding of how this particular induction port performs, given the complexity of the fluid dynamics and particle motion through its flow path, particularly when capturing the ballistic fraction emitted by MDIs, it should not be regarded as an additional impactor stage in routine work.

A preseparator is often required to be located immediately after the induction port when sampling aerosols produced from DPIs, since these formulations in many instances contain the API attached to the surface of much larger (lactose) carrier particles. The shear forces generated by inhalation from the DPI detach some, but not all, of the API particles from the carrier material, but the detached particles are sufficiently fine to penetrate beyond the oropharyngeal region into the lungs [56]. Both pertinent USP and Ph.Eur. compendial monographs refer to the use of a preseparator for DPI-based particle size distribution measurements with the ACI, recommending that its interior surfaces be coated either with a tacky agent in the same

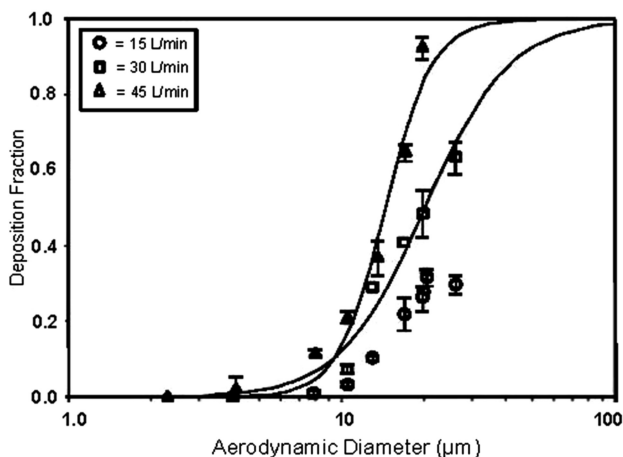


Fig. 2.17 Calibration data for the USP/Ph.Eur. induction port at 15, 30, and 60 L/min (From [55]—used with permission)

way as the collection surfaces of the CI stages or with up to 10 mL of a suitable solvent to eliminate particle bounce and re-entrainment. A similar requirement exists also for use of the NGI under these circumstances.

The preseparator for the ACI and NGI are illustrated in Figs. 2.18 and 2.19, respectively. Ideally, the preseparator should not starve the first stage of the impactor of particles. However, the preseparator used with the ACI has been shown by calibration at 28.3 L/min to have its cut size close to 9 μm in aerodynamic diameter, almost identical with the d_{50} size of the first stage (stage 0 in Table 2.2) at this flow rate [58]. Its sharpness of cut is relatively poor by comparison to equivalent values for the CI stages ($GSD_{pre-sep}$ is about 1.55), due primarily to the strong influence of gravity. The preseparator therefore starves the second as well as the first stage of this impactor.

Recognizing the limitations of the ACI preseparator, the consortium developing the NGI designed its preseparator to function as a single component [57] but with two distinct steps in the size-separation process (Fig. 2.19). The incoming aerosol is first passed through a so-called scalper impingement stage that removes the coarsest particles. The remaining aerosol then passes immediately through a more conventional impaction stage before leaving the preseparator. Calibration with monodisperse particles has demonstrated that its $GSD_{pre-sep}$ is close to 1.3 at 30, 60, and 100 L/min. This value is only slightly greater than estimates of GSD_{stage} for well-designed CI stages in which inertial rather than gravitational or turbulent size-separation predominates. Its measured d_{50} values (10.0, 12.7, and 14.9 μm at 100, 60, and 30 L/min, respectively) are sufficiently separated from the corresponding values for stage 1 (6.07, 8.29, and 11.4 μm) that starvation of the first stage of the CI does not occur to a significant extent.

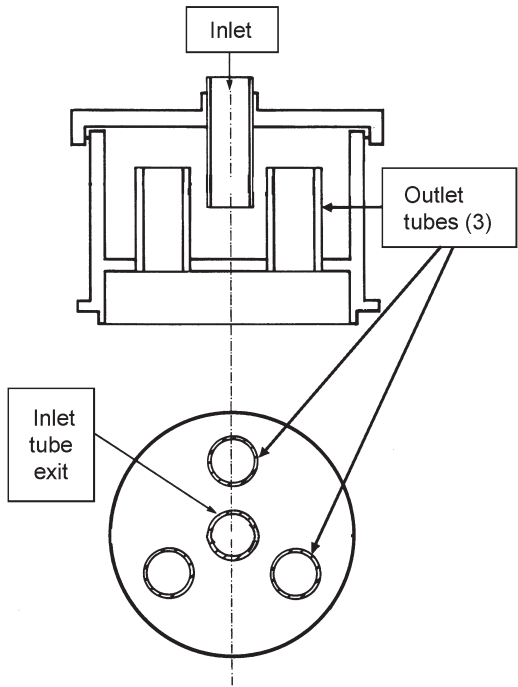


Fig. 2.18 Side cross section and top view of the preseparator for the ACI

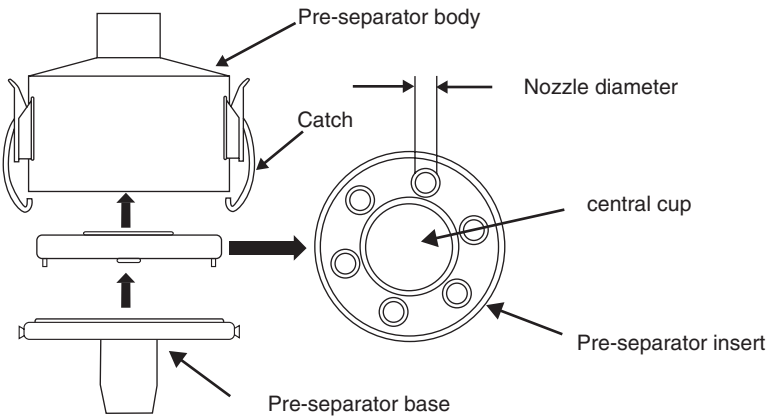


Fig. 2.19 Preseparator for the NGI (From [57]—used with permission)

2.8 Add-On Devices Used with MDIs

The evaluation of add-on devices that are widely prescribed for use with MDIs [59–61] poses some additional considerations beyond those that exist for the testing of the inhaler alone. Spacers are open extensions to the MDI actuator mouthpiece whose primary purpose is to place distance between the inhaler and the patient, such that plume development and impaction of the ballistic fraction takes place within the spacer itself (Fig. 2.20).

As such, they do not retain the medication should the patient fail to either inhale at the time of MDI actuation or exhale into the add-on device. Their evaluation is therefore probably best accomplished following the compendial methods for MDI performance evaluation, without any attempt to simulate delayed inhalation.

The valved holding chamber (VHC), on the other hand, has a valve at its exit that enables the aerosol to be retained if the patient is poorly coordinated. These devices are equipped with either a mouthpiece (Fig. 2.21) or face mask (Fig. 2.22) as the patient interface, as they are used by patients of all ages from infants to geriatrics.

As such, it follows that it is logical that these devices be evaluated simulating delayed inhalation, rather than by the methods in the pharmacopeias that currently require the tester to sample the aerosol immediately upon MDI actuation.

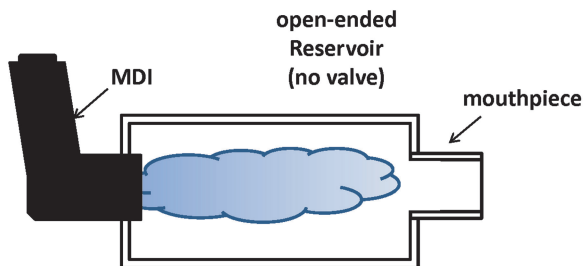


Fig. 2.20 Open-tube spacer for use with MDIs

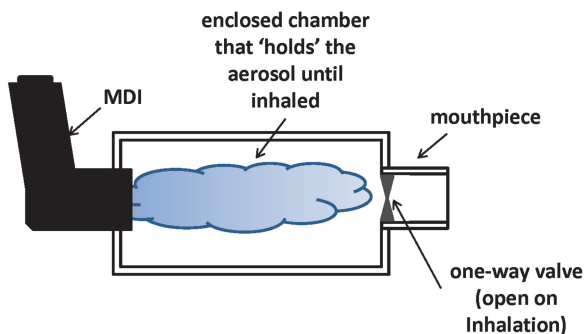
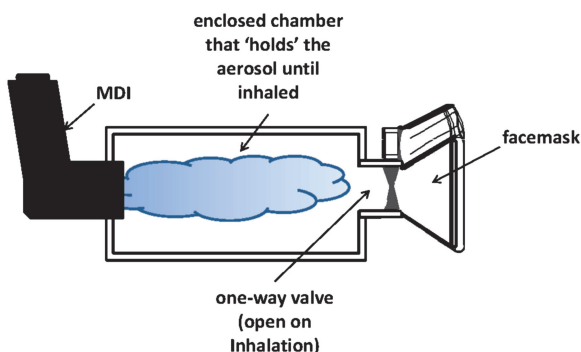


Fig. 2.21 VHC mouthpiece as patient interface for use with MDIs

Fig. 2.22 Valved holding chamber with face mask as patient interface for use with pressurized metered-dose inhaler



Given the lack of guidance in the (then) compendial methods, about 10 years ago, a group of Canadian stakeholders met to develop a national standard that for the first time set out detailed methods for the evaluation of these add-on devices, including sections on the simulation of delayed inhalation following inhaler actuation [62]. This standard retains the CI as the apparatus of choice for the evaluation of emitted aerosol APSD but contains the following extensions to existing methodology [63]:

- Measurements are made initially with the MDI alone following the compendial method to provide benchmark data.
- The VHC is then evaluated simulating a 2 s delay following inhaler actuation, chosen to mimic the behavior of a typical uncoordinated user; testing at other delay intervals is also possible.
- The flow rate chosen should be appropriate for the intended age range of the VHC; for example, an infant VHC might be evaluated at close to 5 L/min, an add-on for a small child at 12 L/min and a product for adult use at ca. 30 L/min.

This approach has recently been proposed for adoption as a future informative chapter in the USP through the publication of a Stimulus to Revision article in *Pharmacopeial Forum*, in which the pharmacopeial organization publishes proposed revisions to USP-NF for public review and comment. [64]. This proposal has been partly driven by the recommendation from at least one regulatory agency that new MDI applications should contain in vitro data with a nominated spacer/VHC [65].

Although the Canadian Standard describes the framework for testing by CI, it does not contain any detail concerning suitable apparatus(es) to undertake measurements simulating delayed inhalation. At the present time, there is therefore no standardized “delay” apparatus. However, work undertaken at Trudell Medical International shortly after the standard was developed resulted in the apparatus shown in Fig. 2.23, seen in conjunction with a model 150P MMI [66].

The use of the NGI at 15 L/min, the lowest flow rate for which calibration data are available, would, in principle, also be suitable at least for testing VHCs intended for use by small children. In the so-called delay apparatus [67], simulation of the

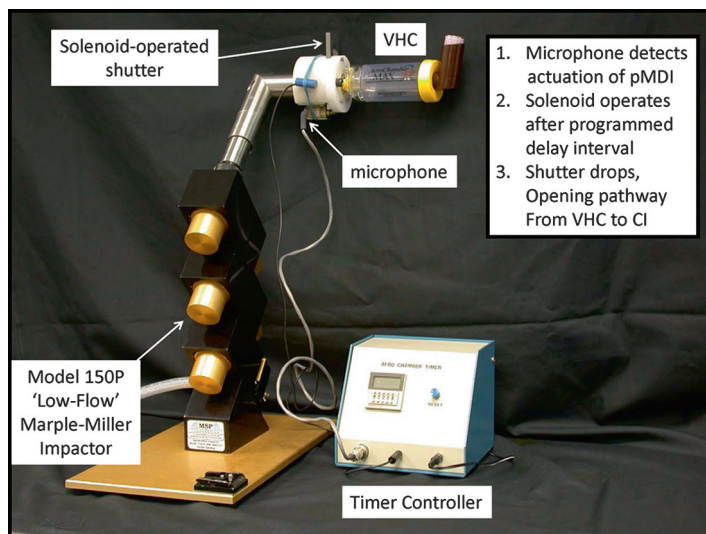


Fig. 2.23 Trudell Medical International “delay” apparatus coupled to USP/Ph.Eur. induction port with low-flow five-stage MMI developed for testing inhalation devices intended for use by infants or small children

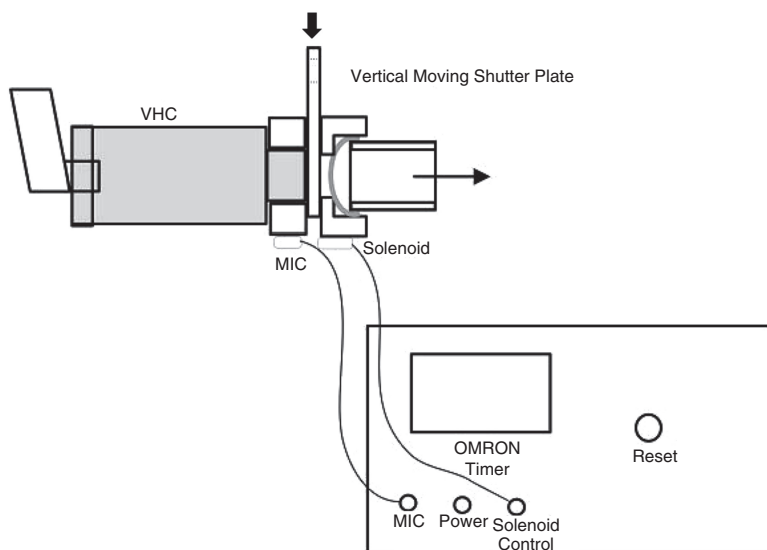


Fig. 2.24 Schematic diagram of Trudell Medical International “delay” apparatus showing working components (*From [67]—used with permission*)

elapsed time between MDI actuation and the onset of sampling is achieved by interposing a mechanical shutter housed in a purpose-built adapter that locates on axis between the VHC and induction port leading to a CI that is operated at a flow rate appropriate for the intended patient category for the VHC (Fig. 2.24).

The shutter is set in the elevated (closed) position during connection of the VHC, MDI actuation, and the subsequent delay period, but air can still be sampled by the impactor at the desired flow rate via a bypass channel located on the side of the shutter facing the induction port. A microphone (MIC) located on the adapter detects the sound emitted at actuation of the MDI, starting a timer that operates a solenoid valve immediately after the expiry of the selected delay period. This movement retracts the shutter support pin, thereby permitting the shutter to drop, opening a direct flow path from the VHC to the CI. The adapter introduces <5 ml additional volume to the aerosol pathway from the VHC to the CI system. The “delay” apparatus avoids the need to start the vacuum pump for the CI after the elapsed delay, a situation that would result in undefined stage d_{50} sizes, while the flow rate is increasing to its final stable value.

Although systems have been developed to enable a CI to be used in conjunction with a breathing simulator [68–70], which would be the obvious extension of the delay technique to mimic more closely tidal breathing, so far a standardized arrangement has not yet been developed to the point at which it could be incorporated as part of a compendial procedure for the evaluation of VHCs.

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