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## Optimisation of dry powder inhalation

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## Chapter 2

### **Characterisation of inhalation aerosols: a critical evaluation of cascade impactor analysis and laser diffraction technique**

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**Abstract**

Cascade impactor analysis is the standard technique for in vitro characterisation of aerosol clouds generated by medical aerosol generators. One important reason for using this inertial separation principle is that drug mass fractions are classified into aerodynamic size ranges that are relevant to the deposition in the respiratory tract. Measurement of these fractions with chemical detection methods enables assessment of the (aerodynamic) particle size distribution of the drug in the presence of excipients. However, the technique is laborious and time consuming and most of the devices used for inhaler evaluation lack sufficient possibilities for automation. In addition to that, impactors often have to be operated under conditions for which they were not designed nor calibrated. For instance, flow rates through impactors are increased to values at which the flow through the nozzles is highly turbulent, whereas they are to be operated at laminar flow. This has an uncontrolled influence on the collection efficiencies and the cut-off curves of these nozzles. In spite of that, the range of attainable (fixed) inspiratory flow curves through impactors is still rather narrow due to their high air flow resistances. Especially for breath actuated dry powder inhalers, higher flow rates and flow increase rates may be desirable than can be achieved in combination with a particular type of impactor. Moreover, the cut-off value varies with the flow rate through an impactor nozzle. This makes comparison of fine particle fractions from different inhalers (with different air flow resistances) tested at the same pressure drop, or from the same inhaler at different pressure drops, rather difficult. Recalculation of the obtained fine particle fractions into the same size class (at least with the same upper class limit) is necessary. This is often quite arguable considering the few size classes obtained from impactor analysis and the deviation of the size distribution from log-normal, which is a consequence of discharging a mixture of primary particles and small agglomerates from a dry powder inhaler.

In this chapter, the applicability of laser diffraction technology is evaluated as a very fast and highly reliable alternative for cascade impactor analysis. With this technique, aerodynamic diameters can not be measured, but for comparative evaluation and development, comprising most in vitro applications, this is not necessary, as will be discussed. In contrast with cascade impactor technique, laser diffraction has excellent possibilities for automated recording of data and testing conditions, and the size classes are independent of the flow rate. Practical limitations can be overcome by using a special inhaler adapter which enables control of the inspiratory flow curve through the inhaler, analysis of the emitted fine particle mass fraction and pre-separation of large particles during testing of dry powder inhalers containing adhesive mixtures. Design and performance testing of such an adapter will be discussed in Chapter 3.

*Keywords:* Aerodynamic diameter, Aerosol cloud, Cascade impactor, Laser diffraction analysis, Particle size analysis

## 1. Introduction

One of the standard routines in development and evaluation of drug inhalation systems is to measure the aerodynamic particle size distribution in the generated aerosol cloud as function of a constant inspiratory flow rate. Thus, to assess the emitted mass fraction of the dose that has the required size range for effective deposition on the site of action in the respiratory tract. The preferred size or size range for inhalation drugs depends on the target area, which is still somewhat controversial for some types of drugs (Chapter 1). Many mean particle diameters or size distributions have been proposed as being optimal for (deep) lung deposition; most of them are within the range between 0.5 and 7  $\mu\text{m}$  (e.g. Byron, 1986; Morén, 1987; Vidgrén, 1994; Staniforth, 1995). Different techniques have been recommended for the measurement of aerodynamic particle diameters. Direct measurement in the cloud from an inhaler is possible with apparatus like (cascade) impactors, time of flight ‘Aerosizers’, sedimentation cells and elutriators, wind sifters, spiral centrifuge aerosol spectrometers and electrical mobility analysers. Some of these techniques require special measures for this rather unusual application, for which none of them was originally designed.

### 1.1. Cascade impactor analysis (cia)

Impactors and impingers are currently considered as ‘the golden standard’ for inhaler testing, because they yield mass fractions of the drug dose (by chemical detection) in the aerodynamic size classes that are relevant to particle deposition in the human respiratory tract.

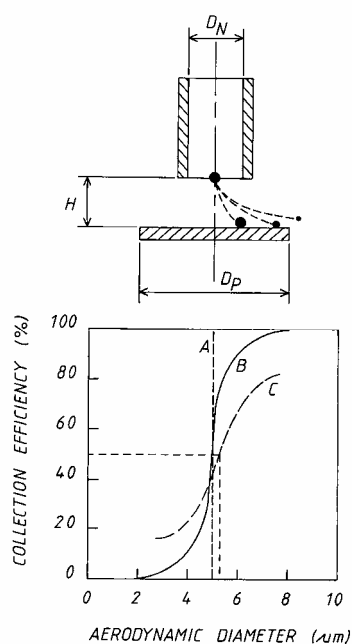


Figure 2.1. Schematic presentation of a single impactor stage (top) and a cut-off curve (bottom).

A single impactor stage is shown in Fig. 2.1. Such an impactor stage consists of a nozzle at a well controlled distance above a collection plate. Air is drawn through the nozzle at a constant flow rate. Whether particles in the air stream collide with the collection plate or not, depends on the ratio of the drag force to the inertial forces acting on the particle in the impactor region. A ratio smaller than one is likely to result in separation from the air stream. The ratio decreases with the particle velocity as well as with the particle diameter (mass) and thus, with particle inertia. Ideally, all particles with a diameter larger than the cut-off diameter

are collected, whereas all smaller particles pass the impactor stage (Fig. 2.1). Practically, the cut-off curve is not steep however, because it depends also on the position of a particle in the nozzle throat, whether the particle is brought into contact with the plate or not. Also particle bounce and local turbulences in the nozzle throat may occur, as a result of which oversize particles may pass whereas undersize particles can be collected.

For calculations it is assumed that the particle leaves the nozzle with the same velocity as the air. The principle of operation of impactors has extensively been described (e.g. Ranz and Wong, 1952a/b; Hinds, 1982), which gives the impression that inertial impaction is well understood and can well be controlled. Many different types of impactors and impingers have been proposed for inhalation aerosols in the last decades. They vary from simple devices like the modified 'Kirk Lung' (Davies et al., 1976) and the 'twin impinger' (British Pharmacopoeia, 1988) to more complex apparatus, having more collection stages, like the Andersen Mark II (Graseby-Andersen, 1985) or the recently developed next generation impactor, NGI shown in Fig. 2.2 (Marple et al., 2000).

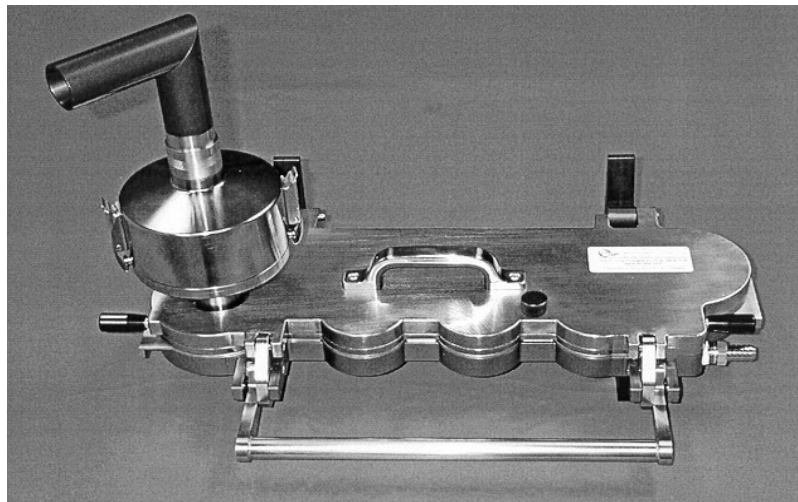


Figure 2.2. Next Generation Impactor, depicted with two-stage pre-separator.

Inertial impactors have to be designed and constructed according to certain aerodynamic rules. They must also be operated under strictly defined conditions in order to obtain the desired cut-off efficiencies and to avoid excessive flattening of the cut-off curve. Theoretical cut-off diameters can be calculated as function of nozzle geometry, particle density and air velocity in the nozzle (Paragraph 2.2). Recently, John (1999) presented a simple theoretical derivation for the cutpoint of an impactor. However, it is generally recommended that impactors are calibrated with particles of well known aerodynamic size (distribution) obtained from another suitable sizing technique. Asking and Olsson (1997) derived a practical relationship from calibration between the cut-off diameter and the flow rate for the nozzles of a multi-stage liquid impinger (MSLI), which has been adapted by the European Pharmacopoeia, 3<sup>rd</sup> edition 1997, supplement 2001.

In the last decade, cascade impactor analysis has been subjected to critical evaluations and suggestions for improvement of their performance have been proposed. Issues that are of concern for the accuracy of size classification are the incidence of bounce and blow off at the stages. Also wall losses between the stages may occur. Hickey (1990) investigated the

deposition characteristics of particles on the individual stages of an inertial impactor and observed size fractionation upon a single stage. He reported that larger particles are deposited at the centre, and smaller ones at the periphery of an impaction plate. Olsson et al. (1996) compared the results from different laboratories obtained with the four different impactors described in the European Pharmacopoeia (3<sup>rd</sup> edition, 1997) for a salbutamol pressurised metered dose inhaler (mdi) and two different dry powder inhalers (dpi's). Their study proves that significant differences exist between the results obtained with different devices, as these devices may have different cut-off values for the fine particle fractions and be operated at different flow rates, which influences the performance of the dpi's too. The within-laboratory variation for obtained fine particle fractions in their study was quite large and ranged from 8 to 15.5% for the mdi, respectively from 5.5 to 20% for the dpi's. For dpi's, only two impactors gave comparable results: they were operated at the same flow rate of 60 l/min and had approximately the same cut-off value (6.4 and 6.8  $\mu\text{m}$ ) for the fine particle fraction.

Developments in impactor use include the application of these devices at higher flow rates than those for which they were originally designed, as well as the re-design of existing impactors for this purpose. However, an increase up to 90 l/min, as for the Marple-Miller Impactor (e.g. Hindle et al, 1996), may not be sufficient, because recent guidelines demand that dpi's are tested at a pressure drop of 4 kPa across the device. For low resistance inhalers, like the Spinhaler (Aventis Pharma) and the Rotahaler (GSK), this pressure drop corresponds with much higher flow rates of 125 and 133 l/min respectively (Chapter 1, Table 1.3). Another limitation of inertial impactors is that breath controlled dry powder inhalers cannot be tested at the variable flow conditions under which they are operated by the patient. Impactors are designed to sample at fixed flow rates (for which they have been calibrated). Operating at a variable flow rate should be avoided as this yields mass fractions with undefined size distributions. As a possible solution for this problem, inhalation simulators have been developed, such as the Electronic Lung<sup>TM</sup> (Brindley et al., 1994), which are used in combination with large spacers for the aerosol. With these simulators, well defined flow curves are drawn through the inhalers. The aerosol clouds generated at these variable flow rates are first discharged in the spacer before they are conducted through the impactor at the prescribed constant operational flow rate. This procedure has the disadvantage that the size distribution of the cloud may change inside the spacer as the result of particle drop out by sedimentation, especially for the larger particles. Also electrostatic separation and droplet coalescence or particle agglomeration in the spacer may occur. Developments in cascade impactor analysis furthermore include their combination with casts of the human throat, serving as the induction port to the first impactor stage, as for instance reported by Niven et al. (1994) and Olsson et al. (1996). Most of these evaluations and developments arise from the desire to predict airway deposition based on in vitro deposition data, for which models like LUDEP (LUng Dose Evaluation Program developed by the UK National Radiological Protection Board, Moore, 2001) are used.

### 1.2. Laser diffraction analysis (lda)

The principle of laser diffraction is shown in Fig. 2.3. Airborne particles are passed through a laser beam in which interaction occurs with the light. Depending on the optical properties of the particles, light may be extinguished by absorption or scattered by refraction and diffraction. The angle of forward diffraction depends on the particle diameter and in a laser diffraction apparatus, the diffracted light is collected on a series of concentric detector rings which correspond with different size classes for the airborne particles. Gustav Mie presented an exact solution of the Maxwell equations that describe the complex light scattering integral for spherical particles. The Mie theory takes account of absorption and refraction phenomena.

Fraunhofer derived a simplified theory that ignores these (refraction and absorption) effects and is therefore particularly applicable for non-transparent particles. A special Fourier lens is applied to make sure that light diffracted by particles of equal size, but at different positions in the laser beam, is collected on the same detector ring. Different lenses can be used to extend the total range of particle sizes measured with the same apparatus. The discussion about which diffraction theory to use for the measurements (Mie or Fraunhofer) is not so much a dispute about which one is the better theory, but rather which theory yields least practical problems in its application. Possible implications of this choice will be discussed more in detail in Paragraph 3.2.

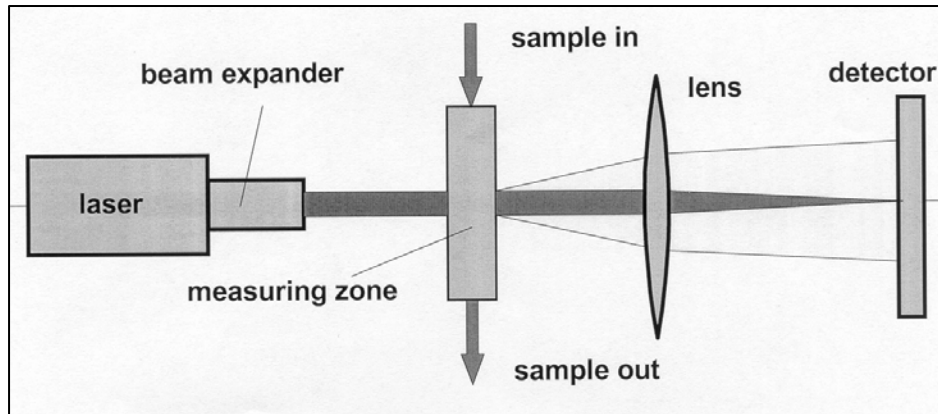


Figure 2.3. Principle of laser diffraction.

The use of laser diffraction technique for particle size measurement in the aerosol clouds from nebulisers dates from the eighties of last century. Ho et al. (1986) concluded that laser diffraction technique provides more realistic size distributions for nebulised aqueous drug solutions than inertial impaction techniques. They claimed that droplet bounce and re-entrainment, as well as droplet evaporation during laser diffraction is less relevant. Ranucci (1992) described the use of laser diffraction technique for particle size analysis in the plumes discharged from mdi's. He concluded that lda can be a valuable characterisation technique for this type of aerosol generator, because it allows real-time plume measurements to be taken as function of distance from the actuator orifice. This is relevant to mdi-testing because the droplets contain volatile components that evaporate in the air stream. As a result, size distribution changes with the distance from the nozzle (actuator), which is an aspect that can not be studied with impactors and liquid impingers. In the nineties of the past century, several studies of medical nebulisers with laser diffraction technique have been reported (Hurley et al., 1994; McCallion et al., 1995/1996; Bridges and Taylor, 1998). It has been concluded that the technique is robust and reliable and that it measures size parameters relevant to the clinical situation (Clark, 1995). However, in most of these studies there is no reference to proper air extraction from the measuring zone. This, to avoid re-entry of aerosol droplets into the laser beam and also to study the effect of the inspiratory flow rate on the droplet size distribution. The reason is that controlled air suction through the nebuliser requires a connection between the mouthpiece of the nebuliser and a vacuum system, which is technically problematic because of interference with the laser beam. Such an interface should be a closed housing that prevents the suction of false air reducing the air flow through the nebuliser.

Previously mentioned references indicate that there is a growing interest in laser diffraction for the characterisation of inhalation devices. This includes breath operated dry powder inhalers for which a well controlled air flow through the device is particularly relevant. In this chapter the applicability of laser diffraction technique is evaluated as an alternative, though not a substitute, for cascade impactor analysis for the in vitro characterisation of various types of medical aerosol generators. Specific pros and cons of both techniques from theoretical and practical viewpoint are discussed. Also, some practical and operational limitations of standard laser diffraction technology for inhaler testing are mentioned.

## 2. Theoretical background

### 2.1. Equivalent particle diameters

Inhaled drugs vary not only in size distribution, but also in their physical state (liquid or solid), particle density ( $\rho_P$ ), particle shape and travelling velocity. All these parameters are relevant to the particle deposition in the respiratory tract, which is the result of a dynamic system of forces acting on particles that are transported by the air stream through this tract. It includes the force of gravity ( $F_G$ ), the drag (resistance) force of the inspiratory air ( $F_D$ ) and inertial forces ( $F_I$ ), which all (at least partially) depend on previously mentioned particle properties. As in an impactor, the ratio of drag force to either of both other forces determines whether the particle is carried on by the air stream into a deeper lung region, or brought in contact with the walls of the airway ducts by sedimentation or by a high particle momentum. This, for the situation in which particles are not charged (no Coulombic forces) and particle interception in narrow passageways does not occur.

In order to predict or compare the deposition behaviour of particles with different densities and shapes, it is standard practice to make corrections for these parameters (e.g. Hinds, 1982). The aerodynamic behaviour of particles with different shapes can be compared by expressing them in terms of equivalent volume diameter ( $d_E$ ), and dynamic shape factor ( $\chi$ ), which is the ratio of the actual resistance force acting on a non-spherical particle to the resistance force acting on a sphere having the same volume and velocity. For aerosol particles inertial effects are negligible compared to viscosity effects. Hence, Stokes's law applies for the drag force. Accordingly, the dynamic shape factor ( $\chi$ ) can be expressed as:

$$\chi = (F_A)/(3\pi.\eta.U_{PA}.d_E)$$

$$\text{So, } F_A = 3\pi.\eta.U_{PA}.d_E.\chi \quad [2.1]$$

where  $F_A$  = the actual resistance force acting on the particle  
 $\eta$  = the dynamic viscosity of the air  
 $U_{PA}$  = the particle velocity relative to the air

Equation 2.1 is valid for particles larger than 3 microns. For smaller particles (within the range 0.1 - 3  $\mu\text{m}$ ), the Cunningham correction factor for slip flow ( $C_C$ ) has to be introduced. Alternatively, the Stokes' diameter ( $d_S$ ) can be used which is the diameter of a sphere that has the same density and terminal settling velocity ( $V_{TS}$ ) in still air as the irregular particle.

A correction for both particle shape and particle density can be made by using the aerodynamic diameter ( $d_A$ ). By definition, the aerodynamic diameter of a particle is the diameter of a sphere with unit density ( $\rho = 1$ ), having the same terminal settling velocity in still air as the particle in consideration. Under the condition of stationary settling, only two



forces act on a particle, which are exactly equal in size and opposite in direction. These are the force of gravity ( $F_G$ ) and the resistance force of the air ( $F_D$ ). A correlation between previously mentioned diameters ( $d_E$ ,  $d_A$  and  $d_S$ ) and the dynamic shape factor ( $\chi$ ) can be obtained by expressing these parameters in the terminal settling velocity ( $U_{TS}$ ), for which  $F_G$  equals  $F_D$ .

In general terms for the diameter ( $d$ ):

$$\pi/6 \cdot d^3 \cdot \rho_p \cdot g = 3\pi \cdot \eta \cdot U_{TS} \cdot d, \text{ so } U_{TS} = (\rho_p \cdot d^2 \cdot g)/(18\eta)$$

$$\begin{aligned} \text{where } \rho_p &= \text{the particle density} \\ g &= \text{the acceleration of gravity} \end{aligned}$$

After substitution of the specific diameters:

$$U_{TS} = (\rho_p \cdot d_E^2 \cdot g)/(18\eta \cdot \chi) = (\rho_0 \cdot d_A^2 \cdot g)/(18\eta) = (\rho_p \cdot d_S^2 \cdot g)/(18\eta) \quad [2.2]$$

Equation 2, after re-arrangement, yields the correlations:

$$d_A = d_E \cdot (\rho_p/\chi)^{0.5} = d_S \cdot \rho_p^{0.5} \quad [2.3]$$

## 2.2. The cutpoint of an impactor

Theoretical cutpoints of impactors are normally presented as particle diameters with 50% collection efficiency ( $d_{50}$ ). Because classification is by two competitive forces, as during stationary settling of a particle, it is believed that impactors separate into aerodynamic size fractions. Diameters with 50% collection efficiency ( $d_{50}$ ) can be derived from the Stokes number ( $Stk$ ), which governs the collection efficiency of a jet (impactor nozzle). Stokes number is defined as the ratio of particle stopping distance ( $S$ ) to the nozzle radius ( $R$ ) of the impactor (Hinds, 1982). Correspondingly, the Stokes number that gives 50% collection efficiency is referred to as  $Stk_{50}$ . The particle stopping distance can be written as the product of particle relaxation time ( $\tau$ ) and particle velocity at the nozzle exit ( $U$ ), whereas the relaxation time is the product of particle mass ( $m$ ) and particle mobility ( $B$ ), which is the particle velocity ( $U$ ) per unit force ( $F$ ). Because particle velocity at the nozzle exit ( $U$ ) is established by the action of the drag force ( $F_D = 3\pi \cdot \eta \cdot U \cdot d/C_c^{-1}$ ), the stopping distance  $S$  (after re-arrangement of terms) may be written as:

$$S = m \cdot B \cdot U = (d^2 \cdot C_c \cdot \rho_p \cdot U)/(18\eta) \quad [2.4]$$

$$\text{So, } Stk_{50} = S/R = m \cdot B \cdot U/R = (d_{50}^2 \cdot C_c \cdot \rho_p \cdot U)/(18\eta \cdot R) \quad [2.5]$$

Rearrangement of the terms in Eq. 2.5 yields the particle diameter with 50% collection efficiency:

$$d_{50} \cdot \sqrt{C_c} = \{(18\eta \cdot R \cdot Stk_{50})/(\rho_p \cdot U)\}^{0.5} \quad [2.6]$$

$Stk_{50}$  is a single number applying for well designed impactors of the same type that are used for a confined range of flow rates. The Reynolds numbers in the nozzles have to be within the range between 500 and 3000. Design criteria for circular nozzles include that the separation distance between the nozzle and the impaction plate is larger than the nozzle diameter. Under

these conditions,  $Stk_{50}$  equals 0.22. It may be clear that  $d_{50}$  obtained with Eq. 2.6 is a geometric diameter, since its value varies with the particle density ( $\rho_P$ ).

Table 2.1. Comparison of theoretical ( $d_{50}$ ) and experimental cutpoints ( $d_A$ ) at 60 l/min for the multi-stage liquid impinger (Eur. Pharmacopoeia, 3<sup>rd</sup> edition 1997), and the dynamic shape factors ( $\chi$ ) necessary to equate  $d_{50}$  with  $d_A$ , using Equation 2.3.

Impactor stage	Theoretical cutpoint ( $d_{50}$ )	$C_C$ used for calculation of $d_{50}$	Experimental cutpoint ( $d_A$ )	Necessary dynamic shape factor ( $\chi$ ) for equation of $d_{50}$ and $d_A$
1	20.97	1	13.0	2.60
2	8.79	1	6.8	1.67
3	3.80	1	3.1	1.50

Note: stage 4 (multi jet) has not been calculated

Table 2.1 compares the theoretical cutpoints ( $d_{50}$ ) of the MSLI for unit density particles, calculated with Equation 2.6 for a flow rate of 60 l/min, with the experimental values ( $d_A$ ) given by the European Pharmacopoeia (3<sup>rd</sup> edition 1997, supplement 2001) for this device at the same flow rate. In spite of the fact that the theoretical values ( $d_{50}$ ) represent aerodynamic diameters (which also equal  $d_E$ , because they have been calculated for spherical particles with unit particle density), both values ( $d_{50}$  and  $d_A$ ) differ considerably from each other. A small difference could (for instance) be the result of droplet deformation in the aerodynamic particle sizers used to obtain the experimental values. Droplet deformation would result in an increase in the dynamic shape factor ( $\chi$ ) for which Equation 2.6 does not have a correction factor. For instance, a 3-chain cluster of spheres or cylindrical particles ( $l/d = 4$ ) have a shape factor of 1.3 (Hinds, 1982). However, the differences in Table 2.1 are too extreme to be explained by the shape factor only, and this suggests that the experimental values are of lower confidence. The shape factors presented in Table 2.1 are necessary for equating  $d_{50}$  with  $d_A$  using Equation 2.3.

### 3. Critical evaluation of cia and lda

#### 3.1. Cascade impactor analysis (cia)

In contrast with the force of gravity during terminal settling, the inertial forces acting on a particle that travels between the nozzle and the collection plate of an impactor are not constant. Neither is the drag force. In the region beyond the impactor jet, both forces continuously increase from zero as a particle travels from the jet to the collection plate, whereas they also change their direction (Fig. 2.4). In Fig. 2.4 the inertial force has been presented as a centrifugal force ( $F_C$ ) for the sake of convenience. In this dynamic force system, irregular particles may exhibit a behaviour which is different from that during stationary settling. They may start to rotate, in which case their (average) dynamic shape factor ( $\chi$ ) is not the same as during stationary settling. Consequently, the aerodynamic diameter measured with an inertial impactor, is not necessarily the same as its equivalent obtained from a sedimentation experiment, which is the only technique yielding the aerodynamic diameter by definition. So, different proportionality constants  $(\chi/\rho_P)^{0.5}$  between  $d_A$  and  $d_E$  for the same particle may apply for different situations and different techniques. This is a neglected aspect when in vitro deposition data from cia are used to predict lung deposition.

The conditions under which inertial impactors should be operated include laminar flow through their nozzles ( $500 < Re < 3000$ ). Most impactors do not meet this criterion during inhaler testing, as shown in Table 2.2 for the four stage ASTRA impactor.

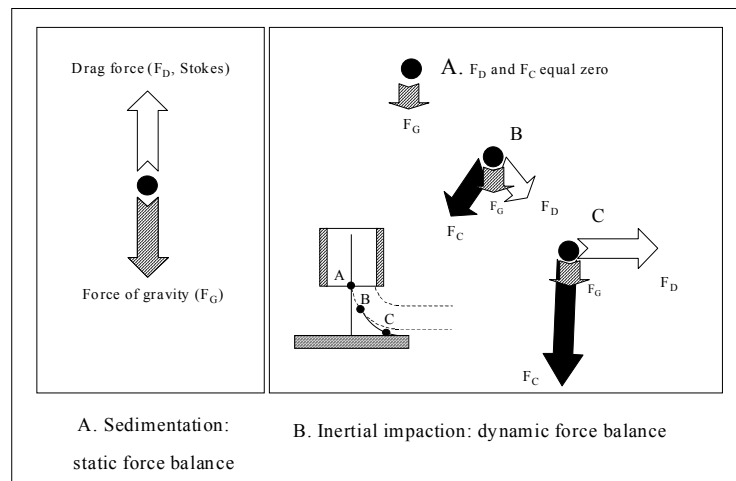


Figure 2.4. Schematic presentation of the forces acting on a particle during stationary settling (left) and in the nozzle exit region (right) of an inertial impactor.

Actual Reynolds numbers during measurement may be even higher than the numbers presented in Table 2.2. This is a consequence of the design of the nozzles, which are relatively short. As a result of that, the contribution of inlet and outlet geometry to the flow regime inside the nozzle is quite large. Especially for the flow through the nozzles of the second and third stages, which are relevant to the fine particle fractions, the Reynolds numbers are much higher than 3000 at flow rates that are still below the range of interest for dpi testing. This, in contrast with the *in vivo* situation, where the target area (for the fine particle fractions) is beyond the segmental bronchi, in which (at 60 l/min) the Reynolds number is  $< 2000$ , and further decreasing with increasing generation (Fig. 1.2).

Table 2.2. Calculated Reynolds numbers in the nozzles of the four stage ASTRA impactor. Stage 4 is a multi-jet with seven identical orifices. Values printed in bold are outside the recommended range ( $500 < Re < 3000$ ).

Stage:	1	2	3	4
Nozzle diameter (mm)	25	14	8	2
20 l/min	1132	2018	<b>3552</b>	1485
30 l/min	1701	3030	<b>5334</b>	2250
40 l/min	2267	<b>4043</b>	<b>7115</b>	3002
50 l/min	2835	<b>5049</b>	<b>8886</b>	<b>3749</b>
60 l/min	<b>3401</b>	<b>6061</b>	<b>10667</b>	<b>4500</b>
70 l/min	<b>3962</b>	<b>7073</b>	<b>12449</b>	<b>5252</b>

Other relevant differences between *in vitro* (impactor) and *in vivo* (lung) deposition have been listed in Table 2.3. Most important is the difference in deposition mechanisms and their efficiencies. In the impactor, deposition is by inertial impaction only, whereas in the respiratory tract, particle collection is also by sedimentation and diffusion, especially in the deeper lung regions for the smallest particles. Deposition efficiencies in all regions of the lungs decrease with decreasing particle diameter to a minimum of approximately 20% for total lung deposition corresponding with a particle diameter of  $0.5 \mu\text{m}$  (e.g. Martonen and

Katz, 1993). In vitro particle collection may be complete for all size classes, providing that the final stage (impinger or filter) performs adequately. Therefore, lung deposition can not be predicted from cascade impactor results, unless these differences in collection efficiencies are taken into account. And even then, predicted values based on cascade impactor results will not reflect actual lung deposition, not even when the inspiratory flow curves during the in vitro and in vivo experiments are kept exactly the same, which requires not only good flow control during in vitro, but also adequate monitoring of the inhalation manoeuvre during clinical studies. Anatomical (e.g. differences between adults and infants) and disease related factors (like severe bronchoconstriction) have to be taken into account as well.

Table 2.3. Some relevant differences between in vitro (impactor) and in vivo (lung) deposition.

<p><b>In vitro:</b></p> <ol style="list-style-type: none"> <li>1. Deposition is by inertial impaction only</li> <li>2. Particle collection is (near-)complete</li> <li>3. The throat is often a dry bent tube (in which powder disintegration is continued)</li> <li>4. The inspiratory flow curve is well controlled and monitored</li> <li>5. The inlet and conducting tubes (between the impactor stages) have fixed dimensions</li> </ol>
<p><b>In vivo:</b></p> <ol style="list-style-type: none"> <li>1. Deposition is by inertial impaction, sedimentation and diffusion</li> <li>2. Collection efficiency varies with particle size</li> <li>3. The throat is wet (particles stick on impact)</li> <li>4. The inspiratory flow curve is highly variable and often not known</li> <li>5. Air passageways differ from person to person and from moment to moment</li> </ol>

The most relevant practical drawbacks and limitations of cascade impactor analysis have been summarised in Table 2.4. The flow rate dependent cut-off diameters of the different impactor stages make it difficult to compare the fine particle fractions from different types of dpi's at the same pressure drop of 4 kPa through these devices. The flow rates for a number of marketed dpi's at this pressure drop are given in Table 2.5. This table also shows the theoretical cut-off values with 50% collection efficiency for the second stage of the MSLI at these flow rates, which is frequently seen as the impactor stage defining the fine particle fraction. The theoretical cutpoints of this stage differ by a factor 2 for the extremes in flow rate.

Table 2.4. Review of some practical drawbacks and limitations of inertial impaction.

<ul style="list-style-type: none"> <li>✓ Classification is into only a small number of size classes</li> <li>✓ The cut-off diameters of nozzles vary with the flow rate through the impactor</li> <li>✓ High impactor resistance limits the adjustable range of flow rates and reduces the flow increase rate</li> <li>✓ Fine particle adhesion occurs onto inner impactor walls</li> <li>✓ Electrostatic charge may disturb particle collection</li> <li>✓ Collection efficiency of the final stage may be less than 100%</li> <li>✓ Droplet evaporation can not be studied</li> <li>✓ Cascade impactor analysis lacks sufficient possibilities for automation</li> <li>✓ Cascade impactor analysis is time consuming and laborious</li> <li>✓ A large inter-device and inter-laboratory variation has been reported</li> </ul>
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Especially for impactors with a relatively low number of stages (2-5), calculations on the basis of cumulative size distribution curves are rather arguable. For instance, deriving a mass median aerodynamic diameter (mmad) for the fine particle fraction by intra- or extrapolation is nearly impossible. This is shown in Fig. 2.5 for an inhalation experiment with

a four stage Fisons type of impactor at 60 l/min. A cumulative size distribution curve of 68.08% < 4.31  $\mu\text{m}$ ; 88.29% < 8.74  $\mu\text{m}$  and 100% < 17.06  $\mu\text{m}$  could be computed from the depositions on the second, third and fourth impactor stage.

Table 2.5. Flow rates through some marketed dpi's corresponding with 4 kPa and cut-off diameters for the second stage of the Erweka impactor at these flow rates.

Inhaler:	Resistance ( $\text{kPa}^{0.5} \cdot \text{min} \cdot \text{l}^{-1}$ )	Flow rate		$U_{\text{NOZZLE}}^1$ (m/s)	$d_{50}^2$ ( $\mu\text{m}$ )
		(l/min)	( $10^{-3} \text{ m}^3/\text{s}$ )		
Inhalator Ingelheim	0.057	35	0.58	3.77	9.38
Astra/Zeneca Turbuhaler	0.043	46	0.77	5.00	8.15
GSK Diskus	0.034	59	0.98	6.37	7.22
Viartis Novolizer	0.028	71	1.19	7.73	6.55
ISF inhaler	0.019	105	1.75	11.37	5.40

<sup>1</sup> $U_{\text{NOZZLE}}$  is air velocity in the nozzle of the second stage corresponding with the flow rate

<sup>2</sup> $d_{50}$  is the theoretical cut-off diameter for the second stage nozzle with 50% collection efficiency (for particles with  $\rho_p = 1.5 \text{ g/cm}^3$ )

Only the fraction < 5  $\mu\text{m}$  is relevant to the target area, but within this fraction the mass median aerodynamic diameter may vary still considerably. This can have serious consequences, because the deposition efficiency in the lungs for particles within this aerodynamic size range decreases from nearly 100% (for 5  $\mu\text{m}$ ) to a minimum of only 20% (for 0.5  $\mu\text{m}$ ). Therefore, extrapolation of the size distribution curve into the size range < 4.31  $\mu\text{m}$  is desirable.

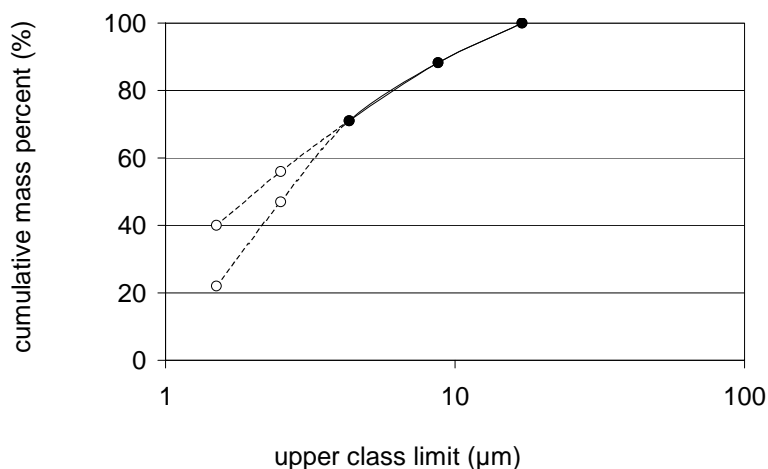


Figure 2.5. Typical cumulative mass distribution curve as function of the theoretical cut-off point for drug fractions retained from a four stage Fisons impactor at 60 l/min. The sum of the mass fractions on the stages 2 to 4 (39.04% of the nominal dose) has been put to 100%. The results are for an adhesive mixture from a special classifier based test inhaler.

However, for the curve shown in Fig. 2.5 this is nearly impossible. Plotting of the data on log-probability paper does not really help, because the distributions obtained from dry powder inhalers are not log-normal. This is the result of the presence of both primary particles and small agglomerates in the aerosol from a dpi, which have different densities and shapes. In contrast, with laser diffraction analysis 13 different classes are obtained within a size fraction smaller than 4.50 micron (with a 50 mm lens). This enables a much better

(comparative) evaluation of devices and conditions, and even a better prediction of lung deposition in spite of the fact that not so much aerodynamic diameters are obtained.

The high Reynolds numbers in the nozzle throats are not the only limitation to the flow rates through dpi's connected to an impactor. The high air flow resistance of most impactors is another, more practical constraint in this respect. This resistance, in combination with the relatively large volume of the impactor, also reduces the flow increase rate which is particularly relevant to the performance of dpi's like the AstraZeneca Turbuhaler (e.g. de Boer et al., 1997). Another practical problem of relevance is the fact that uncontrolled and undesired deposition mechanisms may occur in an impactor, such as particle collection by adhesion and electrostatic forces. Electrostatic particle collection onto inner impactor walls can be reduced by using metal devices that are connected to the earth during inhaler testing. The extent of adhesion highly depends on the design of the impactor. Extreme circulation of the aerosol stream on upper stages of some devices increases the number of contacts between particles and the inner walls of these stages. It is furthermore known that severe corrosion of some currently marketed multi stage impingers (e.g. the Erweka MSLI) occurs. It has recently been discovered that the corrosion is not confined to the surface of the impactor plates and interconnecting tubes. Corrosion is also present inside the nozzles, as shown in Fig. 2.6. This may have a dramatic effect on the cut-off efficiency, particularly for the fourth stage, where the jet diameters are small compared to the size of the lumps of corroded material protruding from the inner wall of the jet.

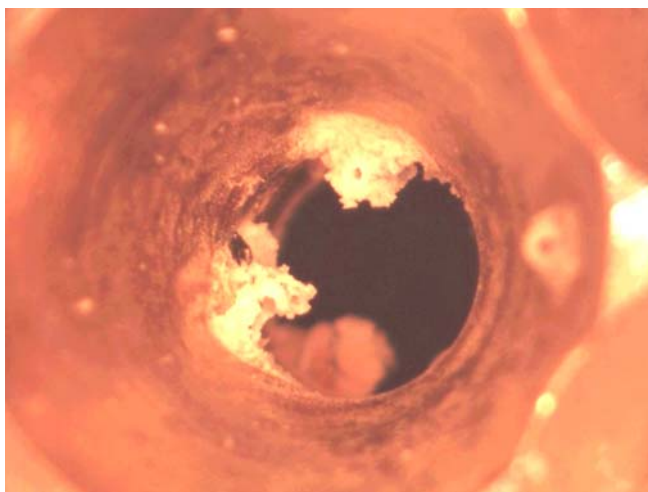


Figure 2.6. Corrosion inside one of the jets of the fourth stage (multi-jet) nozzle of the multi stage liquid impinger (Erweka, Germany).

Finally, it should be mentioned that the design of the induction port described by the European Pharmacopoeia (3<sup>rd</sup> edition, Supplement 2001), used in combination with the MSLI and NGI, is not suitable for testing of dry powder inhalers. This induction port has a double tapered inlet towards a narrow inner diameter and a very sharp 90 degrees bent. Carrier particles from dry powder inhalers collide with the inner walls of the conically shaped parts of this tube, particularly when the inhaler has a tangential discharge flow component. This causes particles with high inertia to diverge from the main direction of the discharge flow. Carrier particles also collide with the back of the throat beyond the 90 degrees bent. During these collisions, drug particles may be detached from the carrier crystals and obtained fine

particle fractions may be higher than to be expected in vivo under the same inspiratory flow conditions. None of these previously mentioned drawbacks of cascade impaction analysis is as problematic as the fact that the technique is laborious and time consuming however.

### 3.2. Laser diffraction analysis

Laser diffraction has the potential to solve some of the major problems related to cascade impactor analysis. The measuring is fast and the obtained size classification is independent of the flow rate. A large number of size classes for the fine particle fraction is obtained and the technique offers excellent opportunities for automation. In addition to that, repeated measurement over very short time periods (5 ms) is possible (so-called ‘time sliced measurement’), which provides the possibility to follow the size distribution in the aerosol as function of the inhalation time. However, micronised inhalation powders, in most cases, are not spherical and do not have unit density. In a few cases, like for instance salbutamol sulfate, particles may even be needle shaped. Therefore, calculated laser diffraction diameters ( $d_{LD}$ ) may differ from the equivalent volume diameters ( $d_E$ ) and aerodynamic diameters ( $d_A$ ). The relevance and possible implications of this discrepancy and some other theoretical limitations of laser diffraction technique (summarised in Table 2.6) are discussed in the next paragraphs.

Table 2.6. Some theoretical limitations and drawbacks of laser diffraction technique being relevant to the characterisation of inhalation aerosols.

<ul style="list-style-type: none"> <li>✓ Measurement of geometrical instead of aerodynamic particle size distribution (<i>at random measurement of numerous planes of symmetry</i>)</li> <li>✓ Volume distribution curves are calculated on the assumption that particles are spherical</li> <li>✓ Apparent particle density and dynamic shape factor of drug agglomerates are not known</li> <li>✓ A choice between Mie and Fraunhofer has to be made</li> <li>✓ Over- and underestimation of fractions in bimodal mixtures may occur</li> </ul>
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#### 3.2.1. $X_{50}$ in relation to $d_E$ and $d_A$

With laser diffraction technique, a (cumulative) volume distribution of the powder is obtained as function of the particle diameter. The principle includes that different geometrical particle dimensions are measured, depending upon how particles pass through the laser beam. For the calculations, it is assumed that the particles are spherical. According to ISO 13320-1 (1999) for laser diffraction,  $X_{50}$  is the proper notation for the median diameter. Correspondingly,  $X_{10}$  and  $X_{90}$  are the diameters for which 10%, respectively 90% of the total powder volume is in smaller particles. Of all aerosols to be measured, only aqueous droplets from nebulisation are spherical and approach unit density. Therefore, their  $X_{50}$  equals the median aerodynamic diameter ( $d_A$ ). As already mentioned, most micronised powders only approach the spherical shape. Yet, the median laser diffraction diameter ( $X_{50}$ ) does not differ much from the equivalent volume diameter ( $d_E$ ). A good indication for this can be obtained from carefully prepared sieve fractions of crystalline alpha lactose monohydrate, having a well defined wedge shape which enables calculation of  $d_E$ . The mean ratio of crystal length to base width (so-called ‘elongation ratio’) for such particles is 1.66 (from scanning electron microscopy observation). For wedge shaped particles, the crystal base is the characteristic particle diameter upon which fractionation during sieving takes place. Therefore, it is not surprising that this elongation ratio is confirmed by laser diffraction analysis, yielding  $X_{100}$ -values being (on average) 1.68 times higher than the upper class limits of the prepared sieve fractions. The calculated median volume diameters ( $X_{50}$ ) from laser diffraction analysis of these fractions are (on average) 1.21 times the mean fraction diameter, which is the arithmetic mean of lower and upper sieve diameter (equals the mean base width). It can also be

calculated that the equivalent volume diameter ( $d_E$ ) of such wedge shaped particles with unit base width is 1.17. These relative values for  $X_{50}$  and  $d_E$  are in good agreement with each other (the difference is only 3%). Especially, when it is considered that not all fractions exhibit a natural size distribution. For narrow size fractions that are taken from the tails of the size distribution of the starting material, the arithmetic mean of upper and lower class limit may not equal the median diameter of the fraction.

From the small difference between  $X_{50}$  and  $d_E$  for typically wedge shaped particles, it may be expected that this difference for most solid micronised inhalation drug particles is of the same order of magnitude, or even smaller. After all, most micronised particles have lower elongation ratios than unmilled lactose crystals. This, if desired, enables the assessment of median aerodynamic diameters from  $X_{50}$  (using Equation 2.3) when particles in the aerosol cloud are single entities, since particle density ( $\rho_P$ ) and dynamic shape factor ( $\chi$ ) can be obtained from other techniques. On the other hand, calculation may not be necessary, as density and shape factor (both being  $> 1$ ) normally widely compensate each other in the proportionality constant between  $d_E$  and  $d_A$  (for solid particles) For instance, the dynamic shape factor ( $\chi$ ) of airborne particles with various shapes ranges from approximately 1.0 (for spheres) to 1.3 (e.g. for a cylinder with  $l/d = 4$ ). The density of solid inhalation drugs ( $\rho_P$ ) ranges from approximately 1.2 to 1.5 g/cm<sup>3</sup>, unless porous particles are being used (e.g. Edwards et al., 1997). So, the proportionality constant  $(\rho_P/\chi)^{0.5}$  for these particles is between 0.96 and 1.22 for the extremes mentioned.

Aerosols from dpi's exist not only of primary particles however. They may also contain small clusters of single particles, and assessments to be made for such small agglomerates are more complex. Table 2.7 shows the data for some chain-type of clusters, containing up to four primary spherical particles of the same size, which is the most unfavourable type of agglomerate for laser diffraction measurement. The ratio of the expected median laser diffraction diameter ( $X_{50}$ ) to the estimated aerodynamic diameter ( $d_A$ ) increases to a factor 1.68 for a 4-chain cluster. The difference is not so much caused by the proportionality constant between  $d_E$  and  $d_A$ , but rather by the difference between calculated  $d_E$  and estimated  $X_{50}$ , which is quite large for chain-like agglomerates. Four-chain agglomerates are highly unlikely to exist in the turbulent air stream from a dpi however. Compact-types of agglomerates stand a much better chance to remain intact during dispersion.

It has to be emphasised that differences between  $X_{50}$  and  $d_A$  (or  $d_E$ ) are not at all relevant to dpi development however. Starting point for device or formulation development is a drug sample in the desired aerodynamic particle size distribution for an optimal therapeutic effect. This size distribution may be obtained from any suitable aerodynamic sizing technique. The same drug sample will also be measured with laser diffraction technique (using a dispersion apparatus like RODOS, Sympatec GmbH, Goslar Germany) yielding the laser diffraction size distribution (in terms of  $X_{10}$ ,  $X_{50}$  and  $X_{90}$ ). Next, the objective of powder formulation and device development is to get as close as possible to this laser diffraction result during the inhalation experiments with this drug. Therefore, errors inherent in the (laser diffraction) measuring principle are the same for all measurements undertaken during development. Inadequate de-agglomeration of the powder, resulting in the release of small agglomerates (or a mixture of primary particles and small agglomerates) from the dpi, reflects on the size distribution of the aerosol cloud which will be different from the result obtained with RODOS dispersion. This does not imply that data interpretation is simple. It requires good understanding of the working principle of a dpi and the properties of powder formulations for inhalation to draw the correct conclusions.



Table 2.7. Clusters of spheres with unit diameter and density  $\rho_p = 1.3 \text{ g/cm}^3$ .

Cluster	$X_{50}$	$V_{TOT}$	$d_E$	$\chi$	$\rho_s$	$(\rho_p/\chi)^{0.5}$	$d_{A(E)}$	Ratio
Single sphere	1	0.52	1	1	1.30	1.140	1.14	0.88
2 chain	1.5	1.31	1.36	1.12	1.04	0.964	1.31	1.15
3 chain	2	2.10	1.59	1.27	0.98	0.876	1.39	1.44
4 chain	2.5	2.88	1.77	1.32	0.95	0.846	1.49	1.68

$X_{50}$  = mean (median laser diffraction diameter) of the extreme particle dimensions

$V_{TOT}$  = total cluster volume

$d_E$  = equivalent volume diameter based on  $V_{TOT}$  ( $d_E = (6V_{TOT}/\pi)^{0.33}$ )

$\chi$  = dynamic shape factor, derived from Hinds (1982)

$\rho_s$  = apparent particle density

$d_{A(E)}$  = aerodynamic diameter calculated from  $d_E$  and  $(\rho_p/\chi)^{0.5}$  (Equation 2.3)

Ratio = ratio of median laser diffraction diameter ( $X_{50}$ ) to calculated aerodynamic diameter ( $d_{A(E)}$ )

### 3.2.2. The choice of a diffraction model

The choice between the Mie and Fraunhofer theory for aerosol measurement is another item needing careful consideration. This choice has been subject of many discussions and is particularly related to the final aspect mentioned in Table 2.6. This has been shown by Annappagada and Adjei (1996) who investigated the nature and magnitude of errors when determining size distributions with the Fraunhofer technique. They concluded that the Fraunhofer diffraction pattern analysis method works well for unimodal systems, but for sharp-peaked multimodal systems, there is a tendency to skew the distribution towards the mode that produces the strongest peak in the diffraction pattern. It should be recognised that the choice between Mie and Fraunhofer is not so much a choice between diffraction theories however, but rather one between deconvolution and smoothing techniques. Therefore, a rational choice between Mie and Fraunhofer can not always be made, unless the algorithms used to solve the complex diffraction integral are known, as well as the effect of the smoothing techniques on the distribution curve. There is no doubt that Mie is the better theory, but practically, Fraunhofer results may give better correlations with cascade impactor data. One important reason for this is, that the optical parameters (refractive index and absorption coefficient) needed for a correct use of the Mie theory are often not exactly known. They appear to depend not only on the chemical nature of the particles measured, but (partly) also on their physical properties, such as size (Boeck, 1983), shape, concentration and temperature, which all may vary during inhalation (e.g. by droplet evaporation). Small variations in these optical parameters may result in dramatic changes in the calculated size distribution curve, as has been shown in several studies (e.g. Müller and Schuhmann, 1996). It must therefore be concluded, that if the correct optical parameters are not known, or if they change during the measurement, the Mie theory is no proper option.

### 3.2.3. Practical and operational limitations of lda

More confining for laser diffraction testing of inhalation aerosols than the previously discussed theoretical drawbacks and limitations, are certain practical and operational limitations. Most frequently mentioned problems have been summarised in Table 2.8. Up to date, these problems have excluded widespread testing of breath controlled dpi's with this technique. Not only flow control through the device is impossible with the present standard laser diffraction apparatus; neither can emitted mass fractions (of fines) be measured. Furthermore, measurement of drug-drug or drug-excipient mixtures may be difficult, if the size distributions of such binary mixtures cover each other largely. Finally, the presence of larger carrier crystals makes accurate fine drug particle measurement impossible. In Chapter 3, the design and development of a special inhaler adapter will be discussed which takes away

most of these operational shortcomings of Ima. The system can be used for all types of inhalers; the configuration for dpi's comprises an airtight in-line arrangement of a pre-separator, a central housing and a fine particle collector in between the inhaler and the vacuum system, through which the inspiratory flow curve can be adjusted.

Table 2.8. Some frequently mentioned practical limitations and drawbacks of laser diffraction technique that are relevant to the characterisation of inhalation aerosols.

<ul style="list-style-type: none"> <li>✓ The flow curve through the inhalation device can not be controlled</li> <li>✓ Fine particle mass fractions are not obtained</li> <li>✓ Measurement of mixtures (drug-drug or drug-excipient) may be problematic</li> <li>✓ Low particle concentrations may not be measurable (dose weights &lt; 4 µg)</li> <li>✓ The measuring range is much wider than the size distribution of the aerosol             <ul style="list-style-type: none"> <li>a. for a 100 mm lens, the measuring range is 0.9 - 175 µm</li> <li>b. for a 50 mm lens, the range is 0.45 - 87.5 µm</li> </ul> </li> </ul>
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Limits to the fine particle concentration in the aerosol cloud or the total mass of fines to be measured are not typically a problem related to laser diffraction technique. Such limits also exist for cascade impactors, for which overload of the impaction plate may result in particle bounce or re-entrainment. With laser diffraction technique, very high particle concentrations in the cloud can be measured quite well, whereas high total mass amounts do not accumulate in the measuring zone, but are extracted with the air. Analytical problems with low particle concentrations in the aerosol cloud (as from very low drug doses) can be solved for impactor technique by inhaling a large number of doses for one single analysis. With laser diffraction technique, single drug doses of 2 to 4 µg can still be measured accurately, as a result of recent improvements in detector sensitivity. The wide measuring range with laser diffraction technique should not be considered as a problem. Lenses with focal lengths of 50 (size range 0.45 - 87.5 µm) or 100 mm (size range 0.9 - 175 µm) have to be used because of the required measuring volume within the aerosol cloud. This volume should not become too small, so as to measure a representative cross section of the cloud. But this overrange is compensated by the large number of size classes within the total measuring range (e.g. 31 for Sympatec HELOS) and the logarithmic increase in class width with increasing mean diameter. As a consequence, there are still 10 size classes within the range from 0.9 to 5.0 µm for the 100 mm lens (R3), against even 14 classes within the range from 0.45 to 5.25 µm for the 50 mm lens (R2) for the Sympatec HELOS/BF-Magic (Sympatec GmbH, Goslar Germany). In comparison, most impactors have only one (e.g. twin impinger) to seven (e.g. Next Generation Impactor) classes within total size ranges (for f<sub>pf</sub>) that are even slightly larger. A clear advantage of laser diffraction is the fact that the size classes are independent of the inspiratory flow rate. Optical concentration expresses particle concentration in the cloud, and this parameter can be used to measure total emission time of an inhaler or to estimate at what moment, from the start of the inhalation, the bulk of the dose is released. But by far the most profitable features of laser diffraction are time saving, reproducibility and automatic data recording and processing.

#### 4. Conclusions

The principle of inertial impaction with so-called multi stage impactors or liquid impingers is widely used for performance testing of medical aerosol generators. However, the relevance of this technique is practically confined to comparative in vitro evaluation of these inhalation devices within rather narrow ranges for the (constant) flow rate and inhalation time. At the highest possible flow rates through impactors (60 to 90 l/min), the cut-off diameters

and collected mass fractions are of lower confidence, because the flow regime inside the nozzles is highly turbulent. Fine particle outputs at flow rates higher than 90 l/min, as can easily be attained by most patients during prescribed use of low resistance dry powder inhalers, can not be measured because of the high impactor resistances. Neither are experiments at high flow increase rates possible, which is the decisive flow parameter for inhalers like the Turbuhaler (AstraZeneca). High inter and intra laboratory variations have been described with impactors of the same design. Comparison of results from different types of impactors with different upper class limits for the fine particle fractions at the same flow rate, is even more problematic. Especially, when the number of size classes is low and composition of a cumulative mass distribution curve as function of particle diameter is impossible. As a consequence of all these limitations, impactor data are a poor source of information for the prediction of (bio-)equivalence or therapeutic efficacy.

With laser diffraction technique, geometric instead of aerodynamic particle diameters are obtained, unless the particles are spherical and have unit density, such as droplets generated from aqueous drug solutions by nebulisers. Standard laser diffraction apparatus offer insufficient control of the inspiratory flow curve through the inhaler. Next to that, the mass fraction of the dose that is emitted as fine particles can not be measured. Therefore, special means are necessary, which should consist of a closed system through which the aerosol cloud from the inhaler can be drawn. It should also include a flow control unit and a fine particle collector for the determination of the emitted fine particle mass fraction. Additionally, for the measurement of dpi's containing adhesive mixtures, a pre-separator for the larger carrier crystals is a requisite. With such means, designed as a modular concept, laser diffraction can become a highly valuable aerosol sizing technique for all types of inhalers, including dpi's. For dpi's, the objective of formulation and device development is simply to get the size distribution of the drug in the aerosol from the inhaler as close as possible to the primary drug particle size distribution. This, under favourable inspiratory flow conditions regarding lung deposition and the patients' preference for the inhalation manoeuvre. The primary particle size distribution for the drug should preferably be known from measurement with an aerodynamic sizing technique (so as to estimate its therapeutic potential) as well as from laser diffraction analysis (to yield the reference for the size distribution in the aerosol from the dpi) using a highly effective dry powder disperser (e.g. RODOS disperser, Sympatec, Clausthal-Zellerfeld, Germany). Whether lda will also become acceptable as a standard for regulatory authorities for certain applications depends on further development of the technique and the execution of validation programs and comparative error analyses (with cascade impaction as the reference). Special advantages of laser diffraction technique over cascade impactor analysis are the many size classes within the relevant drug fraction for lung deposition, the short measuring time, the possibility of size distribution measurement as function of the inhalation time and automatic data recording.

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