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Assessment of the Twin Impinger for Size Measurement of Metered-Dose Inhaler Sprays

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The calibration of the first stage of the twin-stage impinger, an instrument proposed for use in measuring the spray size from metered-dose inhalers, was performed with monodisperse aerosols by a standard technique for cascade impactors. The mean cut point was found to be not particularly sensitive to operating variables which may be expected to occur in practice. The cut point was close to that reported previously, although the collection efficiency curve was found to be slightly sharper. Calculations are reported on the expected results of measurements on aerosols in a two-stage instrument with an idealized perfect collection efficiency curve as well as the curve measured for the twin impinger. These results indicate that important characteristics of spray size distribution cannot be distinguished with an ideal two-stage instrument; the twin impinger is less capable than an ideal instrument.

KEY WORDS: impinger; impactor; calibration; aerosol; spray; size.

INTRODUCTION

Metered-dose inhalers (MDIs) produce a spray of fine drug particles which can be inhaled by a patient. Inhaled drug particles, like particles of any other substance, are deposited in various regions of the respiratory tract, depending on the aerodynamic diameter of the particles (1,2). The spray from an MDI is initially traveling at a high speed and is rapidly changing in both size and velocity (3). These characteristics cloud the concept of aerodynamic size of the spray droplets and render inappropriate the strict application of any method for measuring "classical" aerosol properties. Nevertheless, the importance of monitoring the spray size from MDIs is widely recognized, in both the development of new products and the quality assurance process of routine manufacturing (3,4). Of course, spray size characterization requires a description of the size distribution, not merely a single summary statistic such as the mean size (5).

Various methods have been proposed for measuring the particle size distribution in a spray, including inertial classifiers that measure the aerodynamic diameter (6–9), microscopic examination of impacted sprays to measure physical diameter (10,11), and laser diffraction to measure light scattering characteristics (12). An inertial classifier, known variously as the twin impinger (13), the Copley liquid impinger (7), and Method A in the *British Pharmacopoeia* (14), is one of the more popular of the recently proposed devices. It has been proposed to USP as a method for MDIs in general (15).

The twin impinger is a two-stage cascade impinger which was developed specifically to assess the delivery of drugs from MDIs (13). The instrument, shown schematically in Fig. 1, is fashioned from a series of glassware components. Air is drawn through the instrument at a flow rate of 60 L/min by means of a vacuum at the outlet. Aerosol spray is introduced at the inlet and passes through a glass bulb which is intended to simulate the oropharynx. It then passes into the upper impinger stage, which consists of a nozzle and a bulb containing a measured amount of liquid. Particles larger than the cut point of this first stage are collected in the liquid. Smaller particles are not collected on the first stage but proceed to the lower stage. Here, if they are larger than the cut point of this stage, they are collected in a second volume of liquid. Particles too small to be collected in this stage are emitted at the exit. Two data points are collected to characterize each aerosol spray; the first describes the mass of material captured in the liquid of the first stage as well as all the glassware preceding it, and the second describes that captured in the liquid volume in the lower stage as well as the tubing leading to it.

Little information has been published regarding the calibration and ruggedness of the twin impinger since its initial appearance in 1987 (13). Childers (16) has reported that the twin impinger was a robust instrument, with small changes in operating parameters having no effect on the results, but these studies were done using a standard MDI as test agent and no test of the calibration per se was reported.

This study had a twofold objective. The first was to determine the particle collection efficiency characteristics of the upper impinger stage as a function of various operating parameters. The second was to assess the applicability of the twin impinger for its intended purpose of measuring the significant size properties of MDI sprays.

CALIBRATION

Experimental Procedure

Most of the measurements were performed on a single twin impinger, with a few points repeated on a separate second instrument, each made according to published designs (14). Each instrument was evaluated by passing monodisperse aerosol particles through the unit and determining where the particles were collected, according to the procedure described by Marple *et al.* (18). Variations in flow rate, collecting fluid volume, and collecting fluid composition were tested as shown in Table I and were selected to represent ranges which occur in practice. Test particles of precisely known sizes in the range of 1.56- to 10-μm aerodynamic diameter were used.

The particles were generated with a vibrating orifice monodisperse aerosol generator (17), a standard procedure for calibrating cascade impactors (18,19). In this procedure, a known percentage of oleic acid is dissolved in alcohol and forced by a syringe pump through a small orifice being vibrated at a known precise frequency on a piezoelectric crystal. Each cycle of the crystal will generate one droplet. By

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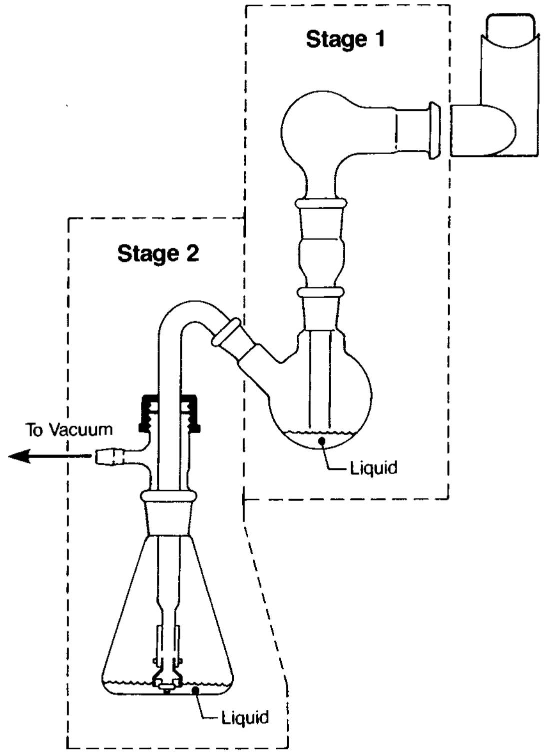

Fig. 1. Schematic diagram of twin impinger.

Table I. Impinger Test Results for First Stage

D_p (µm)	Solution	Amount (ml)	Flow rate (L/min)	Retention (%)
		Twin impinger 1		
1.56	Methanol	7	60	0.30
4.33	Methanol	7	60	15.9
4.33	Methanol	5	60	16.0
4.33	Methanol	10	60	13.6
4.33	Methanol	7	54	12.7
4.33	Methanol	7	66	16.9
4.33	D.I. water	7	60	13.2
6.40	D.I. water	7	60	56.0
8.26	Methanol	7	60	91.6
8.26	Methanol	5	60	93.8
8.26	Methanol	10	60	90.8
8.26	Methanol	7	54	91.1
8.26	Methanol	7	66	90.7
8.26	D.I. water	7	60	91.2
10.0	Methanol	7	60	98.2
10.0	D.I. water	7	60	97.2
10.0	D.I. water	5	60	98.3
10.0	D.I. water	10	60	98.3
		Twin impinger 2		
3.00	Methanol	7	60	1.03
4.65	Methanol	7	60	14.9
8.20	Methanol	7	60	93.1
10.0	Methanol	7	60	99.1

knowing the flow rate of the liquid, the vibration frequency of the piezoelectric crystal and the percentage of oleic acid in the alcohol solution, the particle size of the oleic acid droplet after the alcohol has evaporated can be calculated (17).

To aid in determining the site of particle collection, a fluorescent dye tracer is added to the oleic acid/alcohol solution. The particle droplets in the generated spray therefore contain a proportional amount of dye. The quantity of particles collected in various parts of the instrument is then determined by washing the particles out of these parts with wash solution and measuring the dye concentration in the wash solution.

To perform a test, liquid is put in the impinger and the flow rate set to the predetermined value. Particles are then introduced to the inlet of the impinger for a period of a few minutes. The particles not collected in the impinger pass through the exit and are collected on a filter. After a run, the various components of the impinger are washed with a known volume of wash solution and the concentration of the dye in the wash solutions is measured. The relative amounts of dye concentration in the wash solutions, including that from the filter, indicate the fraction of particles collected in the corresponding parts of the impinger.

Results and Discussion

The test conditions and results are summarized in Table I, which shows the test particle size, the amount and nature of the solution in the impinger, and the air flow rate through the impinger. The amount of material collected in the upper entry portion and the liquid of the impinger divided by the total amount (this portion plus the amount collected on the filter) is shown as "retention." This is the collection efficiency of the impinger stage for particles of the corresponding size.

The collection efficiency curve is plotted in Fig. 2 and shows an "S" shape which is typical for an inertial impactor. The cut point of the impinger, defined as the point of 50% collection efficiency, is at 6.3 µm. A single curve adequately describes all the experimental points, regardless of the flow rate, the volume of collecting liquid, or whether water or methanol are used as liquid. The points measured for the second impinger agree with those from the first. The value of 6.3 µm is not significantly different from the previously reported value of 6.4 µm (13).

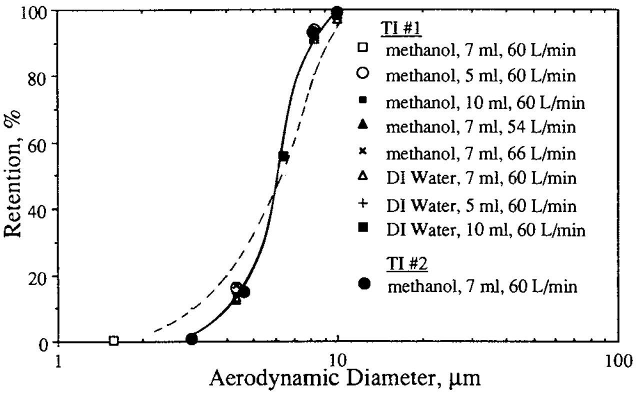

Fig. 2. Twin impinger calibration curve [solid line determined in this study; dashed line reported earlier (13)].

Also shown in Fig. 2, as a dashed line, is the calibration curve obtained earlier (13). Excellent agreement is seen. The test aerosol from the vibrating orifice aerosol generator was corrected for the presence of doublet and triplet particles, and this method is considered to yield more exact results (20) than the somewhat broader distribution from a spinning disk as used by Hallworth and Westmoreland (13).

These results are in agreement with design principles of impaction stages, in which the cut point diameter can be related to a function of parameters known as the Stokes number (21):

$$\mathrm{St} = \frac{\rho_p C V_0 D_p^2}{9 \mu W} = 0.2025 \tag{1}$$

where

ρ_p = density of particle (g/cm^3)
C = Cunningham slip correction factor
V_0 = velocity (cm/sec)
D_p = particle diameter (cm)
μ = fluid viscosity (P)
W = jet width (cm)

This equation describes the cut point diameter over a limited range of conditions. During the impaction process, the liquid in the impinger functions merely as a collecting surface; provided the particles which hit it do not bounce off, the physical properties of the liquid have no effect. Also within the range of validity of Eq. (1), the distance between the end of the nozzle and the impaction surface is not a strong parameter, so the volume of liquid used likewise would not be expected to be important. Finally, the flow rate through the instrument is related to the square root of the cut point diameter. So Eq. (1) predicts that a variation from, say, 90 to 110% of the design flow rate should change the cut point diameter by merely 95 to 105%. This change is rarely of practical significance in particle size measurements on material other than monosized calibration standards.

The lower impinger stage is intended to collect all particles passing the first impinger stage. To test this, the collection efficiency of the lower stage was measured in the same manner as the upper stage, at a single point with a particle size of 1.62 μm. The results showed that 95.4% of the 1.62-μm particles were collected, with 4.6% penetrating this stage. If typical collection efficiency curves hold for this stage, then a significant fraction of submicrometer material would not be captured in this stage. This possibility was not pursued; MDIs normally have a very small proportion below 1 μm. But if the instrument were used for aerosols which did contain significant amounts of submicrometer material, the effect of lost sample could become significant.

APPLICABILITY OF THE TWIN IMPINGER TO MDI CHARACTERIZATION

The performance of the twin impinger as an impactor stage with test aerosols is an important characteristic: Even more important is the pertinence of the data obtained when it is used to measure the spray from MDIs. There are at least two limitations to applying the data from the twin impinger to relate to significant performance characteristics of any aerosol, notwithstanding the complications which arise due to the high initial velocity of the spray from an MDI. One limitation arises from the fact that the twin impinger is merely a dichotomous sampler; i.e., the total sample is divided into only two size categories. The second limitation arises from the fact that the separation between the two categories is broad, rather than perfectly sharp.

To illustrate the limitations, it is useful to discuss the behavior of the twin impinger in terms of its expected performance with hypothetical idealized size distributions. One convenient idealization is that of a log-normal distribution, which may be characterized by two parameters, i.e., a mean and a geometric standard deviation (GSD). The log-normal distribution has been found to be a useful approximation for MDI spray size measurements (21,22).

Consider a hypothetical classifier which has a perfectly sharp division between its two stages at, say, 6.4 μm. Then any material fed into this classifier which had a mass median diameter of 6.4 μm would be divided into two equal portions, one greater than and one less than 6.4 μm. The width of the distribution of feed material would not affect the result—very broad distributions would have the same division into two equal portions as very narrow distributions. So the hypothetical classifier could not yield any information on the width of any distribution which had a mass median diameter of 6.4 μm.

Now consider a slightly larger distribution, say one with a mean of 7.2 μm, with a GSD of 1.25. From elementary properties of statistical distributions (21), 30% of the total distribution lies below 6.4 μm. So if this material were passed through the hypothetical classifier with a cut point at 6.4 μm, 30% of the total would be found to lie in the smaller portion, and 70% in the larger. Next, consider a third material with a size distribution described by a mean of 8.4 μm and a GSD of 1.7. This would yield the identical result: 30% of the total material is below 6.4 μm and 70% above. In fact, there is a family of combinations of mean and GSD which would give the same result.

Figure 3 shows the results of calculations using many size distributions (Appendix). The family of curves is the loci of combinations of mean and GSD which would result in the indicated values of percentage of material lying below 6.4 μm. For example, the line labeled 30% represents all combinations of mean and GSD which would result in 30% of the material falling into the lower classification of this hypothetical two-stage classifier. The classifier could not discriminate between any of the size distributions falling on this line. In general, samples with a size distribution falling on any of the lines could not be distinguished from different samples having size distributions falling on the same line, on the basis of data from only the two stages.

Next, consider the performance of a two-stage classifier with a collection efficiency curve as shown in Fig. 2, which was measured on the twin impinger. As in the case of a device with a sharp cut point, this classifier would not be expected to discriminate between materials of varying width, provided the mass median diameter coincided with the midpoint on the collection efficiency curve, 6.4 μm. But now, because the division between the two stages is not sharp, the data point corresponding to smaller particles will

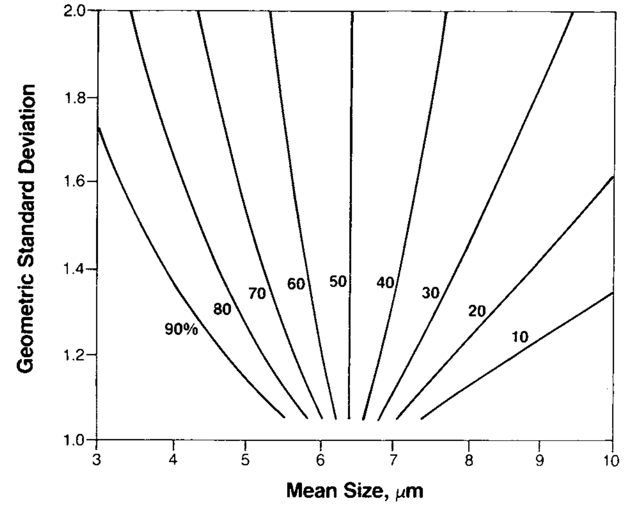

Fig. 3. Combinations of distributions that cannot be distinguished with a perfectly efficient two-stage classifier. Curve label shows the percentage of total sample which would be collected in the finer classification.

include some material larger than the nominal cut point size, while the other data point will include some material smaller than the nominal cut point size. The result will therefore be less sensitive to the width of the particle distribution.

Figure 4 shows results of calculations using various size distributions for a classifier with the collection efficiency characteristic shown in Fig. 2. Note that this has the same general appearance as Fig. 3, but it demonstrates that the resolution of the device is reduced from that for the ideal device; i.e., a wider range of mean and GSD will result in the same relative proportions of mass in the two classification pools.

CONCLUSIONS

The twin impinger has been independently calibrated, and the results are in agreement with previously published values for mean cut point size.

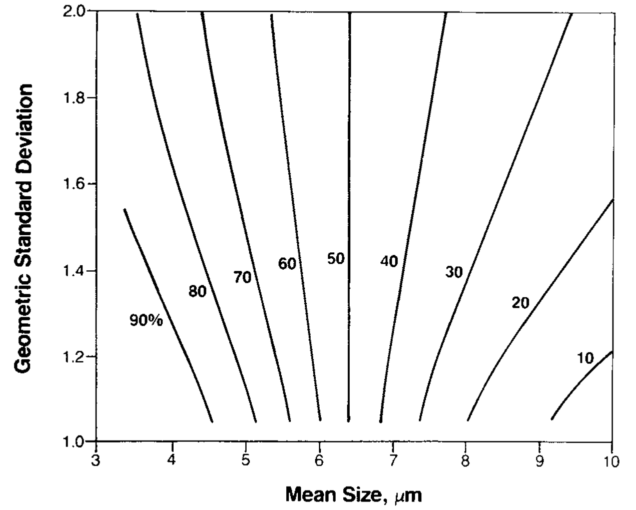

Fig. 4. Combinations of distributions that cannot be distinguished with the twin impinger. Curve label shows the percentage of total sample which would be collected in the finer classification.

The cut point characteristics of the twin impinger show no great sensitivity to operating variables which might be expected to occur. Air flow rate, collecting fluid volume, or fluids of varying density, solvency, and surface tension were found not to influence the cut point size, and good agreement was found between two separate units.

Limitations arise from the fact that the twin impinger divides the total spray into only two components. Because of this, the instrument cannot discriminate among distributions with specific combinations of varying size and width. Therefore, the interpretation of twin impinger data is inherently ambiguous. This conclusion applies strictly to the application of the twin impinger to true aerosols; the more complex behavior of MDI sprays will not reduce the data interpretation uncertainty.

APPENDIX: CALCULATION OF LIMITS TO SIZE DISCRIMINATION

The curves in Figs. 3 and 4 were calculated as follows: The equation which defines collection efficiency of an impactor stage may be rewritten for monosized particles of any size "d" as

$$F(d) = f(d) * \eta(d) \tag{2}$$

where

$F(d)$ = frequency of appearance of particles in the outlet stream
$f(d)$ = frequency of appearance of particles in the inlet stream
$\eta(d)$ = collection efficiency for particles of size d

Since this equation holds for individual particles, it holds for each of the varying sized particles in a distribution. Therefore it may be used to calculate the size distribution of material collected on the stage when the input size distribution is specified. The fraction of the total mass collected on the stage can then be obtained by integrating this collection fraction over the range of sizes present in the original distribution. The calculations summarized in Fig. 3 were obtained by numerically integrating Eq. (2), with efficiency defined by the relationship

$$\begin{aligned} \eta(d) &= 1 \quad \text{for } d \geq 6.4\ \mu\text{m} \\ &= 0 \quad \text{for } d < 6.4\ \mu\text{m} \end{aligned} \tag{3}$$

Hundreds of equations describing log-normal input size distributions with means in the range of 1 to 10 μm and GSD in the range of 1.05 to 2.0 were used as inputs, and the fraction collected was calculated for each of these. The values for this large number of points for the collection fraction as a function of both mean and GSD of the input distribution were then plotted. The lines in Fig. 3 were obtained by connecting points with the same value of collection fraction. Figure 4 was obtained likewise, with the efficiency function $\eta(d)$ obtained by numerically approximating the curve shown in Fig. 2.

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