Is Aerodynamic Diameter a Good Metric for Understanding Regional Deposition?

Jeffry Weers, Nani Kadrichu, and Nagaraja Rao

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The TLD is the fraction of particles that bypass deposition in the URT and are not exhaled.

“Deposition in the airways is controlled by three factors: airway geometry, aerodynamic particle size, and inhaled flow rate”

Lippman, 1977

\[ \text{Stk} = \frac{\rho_p d_p^2 u C_C}{18 \mu D} \sim \frac{d_a^2 Q C_C}{18 \mu D} \]  
(Stokes' Equation)

\[ d_a^2 Q = \text{impaction parameter} \]

\[ v = \frac{\rho_p d_p^2}{18 \mu} g \sim \frac{d_a^2}{18 \mu} g \]  
(Terminal Settling Velocity)


Source: Darquenne C: Particle deposition in the lung, 2006
Is there a link between aerodynamic size and regional lung deposition?

“We propose the terms ‘coarse’, ‘fine’, ‘extrafine’ to differentiate orally inhaled medical aerosols with particle MMADs of >5 µm, 2.1-5 µm, and <2.1 µm, respectively”.

“Regional lung deposition varies according to aerosol particle MMAD as well as GSD. In general, particles > 6 µm deposit preferentially in the oropharynx, those 2-6 µm in the central airways, and those < 2 µm in the peripheral airways and alveoli”.
Cascade impactors are not lung simulators, despite marketing drawings to that effect created historically by some manufacturers of the Andersen cascade impactor. -Dolovich et al, 2018

Q = 28.3 L/min

Are cascade impactors just a QC tool?

While stage cutoff diameters vary with flow rate, the impaction parameter cutoffs do not vary.

**Cutoff Diameters For NGI Stages**

Flow Rate (L/min)

<table>
<thead>
<tr>
<th>Stage</th>
<th>0.1</th>
<th>1</th>
<th>10</th>
<th>100</th>
<th>150</th>
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**Impaction Parameter Cutoffs for NGI Stages**

Flow Rate (L/min)

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<tr>
<th>Stage</th>
<th>0.1</th>
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</table>

**Next Generation Impactor**

Which *in vitro* measure of flow rate dependence is consistent with *in vivo* delivery?

**a**

**CONSTANT MMAD**

<table>
<thead>
<tr>
<th>Stage</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<tbody>
<tr>
<td>Drug Mass (%)</td>
<td>35</td>
<td>30</td>
<td>25</td>
<td>20</td>
<td>15</td>
<td>10</td>
<td>5</td>
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</table>

**b**

**CONSTANT MMIP**

<table>
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<th>Stage</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>MOC</th>
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<tr>
<td>Drug Mass (%)</td>
<td>40</td>
<td>30</td>
<td>20</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</table>

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<table>
<thead>
<tr>
<th>Q (L/min)</th>
<th>MMAD (µm)</th>
<th>(FDP_{&lt;3.3\mu m}) (µg)</th>
<th>MMIP (µm² L/min)</th>
<th>(FDP_{54.3}) (µg)</th>
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<tr>
<td>30</td>
<td>3.5</td>
<td>45</td>
<td>398</td>
<td>58</td>
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<tr>
<td>60</td>
<td>3.5</td>
<td>45</td>
<td>816</td>
<td>38</td>
</tr>
<tr>
<td>100</td>
<td>3.5</td>
<td>46</td>
<td>1282</td>
<td>25</td>
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</tbody>
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<th>Q (L/min)</th>
<th>MMAD (µm)</th>
<th>(FDP_{&lt;3.3\mu m}) (µg)</th>
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<th>(FDP_{54.3}) (µg)</th>
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</thead>
<tbody>
<tr>
<td>30</td>
<td>3.9</td>
<td>38</td>
<td>466</td>
<td>43</td>
</tr>
<tr>
<td>60</td>
<td>2.8</td>
<td>49</td>
<td>466</td>
<td>43</td>
</tr>
<tr>
<td>100</td>
<td>2.2</td>
<td>61</td>
<td>466</td>
<td>43</td>
</tr>
</tbody>
</table>
**Q index:**
A quantitative metric for assessing flow rate dependence

\[
Q_{\text{index}} = \left( \frac{TLD_{6\text{kPa}} - TLD_{1\text{kPa}}}{TLD_{\text{max}}} \right) \times 100
\]

**Sign:**  
+ sign indicates that TLD is increasing with increasing ΔP  
- sign indicates that TLD is decreasing with increasing ΔP

**Magnitude of Q index:**  
≤ 15% = low;  
15-40% = medium;  
>40% = high

If an impactor is used, Q index must be calculated from stage groupings (\(d_a^2\) Q cutoffs as opposed to size cutoffs).

Constant MMIP as a function of $Q$ leads to constant deposition in the URT and LRT (condensation aerosol)

10 mg loxapine

MMIP $\sim 120 \mu m^2 L/min$

$Q$ index $\sim 0$

$R = 0.08 \text{ cm } H_2O^{0.5} \text{ L min}^{-1}$

$\Delta P = 0.2 \text{ to } 4 \text{ kPa}$

$ED = 91-95\%$

Constant MMIP as a function of $Q$ leads to constant deposition in the URT and LRT (dry powder aerosol)

$\Delta P$ (kPa) | $Q$ (L min$^{-1}$) | DD (%ND) | URT (%DD) | TLD (%DD)
---|---|---|---|---
1.0 | 16 | 85 | 17.6 | 82.4
2.0 | 22 | 88 | 14.8 | 85.2
4.0 | 32 | 90 | 16.7 | 83.3
6.0 | 40 | 92 | 14.1 | 85.9

$Q$ index = +2.7%

Delivery of insulin inhalation powder (Exubera®) with an ‘active’ dry powder inhaler

Delivery of insulin inhalation powder with a ‘passive’ dry powder inhaler

A flow/volume simulator and mixing inlet enables assessment of realistic breathing profiles with an NGI

- Bypass flow is added to achieve a constant air flow in the impactor
  - This enables calculation of an aerodynamic size
- Unfortunately, this method shifts the distribution of particles on the impactor stages, thereby destroying the IVIVC with respect to particle deposition in the respiratory tract
- Better off using realistic breathing profiles with no mixing inlet, assessing MMIP and stage groupings!

DPI = dry powder inhaler; LPM = liters per minute.
Flow rate independence in TOBI® Podhaler™
Patients need not inhale forcefully – Reduced Q lowers cough response

Stage deposition post-AIT is largely independent of PIFR for TOBI® Podhaler™ (constant TLD and MMIP)

Realistic Breathing Profiles / Alberta Idealized Throat / Next Generation Impactor

Inertial impaction controls regional deposition of monodisperse albuterol droplets in adult asthmatics

Adapted from Usmani (2005)

Can we develop drug/device combinations that more effectively shift drug deposition from the URT to the small airways?

Current marketed formulations are right in the sweet spot to achieve high interpatient variability in lung delivery

- Deposition in the URT is due to inertial impaction
- Current marketed inhalers have mean $d_a^2Q$ values between ~1,000 and 5,000 µm² L/min
- Large variability in URT deposition is the result of anatomical differences in soft tissue in mouth and throat

Targeting of Inhaled Corticosteroids in the Lungs

Formulation of ‘extrafine’ particles is not a prerequisite for delivery to the lung periphery.


6.5 µm particles can provide significant deposition in the lung periphery if inhaled slowly

- **Test Substance:** $^{99m}$Tc Sulphur colloid in water/propylene glycol (90/10 v/v)
- **Delivery System:** Small-volume nebulizer equipped with a 100-mL aerosol holding chamber, a two-way control valve with integrated mouthpiece
- **Characterization:** Droplet size was determined via laser diffraction (VMD ~ MMAD = 6.5 ± 0.2, GSD ~ 2)
- **Imaging:** Gamma scintigraphy with 24-h clearance measurements to assess peripheral deposition

<table>
<thead>
<tr>
<th>$d_a$ (µm)</th>
<th>$Q$ (L min$^{-1}$)</th>
<th>$d_a^2Q$ (µm$^2$ L min$^{-1}$)</th>
<th>Respiratory Tract Deposition Mean (SD), %ND</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>URT</td>
</tr>
<tr>
<td>6.5</td>
<td>30</td>
<td>1267.5</td>
<td>51.9 (14.2)</td>
</tr>
<tr>
<td>6.5</td>
<td>8</td>
<td>338</td>
<td>28.5 (15.8)</td>
</tr>
</tbody>
</table>

Control of the inspiratory flow rate and volume of nebulized drug improves delivery of ICS to the small airways
Bypassing deposition in the URT of children and infants requires drug/device combinations with smaller impaction parameters.

\[ Stk = \frac{d^2_{a}QC}{18\mu D} \]
Aerosol delivery of ‘surfactant’ to neonates using nasal CPAP may seem impossible...

Breathing cycles – 1:3 or 1:4 inhalation:exhalation ratios

\[ \frac{d_a^2 Q}{m_{\text{nose}}} = 17.1 \]
3 µm MMAD

\[ \frac{d_a^2 Q}{m_{\text{nose}}} = 7.6 \]
2 µm MMAD

\[ Q = 1.9 \text{ L/min} \]

Bypassing deposition in the URT of adults requires that particles have an impaction parameter < 150 µm² L/min.


Extrafine corrugated particles with median aerodynamic diameters less than ~0.7 μm enable total lung doses > 90%

\[ Da = \frac{x_{50}}{\sqrt{\rho_{tapped}}} \]

Dry powder inhalers never fully disperse dry powders

Dispersed particles and their agglomerates must be respirable to bypass deposition in the URT


URT deposition of extrafine corrugated insulin particles is consistent with Stahlhofen’s empirical equation

**Simoon Inhaler: ΔP = 4 kPa (polydisperse particles)**

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Method</th>
<th>Lot A</th>
<th>Lot B</th>
</tr>
</thead>
<tbody>
<tr>
<td>x50 (µm)</td>
<td>Laser diffraction</td>
<td>1.40</td>
<td>1.76</td>
</tr>
<tr>
<td>Bulk density (g cm(^{-3}))</td>
<td>Uniaxial compaction</td>
<td>0.17</td>
<td>0.15</td>
</tr>
<tr>
<td>Da (µm)</td>
<td>Calculated</td>
<td>0.58</td>
<td>0.68</td>
</tr>
<tr>
<td>MMAD (µm)</td>
<td>NGI</td>
<td>1.78</td>
<td>2.02</td>
</tr>
<tr>
<td>(d_a^2Q) (µm(^2) L/min)</td>
<td>Calculated</td>
<td>105</td>
<td>135</td>
</tr>
<tr>
<td>URT deposition (%DD)</td>
<td>AIT</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>


Dry powder aerosols of PP are comprised of ‘large porous agglomerates’

\[ d_{agg} = d_{g} \sqrt{\rho_{agg}} \]

\[ \rho_{agg} = \left[ \frac{1.78}{12} \right]^2 = 0.02 \text{g cm}^{-3} \]

Misconceptions driven by focus on aerodynamic size

- APSDs measured in an impactor are representative of the APSDs of the drug product
- A constant particle size with variations in flow rate leads to flow rate independence *in vivo*
  - Active devices that create the same APSD independent of Q provide flow rate independence
- ‘Extrafine’ particles are needed for effective delivery to the lung periphery
- Regional targeting within the respiratory tract can be achieved with monodisperse particles
- DPIs are inherently flow rate dependent, and the youngest and oldest of patients cannot effectively use a DPI
  - Many asthma and COPD patients cannot generate sufficient airflow with a high resistance DPI to achieve effective dose delivery
Should we continue to measure size or do we really care more about regional deposition?

"I have seen a medicine that's able to breathe life into a stone."

William Shakespeare – All’s Well That Ends Well - Act II, Scene 1