A REVIEW OF THE PARTICLE DIMENSION MEASUREMENT FOR NASAL DRUG DELIVERY SYSTEMS

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ABSTRACT

Decongestants and antihistamines are often administered nasally. However, nasal delivery of systemically active drugs is becoming popular. In pain and migraine treatment, vaccination distribution, and osteoporosis treatment, the turbinate and lymphoid tissues in the back of the nasal cavity allow for rapid and targeted medicine absorption. For Alzheimer's disease medicine administration, the olfactory region provides direct access to the central nervous system. Conventional nasal spray is used most. Their median particle size is 30–120 microns for nasal deposition. Bigger droplets settle on the nose, while microscopic particles may travel deeper. Characterizing the sub-ten micron fraction helps assess lung drug delivery risk. The FDA's draft guidance, "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action" (April 2003), recommends laser diffraction for particle size distribution measurements. Cascade impaction is recommended for distribution analysis. This study covers these two complementary methodologies and shows how they may be used together to generate nasal product evaluation data.

Keywords: *Next Generation Pharmaceutical Impactor, Andersen Cascade Impactor, Inertial technique, Laser Diffraction.*

INTRODUCTION

Cascade impactor1 analysis is the primary in vitro approach for medical aerosol generator aerosol clouds. The inertial separation idea uses aerodynamic size ranges to classify medication fractions for respiratory tract deposition. Chemical detection can measure these fractions to determine the medicine's particle size distribution with excipients. Most inhaler evaluation devices can't automate the process, which is time-consuming. Impactors are typically employed in uncalibrated or unbuilt settings. Impactor flow rates are increased to make nozzle flow turbulent. These nozzles' collecting efficiency and cut-off curves suffer. Impactor nozzle flow rate alters the cut-off value.

However, impactors' high air flow resistances limit these devices' fixed inspiratory flow curves. Especially with breath-actuated dry powder inhalers, higher flow rates and flow increase rates may be desired. This study evaluates laser diffraction technology as a fast and reliable cascade impactor analysis alternative. This approach cannot determine aerodynamic diameters, although comparative evaluation and development, the bulk of in vitro applications, do not need this.

Laser diffraction allows flow rate-independent data collecting and testing. A unique inhaler adapter can adjust the inspiratory flow curve, analyze the fine particle mass fraction, and pre-separate big particles when testing dry powder inhalers with adhesive mixes.

Particle size analysis of general pharmaceutical products

- Why measure particle size of pharmaceuticals?

- Particle size can affect:
  - Final formulation: performance, appearance, stability.
  - "Process ability" of powder (API or excipient).

METHODS FOR DETERMINING PARTICLE SIZE2

- Microscopy
- Sieving
- Sedimentation techniques
- Optical and electrical sensing zone method
- Laser light scattering techniques
- Surface area measurement techniques

Choosing a method for particle sizing

- Running
- Specification requirements
- Time restrictions
- Nature of the material to be sized, e.g.
- Estimated particle size and particle size range
- Solubility
- Ease of handling
- Toxicity
- Flowability
- Intended use
- Cost
- Capital

Microscopy

- For particles between 1 and 150 m, optical microscopy is utilized, and for particles from 0.001 m and larger, electron microscopy.
- Since each particle can be seen separately, microscopy is now regarded as an accurate way to quantify particle size.
- When connected to image analysis computers, each field may be studied and a distribution can be generated.
- may differentiate aggregates from single particles.
- Number distribution.
- Most severe limitation of optical microscopy is the depth of focus being about 10µm at x100 and only 0.5µm at x1000.
- With small particles, diffraction effects increase causing blurring at the edges - determination of particles < 3µm is less and less certain.
- For submicron particles it is necessary to use either
- TEM (Transmission Electron Microscopy) or
- SEM (Scanning Electron Microscopy).
- TEM and SEM (0.001-5µm).

Types of Diameters

Martin's diameter (M)

The distance along the line that splits the particle picture in half. Any direction may be used to create the lines, but it must be kept consistent across all picture measurements.

Ferret's diameter (F)

It is the separation between two tangents that are parallel to one another and on the opposing sides of the particle.

Projected area diameter (da or dp)

When viewed ordinarily to the plane surface on which the particle is at rest in a stable location, it is the diameter of a circle with the same area as the particle.

Manual Optical Microscopy

Advantages:

- Relatively inexpensive.
- Each particle individually examined - detect aggregates, 2D shape, colour, melting point etc.
- Permanent record – photograph.
- Small sample sizes required.

Disadvantages:

- Time consuming - high operator fatigue - few particles examined.
- Very low throughput.
- No information on 3D shape.
- Certain amount of subjectivity associated with sizing - operator bias.

Transmission and Scanning Electron Microscopy

Advantages:

- Particles are individually examined.
- Visual means to see sub-micron specimens.
- Particle shape can be measured.

Disadvantages:

- Very expensive.
- Time consuming sample preparation.
- Materials such as emulsions difficult/impossible to prepare.
- Low throughput - Not for routine use.

Automatic and Image Analysis Microscopes

Figure 1: Sieve shaker

Particle size classification of powders3

Non-analytical sieves can measure powder fineness.

Sieving determines a powder's fineness in relation to the sieve number(s) used, or as a percentage of material through the sieve(s).

Powders are described using these words:

Coarse powder: Not more than 40% by mass and not less than 95% by mass, respectively, pass through a number 355 sieve.

Moderately fine powder: Number 355 sieves must pass 95% of their mass, whereas number 180 sieves pass 40%.

Number 180 sieves must receive at least 95% of the fine powder, whereas number 125 sieves must get no more than 40%.

Let a homogeneous suspension settle in a cylinder and take samples at regular intervals at a fixed horizontal level to determine the size distribution.

Each sample will include a typical suspension sample, except for particles bigger than a threshold size, which will have fallen below the sampling point.

A sample taken at time t is measured for solid concentration by centrifugation, drying, and weighing.

This concentration divided by the beginning concentration gives the fraction of particles (w/w) with falling velocities less than x/t. Substituting the equation yields the comparable Stokes' diameter.

Stokes's Law

- The diameter of the sphere that would settle at the same rate as the particle is known as Stokes's diameter (dst).
- By looking at a powder solution that is sedimenting, it is possible to assess the distribution of particle sizes in fine powder.

Two categories

Incremental: Changes with time in the concentration or density of the suspension at known depths are determined. Can be either fixed time or fixed depth techniques.

Cumulative: The rate at which the powder is settling out of suspension is determined. I.e. the accumulated particles are measured at a fixed level after all particles between it and the fluid's surface have settled.

Electrical sensing zone method – Coulter Counter

Instruments measure particle volume using dv, the diameter of a sphere with the same volume as the particle.

Particles in an electrolyte may be measured by pushing them through an aperture with an electrode on either side.

Variations in electric impedance (resistance) create voltage pulses inversely proportional to particle volume when particles pass through the orifice.

Optical sensing zone method

- Obscuration of light source relates to particle size (area)
- Advantage of not requiring medium to be an electrolyte

Laser light scattering techniques

- Laser Diffraction Particle Size Analysis

Particle size range 0.02-2000µm

- Photon Correlation Spectroscopy

Particle size range :1nm to 5µm

Laser diffraction

Particles pass through a laser beam and the light scattered by them is collected over a range of angles in the forward direction.

The angles of diffraction are, in the simplest case inversely related to the particle size.

The particles pass through an expanded and collimated laser beam in front of a lens in whose focal plane is positioned a photosensitive detector consisting of a series of concentric rings.

Distribution of scattered intensity is analysed by computer to yield the particle size distribution.

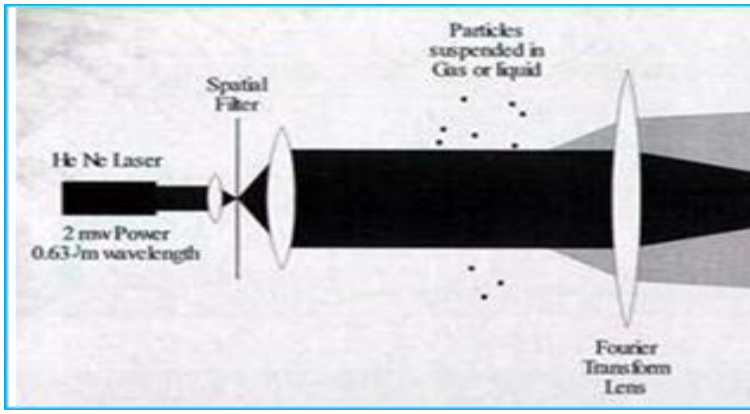

Figure 2: Laser diffraction

Photon Correlation Spectroscopy (PCS)

Large particles scatter light slower than microscopic ones. PCS uses light fluctuation rate to determine light-scattering particle size distribution. Each speckle pattern is matched to a "snap-shot" taken microseconds later.

The speckles move with the particles and so alter particle size. A digital correlator and software sample and correlate the dynamic light signal at varied time intervals. The auto-correlation function's time interval connection estimates particle size distribution.

TECHNIQUE OF NASAL DRUG DELIVERY SYSTEM

FDA guidelines mention nasal sprays and aerosols as the most common nasal medicine delivery techniques 4,5. Mechanical metered near nasal sprays currently dominate nasal drug delivery, replacing droppers and squeeze bottles, which were inaccurate and inconsistent. After suspension or dissolution in aqueous medium, a spray pump atomizes and disperses the active pharmaceutical ingredient (API or "active") as a metered dose nasal spray. Self-administered drugs depend on the patient's ability, physiology, suspension or solution properties, and pump design.

Unit dose devices that administer one or

two injections per nostril are becoming more common. Unit dosage systems are suitable for pain management and vaccines because they minimize microbiological contamination concerns that need preservatives in multi-dose solutions.

Like pulmonary inhalers, pressurized metered dose inhalers (pMDI) may administer drugs to the nasal mucosa. These nasal sprays are "dry" because the propellant evaporates quickly, limiting medicine loss. After the chlorofluorocarbon prohibition, hydrofluoroalkane propellants are used. Nasal aerosols are criticized for their force, thus they utilize reduced actuation forces to deliver "softer"6.

Development of nasal drug delivery products

Nasal medicine delivery systems meet performance objectives through altering device design, formulation, or both. Take nasal sprays. The pump's action, pre-compression ratio, actuator length, shape, and orifice size may be adjusted. Modifiers and additives may be added to the formulation to alter its response to pump shear, including viscosity.

Analytical data help quality control (QC) achieve bioavailability/bioequivalence and manufacturing goals. Laser diffraction and cascade impaction quantify particle size, which impacts in vivo deposition, retention, and uptake. Laser diffraction allows real-time dose measurement, unlike cascade impaction, which examines particles in the sub-ten micron zone and provides API-specific data.

In suspension formulations, API-specific data is needed for the whole dosage4. API particle size impacts absorption and bioavailability. To guarantee medicine administration has not altered particle size, it is characterized before and after actuation. Automated imaging and microscopy meet this regulatory need.

METHODS OF PARTICLE SIZING FOR NASAL PRODUCTS

Laser Diffraction

Laser diffraction quickly analyzes sprays and aerosols. It measures all size fractions of the given near between 0.1 to 3000 um. Laser diffraction is used to produce droplet sizes for clinical efficacy and bioequivalence. It also checks batch-to-batch and dose-to-dose distribution consistency.

Laser diffraction analyzers measure a collimated light beam's diffraction pattern through a particulate sample. Larger particles scatter light at short angles to the entering beam, whereas smaller particles scatter poorly at wider angles. Thus, using the Mie theory of light, the sample particle size distribution may be calculated from the scattered light pattern. Figure 3 shows a typical configuration.

Figure 3: Laser diffraction system (spraytec, malvern) set up for nasal spray analysis.

A typical nasal spray event measured particle size and transmission. Spray analysis uses transmission, a statistic related to source light entering the sample, to calculate droplet concentration. Since it monitors one particle size distribution every 0.1 ms, the device can capture minute details of a 160-ms spray event.

Transmission declines sharply after actuation, suggesting a large droplet concentration increase. In the formation phase of the spray event, the pump transfers liquid from the metering chamber. When the pump atomizes the dose, droplet size reduces and liquid flow increases to a constant rate.

Laser diffraction can assess droplet size while spraying. The fully formed phase appears midway through the actuation profile.

After then, most medicine is given. The pump's continuous flow keeps droplet concentration and size constant.

As the metering chamber empties, pump flow diminishes and droplets grow. The last dissipation cycle also increases transmission and decreases droplet concentration as the pump flow rate drops to zero.

To increase medicine administration, reduce formation and dissipation. The FDA advises using fully developed data for comparative testing. Such data promotes device and formulation modification to meet medicine delivery and product stability objectives.

Cascade Impactor

Since aerodynamic particle size largely correlates with regional deposition in the lungs and respiratory system, API should be inhaled in the fine particle fraction (FPF). Particles larger than 4-6 um will lodge in the upper respiratory tract or trachea rather than the lungs. Pharmaceutical aerosol particle characterization is crucial, and the measurement range is generally less than 10 um.

Cascade impactors are the only particle size measurement technique that can distinguish API from other ingredients in a formulation, so all major pharmaceutical regulatory agencies require their use for inhaled product development and quality assurance. Impactor testing needs time and money due to precision. Understanding the cascade impactor's design, operation, and settings may improve performance1.

Need of Cascade Impaction

The cascade impactor's inertial measuring approach outperforms particle time of flight (TOF), laser diffractometry (LD), and Phase-Doppler particle size analysis (FDA) for particle sizes < 10 um. Only the cascade impactor's inertial mechanism distinguishes API from other formulation components; all other methods detect particle size distribution. The inertial approach also measures aerodynamic diameter, which is important for particle behavior during inhalation, unlike most other methods. Another benefit is that a cascade impactor collects the whole dose and allows comprehensive characterization. Other methods employ real-time measurements to get a quick picture of the dosage as it passes through the measuring instrument, which may not represent the whole amount. Inhalation products need resolution in the 0 to 5 um particle size range, which is provided by the two most prevalent cascade impactor types. The Next Generation Pharmaceutical Impactor (NGI) and Andersen Cascade Impactor (ACI) feature various stages with cut-off sizes that fit most operating conditions.

Figure 4: Andersen cascade impactor

(ACI)

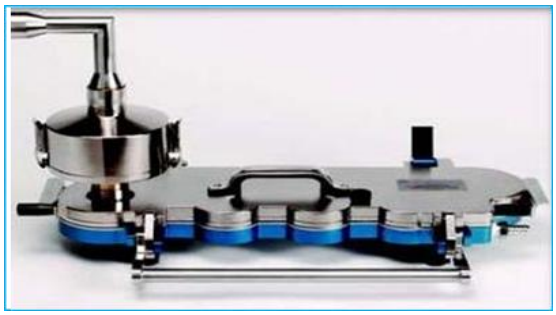

Figure 5: Next generation pharmaceutical impactor (NGI)

Principle of cascade impaction

Inertia, which relies on particle density, shape, and velocity, divides a sample into fractions in cascade impactors. As the number of steps grows in a cascade impactor, the number of nozzles and nozzle area decrease. Each stage has a known number of nozzles. A vacuum pump draws samples through the stages. At each level, particles with enough inertia break out of the air stream, collide, and accumulate on a surface below the stage. The ACI collects on plates, whereas the NGI uses cups. Continuous volumetric air flow increases velocity via the nozzles, allowing smaller particles to reach the collecting surface. HPLC is used to analyze samples from each collecting surface, and any residual material is collected in a final collector or filter. The ACI and NGI are calibrated to maintain a certain particle size fraction on the collecting surfaces at any flow rate in the interest range. Particles collected at each stage are limited by the stage cut-off diameter1.

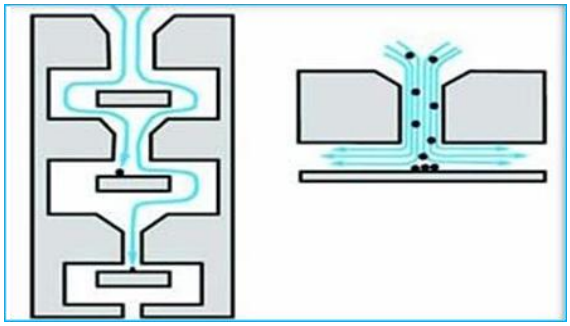

Figure 6: Particles with enough inertia to escape entrainment in the gas stream impact on a collection surface

Factors affecting impactor performance

- Nozzle diameter—the separation characteristics of an impactor are defined by this variable, which must be effectively specified, controlled, and maintained.
- Air flow rate—must be constant, reflect the conditions under which an inhaler device will operate, and be tightly controlled.
- Other dimensions (such as the distance between nozzle exit and collection surface) effective specification and control of these dimensions is vital.
- Re-entrainment—ultimately results in collection on the wrong stage, compromising accuracy; effective collection surface coating to retain impacted particles is often required.
- Interstage losses—sample deposited on internal surfaces other than the collection surfaces will affect the results.
- Leakage—air entering into an impactor through points other than the inlet can affect its aerodynamic performance.

Technique of cascade impaction

Inertial impaction divides dose in cascade impaction (Figure 6). Air with samples is dragged at a predetermined volumetric flow rate through numerous stages with a specific number of precision-engineered nozzles. Because nozzle diameter decreases with stage number, particle velocity increases. Smaller particles generate enough inertia at each step to separate from the dominating air stream and contact the collecting surface below the nozzles. After that, the size fractions are collected and HPLC-analyzed to obtain an APSD for the active.

Glass expansion chambers link the impactor and gadget during nasal product

testing. The dose is completely atomized and dispersed so that it is effectively sucked into the impactor rather than accumulating on the impactor intake when the chamber is triggered. It also allows representative dose atomization, yielding particle size data that better predicts performance. Chambers of different sizes may be tested during method validation to determine the worst-case scenario for pulmonary drug delivery7. In addition to these general comments concerning cascade impaction, regulatory guidance separates nasal sprays and nasal aerosols for testing.

Nasal spray testing

Since nasal sprays produce a little amount of highly fine material, it is sufficient to add up the active from the first step. An expansion chamber of two or more liters (typically five) with a test flow rate of 28.3 L/mm reduces wall deposition.

Since testing requires measuring the penalties' total active rather than APSD, a smaller impactor stack8 simplifies testing. At 28.3 L/min, stages 0, 2, and F of an Andersen Cascade Impactor produce three fractions: >9.0 microns, 4.7 to 9.0 microns, and 0.4 to 4.7 microns. This stack indicates the fraction of the dose that may (a) be retained in the intranasal passageways (>9.U microns), (b) be directed to the gastrointestinal tract [via the upper respiratory system] (4.7 to 9.0 microns), and (c) penetrate to the deep lungs (0.4 to 4.7 microns). This is enough to determine nasal spray bioequivalence.

Nasal aerosol

In nasal aerosol testing, the recommendation specifies that drug deposited below the first stage of the impactor is "of the same order of magnitude as from orally inhaled products." This suggests measuring a full APSD. Again, testing is done at 28.3 L/min, but smaller expansion chambers, such as a one-litre chamber, are used as propellant-based devices sometimes require lesser quantities for aerosol growth.

QC and bioequivalence testing is comparative, hence chamber size/test conditions are important. However, chamber size research is underway to make testing more representative of in-use performance12.Research suggests that an expansion chamber size restriction of one litre or less reduces fine particle concentration, making lung deposition worse. Smaller chambers, which hold 15 ml9, may better reflect nasal cavity activity.

Achieving optimal performance

Cascade impactor operation and maintenance must be precise to separate true sample variations from analytical errors. Analysts must follow the USP and European Pharmacopeia (Ph.Eur.) monographs for inhaled product analysis while performing these tests. Cascade impaction requires rigorous calibration, cleaning, and inspection for consistent results. Semi-automation may reduce analyst performance fluctuation.

Cascade impactor components, especially flow controllers and flow meters, affect measurement accuracy and must be calibrated regularly. Every day, the impactor's nozzles must be carefully inspected. Clean the impactor, check for wear, and replace seals as required. To maintain jet-to-plate distance and coating consistency, damaged, twisted, or dented collecting surfaces must be replaced. Routine impactor leak testing evaluates system integrity.

CONCLUSION

Nasal sprays and aerosols' deposition

behavior and in vivo uptake depend on particle size. Laser diffraction and cascade impaction provide particle size information for dose fractions, facilitating development and QC. Laser diffraction provides real-time droplet size measurement over the particle size range, while cascade impaction allows active-specific line interrogation to assess pulmonary deposition risk. Knowing each technique's pros and cons helps commercialize successful nasal goods according to regulatory guidelines.

This page covers nasal aerosols and sprays, however additional technologies like dry nasal powders are gaining prominence. Dry powders are ideal for moisture-sensitive active compounds, peptides, hormones, and antigens, and high dose concentrations because they discourage microbial growth. This improves product sterility. They have fewer adverse effects than suspension- or solution-based medicines and have longer nasal retention than liquids10.

Product makers must characterize such commodities to manage the dispersion behavior of dry, small particles. Analytical procedures are being optimized. However, laser diffraction and cascade impaction are widely used in nasal goods and dry powder inhalers, so both may help expand this exciting new sector.

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