Laser Diffraction Size Analysis of Products for Nasal Inhalation: A Survey of Expert Users

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BACKGROUND

- Laser diffraction (LD) is a non-invasive light scattering technique that is frequently used within the pharmaceutical industry for the sizing of liquid droplets or solid particles in aerosol form, especially for nasal delivery devices, where the particle size range is typically larger than that suitable for sampling by cascade impactor [1]
- Regulatory agencies have recommended LD in recently issued guidance documents [2]
- The method is described in the pharmacopeial compendia for nasal aerosols (also known as pressurized metered dose inhalers (nasal pMDIs)), nasal sprays and powders [3]
- This survey was undertaken by a working group of the International Consortium on Regulation and Science (IPAC-RS)
  - generated by users of the method drawn from pharmaceutical manufacturers, contract testing companies, and instrument makers who are members of IPAC-RS and have experience with OINDP development and/or characterization, with the purpose of providing insight into the current state of the use of the method for characterizing nasal products

PURPOSE

- **To provide insight into the current state of the use of the method for characterizing nasal products**

MATERIALS AND METHODS

- 13 responses were received from experts at IPAC-RS member companies to the structured survey primary questions, that led to further clarifying responses
  - A ternary layer was added to aid in interpreting responses where more detail was requested
  - More than one participant within a particular organization may have contributed to the survey
  - The questions focused on issues associated with LD methodology in practice associated with nasal inhaler quality performance testing
  - Each contribution was based on the respondents self-selected experience with LD
- For most questions, respondents were advised to select as many answers as applicable based on experience in their laboratories, and for which they felt they had relevant information to share. For this reason, the fractional responses may not total to 100%.

RESULTS:

- Figure 1 summarizes responses based on OINDP dosage form together with how LD is used in batch variability studies and in aqueous nasal spray priming practice
  - It was assumed that responses would subdivide into the four different dosage forms, (a) aqueous nasal sprays, (b) nasal powders, (c) nasal pMDIs and (d) other nasal products not classifiable within the other three sub-classes. Most respondents (92%) had experience testing nasal sprays. 50% also evaluated nasal powders
  - Only 8% reported using LD with nasal pMDIs. Priming and shaking suspension nasal spray products was carried out either manually or by automated inhaler actuation equipment
  - This procedure is important to achieve homogeneity of suspension formulations before inhaler actuation
  - The questions relating to batch variability focused on establishing whether LD was used to assess inter- (54%) or intra- (85%) variability as well as through unit life testing (62%)
  - hat responses would sub-divide into the four

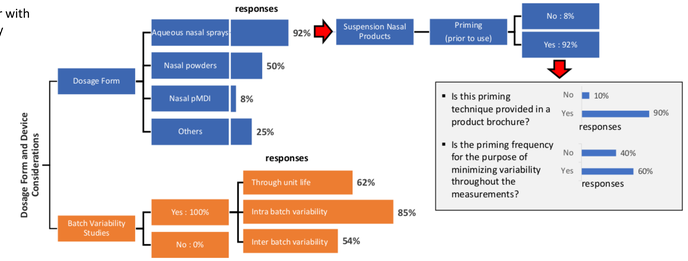

Figure 1. Responses to IPAC-RS Survey on LD Based on OIP Dosage Form, Batch Variability Studies, and Aqueous Nasal Spray Priming Practice

- Figure 2 summarizes background information concerning the use of the LD method. Most respondents used LD analysis in research and development (85%), with 62% in quality control and 38% in both environments.
- Organizations were allowed to submit replies from multiple LD users; no weighting was applied per role in the organization.
  - Cascade impaction was reported as the most used technique to characterize nasal product based on sprayed particle size (70%), followed by morphologically directed Raman spectroscopy (MDRS (20%))
  - 40% reported using LD for multiple dosage forms
  - Other alternative techniques reported were Raman spectroscopy (RS) by itself (10%) and phase/laser Doppler anemometry (10%)
  - The low reporting of MDRS/RS was unexpected, given regulatory requirements for MDRS-based data in some recently released guidances for industry, for example reference [1]
  - However, it may have arisen if some respondents interpreted the question as being limited to other methods providing similar metrics as LD or because automated MDRS systems are relatively recent innovations with limited adoption
  - 71% responded when asked: 'Do you observe results obtained via these alternative techniques, that are statistically different from your LD results?', providing feedback that showed recognition of the different operating principles of LD and cascade impaction.
  - Each respondent decided their own test and criteria for statistical significance.
  - Only 1 respondent correctly observed that cascade impaction is only suitable for sizing particles finer than 10 µm and cannot size-assess nasal sprays that are almost entirely comprised of larger droplets.

Do you use Laser Diffraction (LD) to characterize any of your products? Y

Division:
- 85% Research & Development
- 62% Quality Control
- 38% Both

Role in Organization:
- 31% LD User
- 15% Lab Manager
- 15% QA/AC Professional
- 39% Others (Technical Director/Supervisor, Area Director, SME, R&D)

For what purpose do you use LD?
- 92% Aqueous nasal sprays
- 50% Nasal powders
- 8% Nasal pMDI
- 25% Others (pMDI and DPI, Nebulizers & non-aqueous nasal sprays, API and excipient powders, and nebulizer solution)

What additional method(s) do you use to characterize nasal products?
- 70% Cascade Impaction (CI)
- 10% Phase- (or laser-) Doppler Anemometry (PDA or LDA)
- 20% Morphologically-Directed Raman Spectroscopy (MDRS)
- 20% CI & MDRS
- 10% Raman Spectroscopy, SP, PG
- 10% CI, Raman Spectroscopy, SP, PG
- 10% CI, P(LI)DA, & MDRS
- 30% None

Using any of the methods indicated above; do you observe results that are statistically different from your LD results?

Responses — Comments:

71% : Yes
- Cascade impaction and laser diffraction don't really report the same kind of data, so we wouldn't expect them to agree quantitatively.
- There are different methods that used for different purposes in case of Nasal solution/suspension
- We have observed differences between LD and NGI, although this type of comparison is rarely requested to be performed by our clientele.
- Impaction method can only determine the mass and % below 10um and not able to measure the size distribution of nasal spray which LD can.

29% : No
- Impaction method can only measure mass and percentage less than 10um but not able to measure droplet size distribution of the nasal spray
- See small differences but have not assessed these to be statistically significant.

Have you encountered problems with making LD measurements for nasal inhalation products for which you have devised work-arounds or would like to see changes made in accepted (regulatory) procedures?

Responses — Comments

25% : Yes
- Very limited guidance that is appropriate for nasal dry powders
- Standardization of the procedure (for nasal products)
- Validation for mono- or bi-dose device more difficult than multi-dose device

75% : No

MDRS – Morphologically directed Raman spectroscopy; CI – cascade impaction; PDA – phase Doppler anemometry; LDA – laser Doppler anemometry; SP – spray pattern; PG – plume geometry.

Figure 2. Background Information

- The final question in this series requested feedback regarding problems applying the LD method.
  - Most (75%) reported no concerns, but some respondents (25%) noted a lack of guidance on its application to nasal powders, method standardization for nasal products and how to validate the method for testing single or two (bi-) dose products.
- Figure 3 summarizes the responses to the survey based on a series of key LD method parameters.
- Those using the Mie model (36%) to interpret the raw light scattering pattern were matched by respondents reporting application of the simpler Fraunhofer approximation
  - This outcome is unsurprising, given the comparatively large particle/droplet size range of nasal product sprays and powders compared with aerosols from orally inhaled products
  - 27% reported using both models
- Almost all respondents (92%) reported using automated inhaler actuation with some (45%) using both top (vertical plane) and side actuation depending upon the product design
- More respondents reported velocity- (69%) compared with force-controlled (38%) actuation
  - Some reported using both methods (15%)
- A few sampled the entire plume duration (23%), but the majority assessed it when stable (85%)
- The question ascertaining how the laboratory environment is managed was sub-divided into five parts;
  - (i) are the temperature and relative humidity controlled? (58% YES),
  - (ii) is an inhalation cell used to transport the aerosol through the measurement zone? (62% YES),
  - (iii) are precautions taken to minimize fall back of larger droplets/particles through the measurement zone? (27% YES),
  - (iv) are measurements made at constant flow rate without sheath flow to contain the airborne particulate and thereby avoid optical window fouling? (100% YES)
  - (v) is a sheath air flow used? (42% YES).

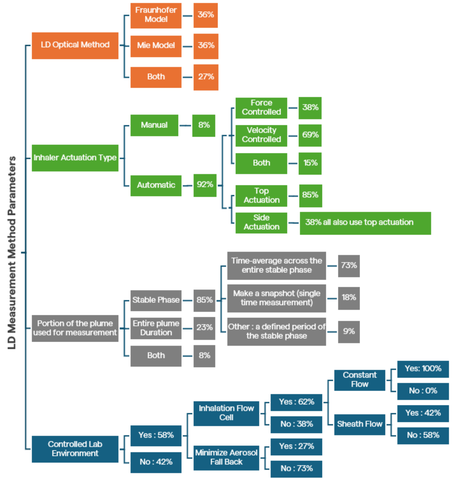

Figure 3. Responses Based on Key LD Measurement Method Parameters

- An important aspect of the survey was the question asking for information how inhaler actuation parameters are selected and justified.
- The responses from this question are summarized in Figure 4 and represent replies from individual scientist respondents to the survey based on their experience (more than one respondent could have replied from the organization submitting the survey response).

Q: How do you select and justify actuation parameters?

A:
- Based on results comparable to human use and to ensure full actuation in repeatable manner.
- Human hand handling study with volunteers
- Human hand handling study, followed by method validation
- Human hand handling study (six volunteers; 3 females + 3 males)
- Different approaches by clients, including:
  1) Use of hand actuation studies to evaluate forces, accelerations and timings of real humans.
  2) Empirical approach whereby recommendations of device manufacturers are incorporated and evaluated with a goal to minimize variability.
  3) Device supplier methodology, force studies
  4) Set to be in excess of the product firing force (when testing nasal pMDIs in R&D activities)
  5) Based on feasibility work and observing the actuation of the device

Figure 4: Responses Regarding Inhaler Actuation Parameter Selection

CONCLUSIONS

We have highlighted a series of questions and responses to a survey within IPAC-RS members on the use of LD to size-characterize aerosols produced by the main classes of nasally inhaled products. The response to this survey is consistent with its recognition by the regulatory authorities as a requisite for the in vitro evaluation of these products [2]. The results provide insight into the current application of this technique with the aim of encouraging clearer methodologies in the pharmacopeial compendia for the performance evaluation of these products.

REFERENCES

[1] Mitchell JP, Nagel MW, Nichols S, Nerbrink O. Laser diffractometry as a technique for the rapid assessment of aerosol particle size from inhalers. J Aerosol Med 2006, 19(4): 409–33.
[2] United States Food and Drug Administration. Draft Guidance on Azelastine Hydrochloride and Fluticasone Propionate. 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Azelastine%20Hydrochloride%3B%20Fluticasone%20propionate%20nasal%20metered%20spray%20NDA%20202236%20PSG%20Page%20RV%2002-2019.pdf.
[3] United States Pharmacopeia. Chapter <601> Inhalation and nasal drug products: Aerosols, sprays and powders – Performance quality tests. Rockville, MD, USA, 2023. Available at: https://www.usp.org/.