

EVALUATION OF AERODYNAMIC PARTICLE SIZE DISTRIBUTION OF DRUGS USED IN INHALATION THERAPY: A CONCISE REVIEW



Smita Nayak *¹✉, Priyanka Ghugare ¹, Bhaskar Vaidhun ¹

*¹ Department of Quality Assurance, Gahlot Institute of Pharmacy, University of Mumbai, Sector 14, Koparkhairane, Navi Mumbai-400709, Maharashtra, India



DOI: <https://doi.org/10.29121/granthaalayah.v8.i7.2020.579>

Article Type: Research Article

Article Citation: Smita Nayak, Priyanka Ghugare, and Bhaskar Vaidhun. (2020). EVALUATION OF AERODYNAMIC PARTICLE SIZE DISTRIBUTION OF DRUGS USED IN INHALATION THERAPY: A CONCISE REVIEW. International Journal of Research -GRANTHAALAYAH, 8(7), 264-271.

<https://doi.org/10.29121/granthaalayah.v8.i7.2020.579>

Received Date: 25 June 2020

Accepted Date: 31 July 2020

Keywords:

Metered Dose Inhaler
Dry Powder Inhaler
Inertial Impaction
Anderson Cascade Impactor
Next Generation Impactor
Laser Diffraction
HELOS

ABSTRACT

Most of the inhalation products in the market use metered dose inhaler (MDI) technology or dry powder inhaler (DPI) technology. MDIs use propellant to deliver desired dose of liquid formulation in aerosol form. DPI contains active in fine particulate form embedded onto an inert carrier. In both cases, amount of drug dispensed from the device reaching the lungs is dependent upon drug product characteristics as well as formulation-device relationship. Hence, in addition to particle size, aerodynamic distribution of the drug upon delivery by the device plays an important role in determining amount of drug reaching the lungs. Therefore, particle size characterization is an important tool in determining the extent of drug delivery from the metered dose inhaler. Aerodynamic particle size distribution is frequently determined by use of cascade impactors and data so generated is accepted by regulatory agencies as a tool for predicting efficacy of MDIs and DPIs. This review discusses principle and working of cascade impactors. Additionally, the review also examines the role of laser diffraction technique in estimating size of dispersed particles.

1. INTRODUCTION

Patients suffering from respiratory disorders rely on inhalation route for better control of disease [1], [2], [3]. Particles in size range of 1-10 μ are capable of being deposited in lungs on inhalation. Larger particle impact the oropharynx and are eliminated systemically while finer particles are exhaled. Thus performance of the drug delivery system can be correlated to the particle size and aerodynamic distribution of the actives [4], [5]. In conclusion, measurement of particle size and aerodynamic size distribution of administered formulation is critical to evaluate its effectiveness in depositing the drug in the lungs and thereby achieving control of disease [6], [7]. Different devices available in the market for aerosolized drug delivery include metered-dose inhalers, dry powder inhalers, aqueous droplet inhalers and nebulisers. Recently, cascade impactors have been used for characterization of drug particle and aerodynamic size distribution. In this review, principle and working of cascade impactor has been detailed. In addition, laser diffraction technique for measurement of size of aerosolized particles has been discussed.

1.1. CASCADE IMPACTOR

Cascade impactor is most commonly used system for measurement of particle size distribution of inhaled products due to following features [8], [9].

- It measures aerodynamic particle size which is a function of particle density as well as physical dimensions and shape of particles.
- It explains how particles behave in a moving air stream as opposed to simple geometric size.
- It measures active pharmaceutical ingredient (API) contained in the aerosol cloud as opposed to the overall formulation.
- It captures entire dose allowing determination of formulation characteristics.

The material of construction is aluminium, stainless steel ss 316 or titanium. The impactor is arranged in the form of stack consisting of one or more stages. The entrance to the impactor is fitted with a right angled induction port designed to act as a throat. The inhaler is connected to the induction port by means of a mouthpiece adaptor which provides an airtight seal between the induction port and the device (fig. 1). Once discharged from the inhaler, the aerosol cloud is drawn through the impactor by means of a vacuum pump connected to the outlet of the impactor by a suitable length of tubing [10], [11].

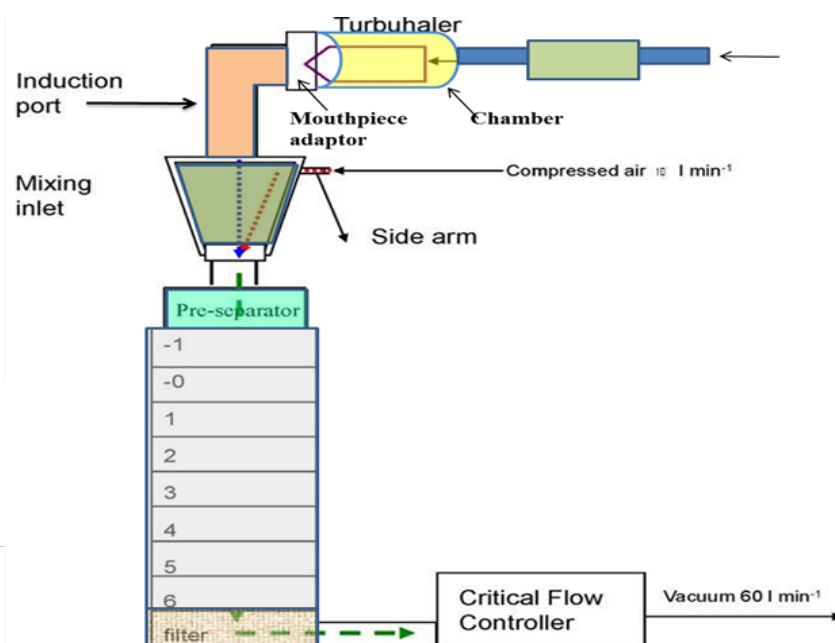


Figure 1: Schematic representation of cascade impactor

Principle and Working

Cascade impactors operate on the principle of inertial impaction [12], [13]. Each stage of impactor comprises a single or series of nozzles or jets through which the sample laden air is drawn and collection surfaces. As particles pass through the nozzles they break through the lines of flow and impact on collection surface. If particles are smaller than the collection surface orifices, they remain entrained in the air stream and exit from the nozzle (fig. 2). Particles with sufficient inertia are collected, the remaining pass onto the next stage [14].

1.2. LIMITATIONS OF CASCADE IMPACTOR [15]

- In some cases, particles may bounce as opposed to impact when they come in contact with collection plate, in which case they are re-entrained into the air stream and carried to a lower stage, ultimately collecting on the wrong stage further downstream.
- Particle get deposited on impactor parts other than the designated collection plates or cups leading to inter-stage losses.

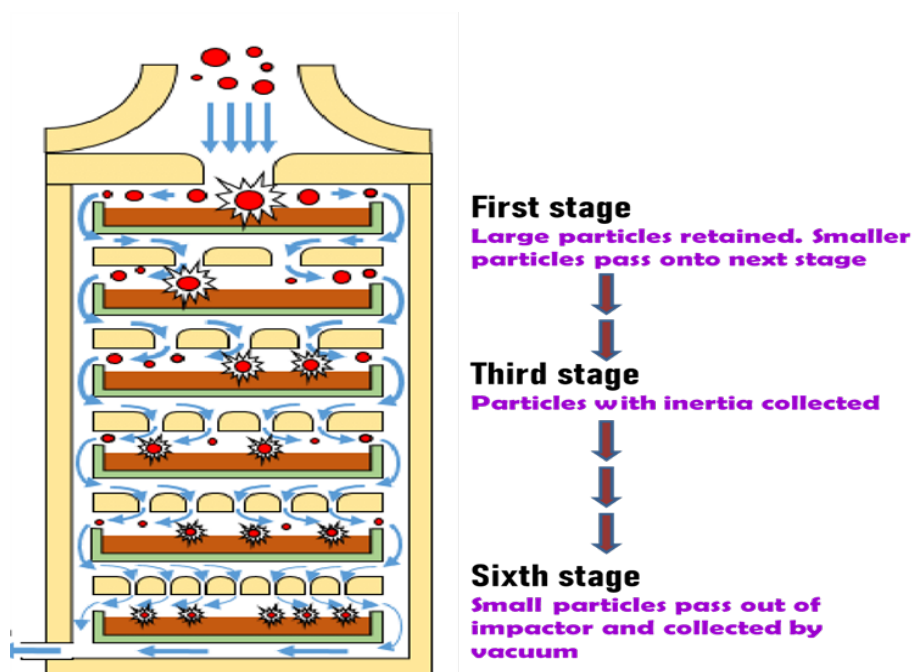


Figure 2: Working principle of cascade impactor

1.3. ANDERSON CASCADE IMPACTOR [16]

Anderson cascade impactor, based on above principle is commonly used in the pharmaceutical industry. It was originally designed as a bacteriological air sampler but later on adapted for inhaler testing. It complies with regulatory requirements of U.S.P. as well as E.P. and has 8 stages from size 0.4 to 9 microns. Material of construction is aluminium, ss 316 or titanium. It can be operated at flow rates of 60 and 90 L/min. It is compact and space saving in design. The number of stages can be reduced when used for measurement of particles from nasal aerosols and sprays. It is easy to clean and maintain. It is economical and therefore a popular choice for study of aerosolised particles.

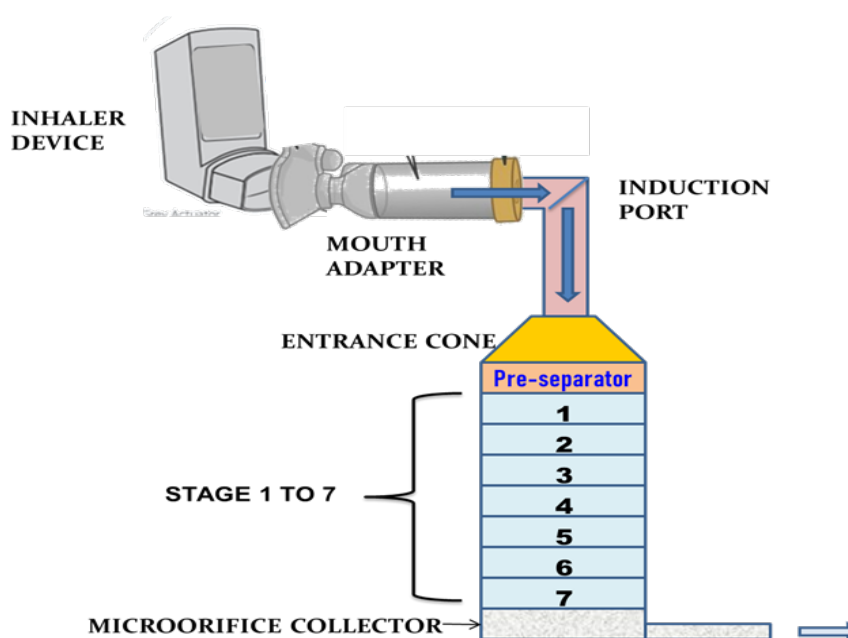


Figure 3: Diagrammatic representation of Andersen impactor

Principle and Working

The induction port connects the impactor to an inhaler device through the mouth adapter. The device is a cascade impactor with seven stages and a micro-orifice collector (MOC) (fig. 3). There are three main sections to the impactor: the bottom frame that holds the impaction cups, the seal body that holds the jets, and the lid. When necessary, a pre-separator can be added to avoid overloading the first stage. This pre-separator connects between the induction port and the impactor. A suitable mouthpiece adapter is used to provide an airtight seal between the device's mouthpiece and the induction port. The apparatus contains a terminal MOC that for most formulations may eliminate the need for a final filter. The MOC is an impactor nozzle plate and collection cup. The nozzle plate contains, nominally, 4032 jets, each approximately 70 μm in diameter. Most particles not captured on Stage 7 of the impactor will be captured on the cup surface below the MOC [17].

1.4. NEXT GENERATION IMPACTOR (NGI) [16]

The NGI was launched by MSP Corporation, USA in 2000. NGI has been designed with a horizontal planar layout for ease of operation. It has seven stages with cut off diameters in the 0.5-5-micron range. Impinged air passes through the impactor in a saw tooth pattern. Particle separation and sizing is achieved by forcing particles through a series of nozzles containing progressively reducing jet diameters (fig. 4). The impactor has three main parts-

- Cup tray containing the eight collection cups used to collect the samples prior to analysis
- Bottom frame which supports the cup tray
- Lid containing the inter-stage passageways and the seal body which holds the nozzles in place

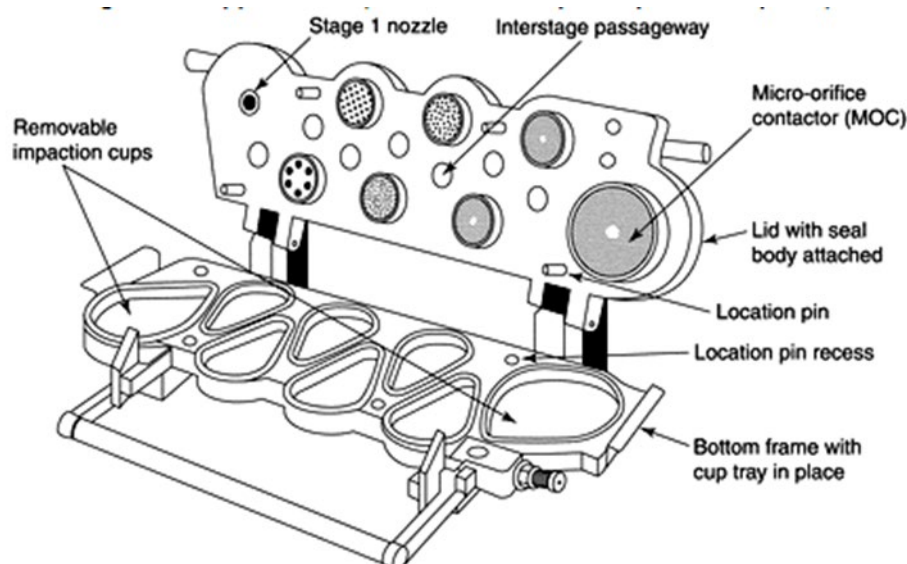


Figure 4: Diagrammatic representation of Next Generation Impactor

Principle and Working

The NGI induction port is made up of ss 316. The NGI uses the pre-separator when it is used with dry powder boluses & large non-inhalable particles. It has seven stages and can be operated at flow rate between 30 and 100 L/min. It can collect and estimate aerodynamic size of particles between 0.24 to 11.7 μm . Here, particles are deposited on collection cups that are held in a tray. This tray is removed from the impactor as a single unit, facilitating quick sample turn-around times if multiple trays are used. Drug recovery is facilitated by adding solvent to collection cup. A micro-orifice collector (MOC) present at the distal end entraps extremely small particles normally collected on the final filter in other impactors. The NGI boasts of user-friendly features and aerodynamic design principles well suited to inhaler testing.

Advantages: -

- It meets U.S.P. and E.P. specifications.
- It measures particle size in the range of 0.24 – 11.7 microns.

- It has seven stages, five with cut-offs between 0.54 and 6.12 microns at flow rates from 30 to 100 L/min.
- It has excellent stage efficiency, accuracy and reproducibility.
- Possesses calibrated flow rate range of 30 – 100 L/min.
- Additional calibration capacity at 15 L/min is useful for nebuliser applications.
- It is supplied with full stage mensuration report (system suitability).
- Low inter-stage wall losses ensure good drug recovery (mass balance).

2. PARTICLE SIZE EVALUATION BY LASER DIFFRACTION TECHNIQUE [17], [18], [19], [20]

Dispersed particles that are actuated from the inhaler can also be measured by laser diffraction technique. Measurement of particle size using laser [diffraction](#) involves passing the aerosol through a laser beam, resulting in [light scattering](#) (Fraunhofer diffraction) by the edges of the aerosolized particles. It has been reported that angle of light diffracted by a particle corresponds to the size of the particle. In a complex sample containing particles of different sizes, light diffraction results in a specific diffraction pattern. By analyzing such a pattern the exact size composition (i.e. particle size distribution) of the sample can be deduced.

2.1. PRINCIPLE

Laser diffraction measures particle size distribution by measuring the angular variation in intensity of light scattered as a laser beam passes through a dispersed particulate sample [21]. Large particles scatter light at small angles relative to the laser beam and small particles scatter light at large angles (fig. 5). The angular scattering intensity data is then analyzed to calculate the size of the particles responsible for creating the scattering pattern, using the Mie theory of light scattering. The particle size is reported as a volume equivalent sphere diameter. Application of Mie theory requires knowledge of the optical properties of the sample and refractive index of the dispersant. A simplified approach is to use the Fraunhofer approximation, which does not require knowledge of the optical properties of the sample.

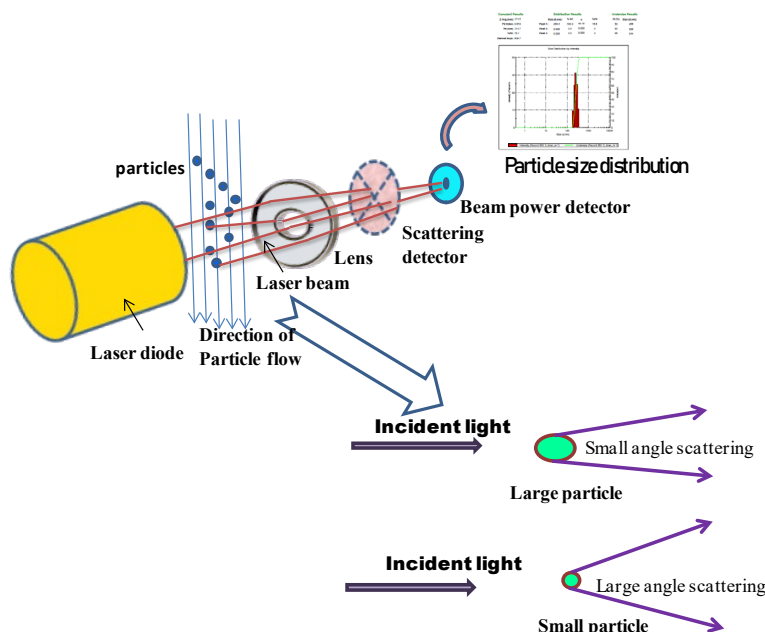


Figure 5: Principle of laser diffraction

Advantages

- Wide dynamic range - from submicron to the millimeter size range.
- Rapid measurements - results generated in less than a minute.
- Repeatability - large numbers of particles are sampled in each measurement.

- Instant feedback - monitors and controls the particle dispersion process.
- High sample throughput - hundreds of measurements per day.
- Calibration not necessary - easily verified using standard reference materials.
- Well established technique - covered by ISO13320 (2009).
- Faster particle analysis as compare to the cascade impactor.

A number of instruments working on this principle are commercially available. This review discusses Helos/BR range of instruments introduced by Sympatec GmbH which uses parameter-free Fraunhofer evaluation for best resolution.

2.2. HELOS

HELOS series with its parallel beam laser diffraction set-up offers a powerful tool for particle size distribution analysis of powders, granules, suspensions, emulsions, sprays and numerous other particulate systems (fig. 6). A size range from below 0.1 μm to 8,750 μm can be measured. The modular sensor when operated with feeding and dispersing systems is best adapted to the product sample. These are found to be suitable for use with inhaler systems [22].



Figure 6: HELOS/BR instrument for particle size measurement

Principle

When a narrow beam of monochromatic light is passed through the measuring area containing the sample, the light wave breaks upon hitting the edge of a particle. The resulting light wave phenomenon forms a characteristic diffraction pattern. This pattern is focused on a detector, which records the angular distribution of light intensity and converts it to size distribution profile.

Advantages:

- Fast analysis of the fine particle fraction of pharmaceutical formulation for inhalation.
- Controls dispersion quality of new formulation.
- Quality control during & after method transfer.
- Characterisation of the discharge behaviour and dose homogeneity.

- Chemical analysis of the particle fractions in combination with a cascade impactor.
- Laser diffraction fully compliant with ISO 13320 for the complete size range from 0.1 μm to 8,750 μm
- Highest precision and resolution of the particle size distribution by 8 measuring range modules
- Automated multi range combination for broad distributions
- Modular design structure with a great variety of dispersing and dosing units for flexible adaption to the sample
- 2,000 particle size distributions per second are acquired by using the integrated time resolved mode
- Unrivalled reproducibility of results and excellent system-to-system comparability.
- Powerful evaluation with parameter-free Fraunhofer or with Mie, if optical properties are known.

3. CONCLUSION

Drug delivery to lungs is a challenging field. The success of this technique lies in effective evaluation of the drug delivered to site of action. There is a need to test the product as a whole rather than the individual components. Designing the right analytical instrument and accurate evaluation of the device performance is critical to maintenance of product quality over the product lifecycle and for continual improvement. Measurement of aerodynamic particle size distribution can give broad indication of the likely in vivo behaviour of the drug. However, cascade impactor is not designed to simulate the lung, rather it is a device that can provide valuable inputs about the inhalation system in terms of screening of early stage candidate formulations to device screening to formal stability studies upto commercial batch release. This review attempts to explain the instrumentation and principle of measurement of aerodynamic particle size distribution using current technologies. Newer, more efficient devices which are predictive of in vivo performance of the systems are in the pipeline.

SOURCES OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

The author have declared that no competing interests exist.

ACKNOWLEDGMENT

The authors thank the Management of Gahlot Institute of Pharmacy for providing support for carrying out the work. The authors acknowledge Sympatec GmbH for providing technical matter for writing this review.

REFERENCES

- [1] Ibrahim, M., Verma, R. and Garcia-Contreras L. Inhalation Drug Delivery Devices: Technology Update. *Medical Devices (Auckl)*. 8, 2015, 131–139.
- [2] Simkovich, SM., Goodman, D. and Roa, C. The Health and Social Implications of Household Air Pollution and Respiratory Diseases. *NPJ Primary Care Respiratory Medicine*. 29, 2019, 12 -24.
- [3] Rau, JL., The Inhalation of Drugs: Advantages and Problems. *Respiratory Care*. 50, 2005, 367-382.
- [4] Garmise, R. and Hickey, J. Calibration of the Andersen Cascade Impactor for the Characterization of Nasal Products. *Journal of Pharmaceutical Sciences*. 97(8), 2008, 3462-3466.
- [5] Roberts, D. and Romay, FJ. Relationship of Stage Mensuration Data to the Performance of New and Used Cascade Impactors. *Journal of Aerosol Medicine*. 18(4), 2005, 396 – 413.
- [6] Copley, M. Cascade Impactors Enter a New Decade. *Manuf. Chem* 2007.
- [7] Lawrence, S. and Sonkin, L. Application of the Cascade Impactor to Studies of Bacterial Aerosols. *American Journal of Epidemiology*. 51(3), 1950, 319–342.

- [8] Mitchell, JP., Nagel, MW., Avvakoumova, V., MacKay, H. and Ali, R. The Abbreviated Impactor Measurement (AIM) Concept: Part 1--Influence of Particle Bounce and Re-Entrainment-Evaluation with a "Dry" Pressurized Metered Dose Inhaler (PMDI)-Based Formulation. *AAPS PharmSciTech*. 10(1), 2009, 243-251.
- [9] Stein, H. and Olso, BA. Variability in size distribution measurements obtained using multiple Andersen Mark II cascade impactors. *Pharmaceutical Research*. 14(12), 1997, 1718-1725.
- [10] Hata, M., Linfa B, Otani, Y. and Furuuchi, M. Performance Evaluation of an Andersen Cascade Impactor with an Additional Stage for Nanoparticle Sampling. *Aerosol and Air Quality Research*. 12, 2012, 1041-1048.
- [11] Sethuraman, VV. and Hickey, AJ. Evaluation of preseparator performance for the 8-stage nonviable Andersen impactor. *AAPS PharmSciTech*, 2, 2001,34-52.
- [12] Bonam, M., Christopher, D., Cipolla, D., Donovan, B, Goodwin, D. and Holmes, S. Minimizing variability of cascade impactation measurements in inhalers and nebulizers. *AAPS PharmSciTech*. 9(2), 2008, 404-413.
- [13] Marple, VA., Olson, BA., Santhanakrishnan, K., Roberts, DL., Mitchell, JP. and Hudson-Curtis, BL. Next generation pharmaceutical impactor: a new impactor for pharmaceutical inhaler testing. Part III. extension of archival calibration to 15 L/min. *Journal of Aerosol Medicine*. 17(4), 2004, 335-343.
- [14] Byron, PR., Cummings, H., , SC., Poochikian, G., Smurthwaite, MJ., Stein, SW. and Truman, KG. Selection and Validation of Cascade Impactor Test Methods. *Respiratory Drug Delivery IX*. 1, 2004, 169-178.
- [15] Mitchell, J. and Nagel, M. Cascade Impactors for Size Characterization of Aerosols from Medical Inhalers: Their Uses and Limitations. *Journal of Aerosol Medicine*. 16(4), 2003, 341-377.
- [16] Malcolmso, RJ. and Embleton, JK. Dry Powder Formulations for Pulmonary Delivery. *Pharmaceutical Science & Technology Today*. 1, 1998, 394-398.
- [17] HORIBA Scientific. "Principles and Applications of Laser Diffraction Technology". Available from <https://www.azom.com/article.aspx?ArticleID=16153>. (Accessed on May 16, 2020).
- [18] Xu, R. Laser Diffraction. In: Scarlet B, editor. *Particle Characterization: Light Scattering Methods*. Dordrecht: Springer Netherlands, Kluwer Academic Publishers; 2002. 111-181.
- [19] Merkus, H, editor. *Particle Size Measurements*. Dordrecht: Springer Netherlands;2009.
- [20] ISO 13320:2009, Particle size analysis - Laser diffraction methods.
- [21] Bohren, C., Huffman, D. editors. *Absorption and Scattering of Light by Small Particles*. Weinheim: Wiley-VCH Verlag GmbH & Co. KGaA, 2007.
- [22] Helos/BR. Available on <https://www.sympatec.com/en/particle-measurement/sensors/laser-diffraction/helos/> (Accessed on May 16, 2020).