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Comprehensive Review of Pressurized Metered Dose Inhalers for Inhalation Therapy

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Abstract: ***There is growing scientific evidence that air pollution has detrimental impacts on almost every organ and cell in the human body, making it one of the most important global health issues of the twenty-first century. Exposure to airborne pollutants, mostly ultrafine particles, has been associated with a variety of diseases, such as reproductive disorders, emphysema, asthma, cardiovascular problems, and cognitive impairment. The World Health Organization claims that air pollution is a global public health emergency, contributing to almost 8.8 million preventable deaths annually. Given these alarming consequences, this review explores pharmaceutical inhalation aerosol technology as a possible therapeutic approach to address respiratory and systemic diseases caused by or exacerbated by contaminated air. Optimized aerosol characteristics, such as droplet size and velocity, are critical to the operation and effectiveness of Pressurized Metered Dose Inhalers (pMDIs). There includes a thorough discussion of key elements that influence atomization, such as internal turbulence, nozzle shape, and propellant behaviour. In order to enhance drug absorption and reduce systemic adverse effects, the study also concentrates on theoretical, experimental, and computational studies aimed at improving aerosol distribution to the peripheral lungs. In conclusion, future strategies that incorporate patient-specific modeling, lifelike breathing simulations, and advanced validation procedures will serve as a guide for the next generation of inhalation medications.***

Keywords: Mean Median Aerodynamic Diameter (MMAD); Inhalation Therapy; Oropharyngeal Deposition; Phase-Doppler Particle Analysis (PDPA); Atomizers Models; and Chemotherapy

1. Introduction

According to a comprehensive global review conducted in recent years, air pollution continues to pose a severe threat to human health, with evidence suggesting it can damage virtually every organ and cell in the human body (Clayton and Swim, 2025). Scientific findings indicate that the harm caused by toxic air extends from cardiovascular and respiratory diseases to metabolic, neurological, and reproductive disorders. This includes conditions such as Asthma, emphysema, lung cancer, and an increased risk of heart attacks due to arterial narrowing and cardiac muscle degradation (WHO, 2024). Moreover, neurological impacts include stroke, dementia, and cognitive decline, with studies showing a notable reduction in intelligence among populations exposed to chronic air pollution (Wang and Yang, 2021).

Pollutants, especially ultrafine particles, enter the body primarily through inhalation, instigating systemic inflammation, and traveling through the bloodstream to impact multiple organ systems (Björnson et al., 2020). The liver, bladder, gastrointestinal tract, bones, and skin show signs of pollution-induced damage (Kelly and Fussell, 2015). Significantly, the reproductive system is not spared. Research indicates a decline in fertility rates, increased miscarriage risk, and the presence of toxic particles in placental tissue directly affecting fetal development (Tran et al., 2023).

The World Health Organization has declared air pollution a global public health emergency, noting that over 90% of the world's population breathes air that exceeds recommended pollution levels (WHO, 2024). Alarmingly, approximately 8.8 million premature deaths annually are attributed to air pollution, surpassing mortality rates from tobacco smoking (Lelieveld et al., 2019).

Since there are so many problems caused by just inhaling polluted air, we can think of treatments of these diseases by aerosol inhalations of medicines, leading to increased absorption of the drugs and increased efficiency of the treatment method. Pharmaceutical Inhalation Aerosol Technology has become a key way for the treatment of both respiratory and non-respiratory diseases. Many diseases can be successfully treated by using aerosol technology to target medications to the lungs' tiny airways. Adequate drug reach is ensured in situations of respiratory illness by delivering aerosol directly to the site of action. Additionally, it lessens adverse effects, such as those caused by high systemic concentration. According to Newhouse and Strand (1999), the lung's periphery provides a vast region (about 100 m2) for rapid absorption into the bloodstream in non-respiratory diseases.

Regardless, to target the lung periphery, spray characteristics of MMD<5μm and as low a velocity as feasible are required (S. Suarez and A. J. Hickey, 2000; Byron and J. S. Patton, 1994; Brain and P. A. Valberg, 1994; Zainudin, 1993). The aerosol droplet size in inhalation technology, particularly Pressurized Metered Dose Inhaler (pMDI), is determined by the atomization process, which is subject to variables such as propellant volatilization, nozzle shape, and turbulence within the nozzle. This study examines nozzles utilizing several models of atomizers in order to enhance the current therapy for pressurized metered dosage inhalers. The following lists a few crucial medical inhalations therapies.

2. Medical Inhalation Therapy

Medical inhalation therapy is a targeted treatment method that delivers medication directly into the lungs through inhalers or nebulizers. It is commonly used for respiratory conditions like Asthma, COPD, and bronchitis, ensuring rapid drug action, reduced side effects, and improved patient outcomes through localized and efficient drug delivery to the airways.

2.1 Respiratory Disease Treatment

Small airways are vulnerable to bacterial infections, cancer, emphysema, and asthma, among other respiratory conditions. Effective delivery of medications to the tiny branches of the pulmonary airways is necessary to treat these conditions. We can use the management of asthma as an illustration. Breathlessness caused by varied degrees of airway blockage is a hallmark of asthma, a chronic inflammatory condition.

Consequently, it can be treated using bronchodilator drugs and corticosteroids, which have anti-inflammatory properties. These bronchodilator drugs target specific drug receptors called B2 adrenoceptors. These receptors are mostly located in the lung's alveolar areas, though their distribution throughout the respiratory system varies.

So, to treat Asthma effectively, we need to deliver drugs to these alveolar regions, for which we need tiny particle sizes, as the size of the bronchioles before alveoli is 0.3mm.

The lungs are common sites for primary cancer. It is suggested that one of the potential treatment approaches is targeted dose drug delivery using inhaled chemotherapy. With few adverse effects, this kind of treatment could raise the amount of medication in tissues without requiring the patient to undergo extensive surgery. Compared to oral delivery, the total amount of medication needed for inhalation is significantly less. Medications delivered through the lungs will reach the affected site easily through the local blood supply (Sharma et al., 2001).

2.2 Non-Respiratory Disease Treatment

Pulmonary medication administration has two advantages for the treatment of non-respiratory diseases:

- For big molecules like insulin, pulmonary administration provides a non-invasive option for systemic therapy. Also, often, these drugs are injected because if taken orally, the enzymes in the stomach destroy the drugs. Thus, inhalation can work as an alternative to injection.
- Inhalation provides a much faster absorption of drugs into circulation as compared to other methods of drug delivery (Sharma et al., 2001). The lungs' high permeability allows macromolecules to enter the bloodstream.
- Also, as the alveolar region has the highest area of contact to the circulation (around 100 m2), the delivery of drugs to this alveolar region can increase the absorption of drugs even more.

3. Status of Current Available Inhalation Devices

The three significant categories of inhalation devices used are Pressurized Metered Dose Inhalers (pMDI), Dry Powder Inhalers (DPI), and Nebulizers. All these devices have advantages and drawbacks, which are discussed below:

3.1 Pressurized Metered Dose Inhaler

Figure 1.1 below illustrates the basic parts of a metered dose inhaler. These consist of a metering chamber, an actuator, and a pressurized canister that holds a medication suspension or solution with pressurized propellant and surfactant. Although the gadget is affordable, lightweight, portable, and manageable, it has many drawbacks, including

- Often, there is poor coordination between actuation and breathing, especially in children and old people, leading to poor drug delivery.
- The device first injects the particles at a high velocity and big droplet size, which causes poor deposition in the pulmonary airways and substantial oropharyngeal deposition. (only up to 10%). The particles start with 35µm diameter size and 15-30 m/s velocity.

To get around many of the restrictions, several add-on devices have been developed. For example, spacers and valve-holding chambers can decrease oropharyngeal deposits and improve breath actuation synchronization.

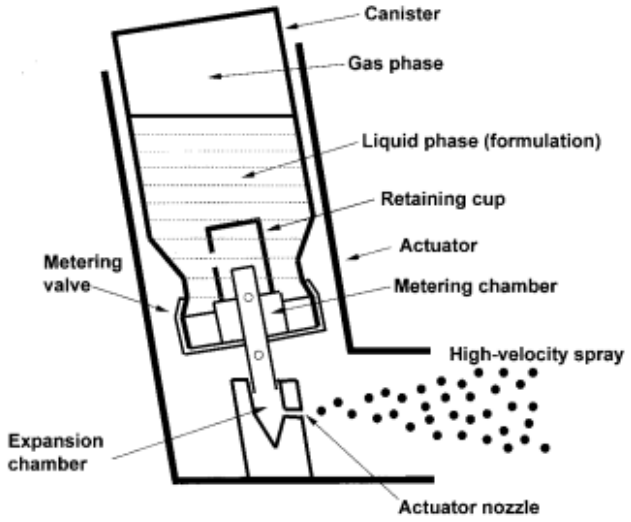

Figure 1.1: pMDI Schematic [Newman, 2005]

3.2 Dry Powder Inhaler

The medication in a dry powder inhaler is a finely ground powder, either alone or in combination with a carrier material. Fig. 1.2 illustrates the device's rotational planar configuration., or it can also be breath actuated. It has the following drawbacks:

If breath triggered, they rely on the patient's inspiratory flow to break down and provide the medication. To release particles of size (MMAD<5µm) and to deliver the drug into the alveolar region, a very high inspiratory flow (30-120 L/min) is needed (Suarez and Hickey, 2000; Byron and

Patton, 1994). This high requirement of inspiratory flow rate has raised concerns about DPI effectiveness for patients with severe airway obstruction.

- Aggregation of small particles due to their hygroscopic nature and its electrostatic discharge create bigger lumps of drugs needing higher inspiratory flow rate.
- DPI are available with only some anti-asthma drugs and are expensive(Suarez and Hickey, 2000).

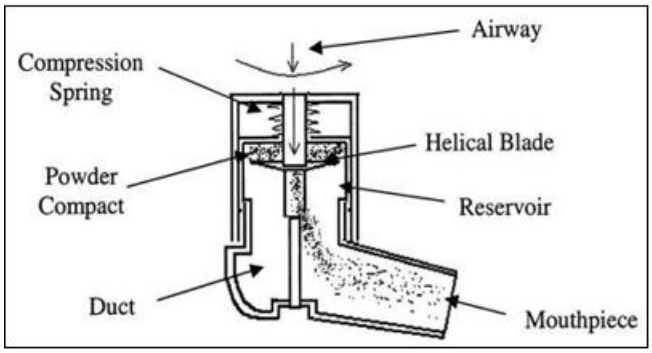

Figure 1.2: Rotary Planar DPI (Wolff and Niven, 2009)

3.3 Nebulizers

There are two types of nebulizers:

- Air jet type
- Ultrasonic Type

Jet nebulizers work on the aerosolization of liquid using a stream of compressed air forced through a narrow tube that lies just above the surface of the liquid to be nebulized. The liquid is drawn up by the venturi phenomenon and broken up into droplets as shown in Fig. 1.3. They have baffles to make sure that the particles are generated in the respirable range of 1-5µm (MMAD).

But only 10 % of the drug is inhaled because the rest is trapped in the reservoir, tubing, and mask.

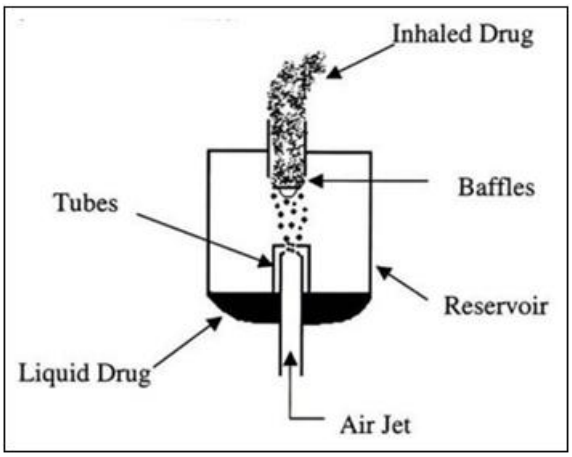

Figure 1.3: Jet Nebulizer (Ariyananda et al., 1996)

Ultrasonic nebulizers use piezoelectric crystal vibrations to produce aerosols. They are quiet in operation and need little breath-actuation coordination. They also produce particles in the range of 1-6µm (MMAD), but are prone to electrical and mechanical breakdown.

Both varieties of nebulizers need a power source to function, take a long time to administer medications, and are somewhat costly.

4. State of art of inhalation therapy

Among the three primary inhalation devices, pressurized Metered Dose Inhalers (pMDIs) are the most cost-effective, portable, user-friendly, and widely utilized tools for aerosol drug delivery. When used correctly, pMDIs can be as effective as other advanced inhalation devices. With continued innovation and optimization, pMDIs hold the potential to become the most optimal platform for delivering drugs directly to the lungs.

Introduced in the 1950s by Riker Laboratories, the pMDI marked a significant advancement in aerosol-based drug inhalation. The device operates by releasing a pressurized drug formulation through a nozzle, producing an aerosol spray for inhalation. Since its inception, extensive experimental, theoretical, and computational research has been conducted to enhance the drug delivery efficiency of pMDIs. Effective drug deposition primarily occurs within the narrow pulmonary passages of the lungs, particularly in the alveolar region, where β_2-adrenoreceptors are predominantly located. These receptors absorb bronchodilator drugs, making it essential to generate aerosol particles with a Mass Median Aerodynamic Diameter (MMAD) ≤ 5 µm to ensure effective treatment.

In this study, a parametric investigation of nozzle designs is carried out to optimize critical parameters aimed at producing aerosol particles of minimal size and velocity. The following chapter presents a detailed review of the existing literature in this domain, which provides a foundation for understanding and improving the performance of pMDIs.

4.1 Theoretical studies on Pressurised Inhaler

As the phenomenon of atomization is basically the vast increase of surface area for a particular volume of fluid, surface tension force is one of the most important parameters which defines the size of droplets formed as the result of atomization. Surface tension being a surface phenomenon is difficult to model in control volume approach so a model for modelling surface tension effectively and easily was given by Brackbill et al. (1992). In his theory, he considered fluid-to-fluid interfaces as transitional areas with a finite thickness where properties change continually. The force density at each position in the transition region is determined by the curvature of the surface of constant property at that location.

When the ratio of the local radius of curvature to the thickness of the local transition zone approaches zero, it is normalized so that the traditional definition of surface tension on an interface is restored.

The continuum approach removes the need for interface reconstruction, makes surface tension calculations easier, allows for precise modeling of fluid flows driven by surface forces in two and three dimensions, and does not place any modeling constraints on the quantity, complexity, or dynamic evolution of fluid interfaces with surface tension. Next,

Senecal et al. (1999) have described how to represent high-speed viscous sheets. He has developed a linear stability study for a liquid sheet that takes into account the surface tension, surrounding gas, and liquid viscosity's influence on the wave generation process. Similar to the first and second wind-induced breakdown regimes of cylindrical liquid jets, the shift from a long wavelength domain to a short wavelength phase is identified using a dispersion relation for inviscid flows.

For pressure-swirl atomizers, the dispersion relation is utilized to forecast the wave duration, maximum unstable growth rate, sheet breakup length, and drop size that results. The findings demonstrate that the model correctly forecasts the overall spray form, local Sauter mean diameter, and liquid spray penetration. Ommi et al. (2009) have also performed a linear instability analysis of an inviscid annular liquid sheet originating from an atomizer exposed to inner and outer spinning air streams.

In order to examine the impact of the liquid-gas swirl orientation on the maximum growth rate and the associated wave number that generates the finest droplets, the dimensionless dispersion equation governing the instability is constructed and solved numerically.

4.2 Experimental studies on Pressurised Inhaler

Dunbar et al. (1997) conducted an experimental evaluation of the spray that was released from a pMDI for various propellants and their combination with medicines. The pressing need to replace the environmentally damaging CFC propellants served as the impetus for his study.

The single particle light scattering method known as Phase-Doppler Particle Analysis (PDPA), which allows for the simultaneous assessment of drop size, velocity, and concentration, was used in the experimental investigation. The performance of three formulations of hydro-fluoro alkane propellant was compared to that of a commercially available CFC formulation that contained medication and surfactant, as well as the conventional CFC propellant mixture. Smyth et al. (2006) examined work on spray pattern analysis for changes in orifice size and particle size on the impact of spray plume for pMDI. Particle size profiles, estimations of the particle-size dynamics of plumes during a spray, and variables influencing spray pattern were all associated with variations in actuator orifice diameter in this study.

Regardless of orifice diameter, ellipsoid vertical spray patterns were produced. Orifice size has a strong and nonlinear impact on elliptical ratio measurements. Measurements of the particle size profile and spray geometry were also connected with the spray patterns. Moraga-Espinoza et al. (2018) used the Plume Induction Port Evaluator (PIPE) to measure the plume geometry using the mass deposition pattern. He discussed how the PIPE technique is more reproducible than the High-Speed Laser Imaging (HSLI) method, which is frequently used to characterize plume geometry.

The experimental study of a pressure swirl atomizer followed, whereby the high-speed shadowgraph technique was used to examine the flow structure inside the atomizer. In their study, Sumer et al. (2012) employed a Phase Doppler Particle Analyzer to identify hollow cone spray characteristics. Using a high-speed shadowgraphy device, the air core inside the pressure swirl atomizer was seen at high temporal and spatial resolutions. The last step is the experimental examination of the near-nozzle and exterior spray properties of a continuous spray that is atomized from a nasal spray device.

The study by Inthavong et al. (2012) involved atomizing water using a commercial nasal spray device and measuring the spray properties, such as Sauter mean diameter and drop velocity, in various locations to provide information on the formation of spray droplets following the atomization of a drug formulation using a nasal spray device. In this case, the Sauter mean diameter is the mean diameter that is obtained by dividing the second moment of the Probability Density function (PDF) of the diameter of particles generated by the third moment of the PDF.

It can alternatively be thought of as the mean diameter that is calculated by dividing the area mean value by the volume mean of all the particles. The purpose was to simulate the flow via a nasal channel by offering a realistic beginning condition.

4.3 Computational studies of Pressurised Inhaler

A lot of computational work has been done for various flow properties regarding fine particles individually and when injected as a spray. One of the works for individual particles was done by Longest and Kleinstreuer (2004). For low Reynolds number conditions, they examined the separate and combined impacts of near-wall proximity, plane shear, and uniform flow on spherical droplet heat and mass transfer. Heat and mass transport surface gradients of two-dimensional axisymmetric droplets and three-dimensional spherical droplets close to wall borders were calculated using volume simulations under environmental circumstances that are compatible with inhalable aerosols ($5 \leq d \leq 300$ µm). The findings show that for shear-based Reynolds values larger than 1, which happen for near-wall respiratory aerosols with diameters bigger than 50 µm, plane shear has a major effect on droplet heat and mass transfer. It is demonstrated that, for lower Reynolds numbers and at distances smaller than five particle diameters, wall proximity greatly improves heat and mass transfer caused by conduction and diffusion.

Other particle studies, including one on sub-micron particles, were carried out by Longest and Xi (2007). The models on sub-micron particle mobility and deposition do not account for particle inertia for aerosols smaller than 200 nm. In the absence of inertial effects, a very efficient Eulerian transport model can be applied, treating the particle phase as a diluted chemical species. For aerosols in the fine and very fine ranges, the influence of inertia is not completely measured. The conditions under which submicron particle deposition characteristics can be predicted using Eulerian and Lagrangian particle transport models were assessed in this study. The conditions under which particle inertia becomes significant in relation to diffusional effects were assessed using the differences between the Eulerian and Lagrangian model results.In another study, Longest and Vinchurkar (2007) used numerical analysis to examine the impact of transition and turbulence on the deposition of highly localized

particles in a respiratory double bifurcation model. Two geometric scenarios were examined in order to accomplish this goal: the double bifurcation model and a section of the experimental particle delivery geometry, where transitional flow was anticipated. Laminar, conventional k-ω, and low Reynolds number (LRN) k-ω models were used to calculate the solutions in order to assess the performance of two-equation turbulence models in these systems. The findings show that transition and turbulence significantly affect the local particle deposition patterns, even if the Reynolds number stayed below the critical limit needed for full turbulence.

Longest et al. (2012) also worked on the creation of a new heat exchanger system that creates sub-micron particles that emerge from a nebulizer with bigger particle sizes. In order to create sub-micron particles and regulate the temperature of inhaled aerosols, a nebulizer was connected to the study's add-on devices and heat exchanger component. The outcome showed that while the counter-flow heat exchanger design effectively controlled both the particle size and temperature, the coupled parallel flow wire-heated design raised the aerosol's temperature to an extremely high value. Computational research on the accumulation of particles in the airways of the lungs has been extensive [Tian et al., 20011; Dalasm et al., 2015; Bass and Longest, 2018; Cheng, 2003; Farkas et al., 2018; Longest and Vinchurkar, 2009]. In a study by Kleinstreuer et al. (2007), a computational fluid-particle dynamics technique that has been experimentally validated was used to simulate aerosol deposition, droplet spray transport, and airflow in a pMDI connected to a human upper airway model, taking into account various device propellants, nozzle diameters, and spacers. By measuring the droplet distribution using the inertial deposition phenomena, cascade impactors like the Anderson cascade impactor are employed.

In order to assess the effects of particle charge on deposition, Vinchurkar et al. (2009) conducted a computational study in which they developed a verified CFD model for the Mark II Andersen cascade impactor (ACI). To simulate the flow field, a commercial CFD code was used. The Lagrangian tracking approach, which took into consideration impaction, sedimentation, diffusion, and electrostatic attraction, was used to assess particle trajectories and deposition. Now coming on to the topic of atomization and computational study of sprays we have firstly the work done by Oliveira et al. (2010) in which the spray of propellant from a pMDI nozzle was done using simple cone injection in the Discrete Phase Method capability of ANSYS Fluent. In this study, an experimental result of pMDI actuated spray was validated using a solid cone injection model. The atomization of the propellant was not modeled numerical model that can simulate the atomization, break-up, and in-flight spray phenomena in the spray forming process is presented in the following study by Gjesing et al. (2009). The open FOAM freeware code was used to create and implement the model. The coupling impact of the breakup phenomena with the local gas and droplet flow fields served as the primary foundation for the investigation. The Eulerian-Lagrangian description served as the foundation for the work. The incompressible RANS equations are used to simulate the gas phase, while a tracking technique and a complete thermal model for droplet cooling and solidification are used to model the droplet movement. Fung et al. (2012) conducted a study to assess numerical modeling methods for simulating spray atomization from a nasal spray device and to confirm the results with earlier experimental observations.

Instead of being used for nasal spray applications, the spray breakup versions were used for high-pressure applications, including combustion and spraying in industry and agriculture. When using a small-scale atomizer for this type of low-pressure injection, the breakdown model's parameters were not optimized. For low-pressure atomization conditions, the linear instability sheet atomization (LISA) model's spray model parameters were adjusted, and the model's performance was assessed for low-pressure applications such as nasal spray devices.

5. Conclusion

In this study, the atomization process in pressurized Metered Dose Inhalers (pMDIs) was investigated using computational simulations in ANSYS Fluent. Unlike previous works that predominantly used simplified injection methods under the Discrete Phase Model (DPM), this work applied detailed atomization models to simulate the actual spray formation process from a pMDI device. By comparing the simulation results with the experimental data, the study identified the atomization model that best replicates real-world spray behaviour.

The selected model was further analysed under varying parametric conditions to identify configurations that produce the lowest particle diameters and velocities. These optimized parameters aim to enhance drug deposition in the deeper, narrower airways of the lungs specifically targeting regions rich in β_2-adrenoreceptors. The results from this study suggest that careful tuning of atomization parameters can significantly improve the efficiency and therapeutic performance of pMDI devices.

6. Future Aspects

- Further studies can focus on patient-specific airway modelling to assess how the optimized spray interacts with different lung geometries.
- Transient inhalation profiles can be incorporated to reflect realistic breathing conditions and their impact on deposition.
- The incorporation of advanced turbulence and droplet breakup models could yield even more accurate predictions of spray dynamics.
- Experimental validation using high-speed imaging or laser diffraction methods can be conducted to further corroborate CFD findings.
- Lastly, the study can be extended to assess the bioavailability and pharmacokinetics of the drug under optimized spray conditions for better clinical relevance.

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