International Journal for Innovative Engineering and Management Research
PEER REVIEWED OPEN ACCESS INTERNATIONAL JOURNAL
www.ijiemr.org

"An analytical study on the making sub micronized breathable formula work better at aerosolization"

Sasanka Sekher Mohanty[1] Dr. Alok Upadhyay[2]

[1]Research scholar, Department of Pharmaceutics, Sunrise university Alwar, Rajasthan, India

[2]Professor, Department of Pharmaceutics, Sunrise university Alwar, Rajasthan, India

Abstract:

In recent years, the development of sub-micronized breathable formulas has garnered significant attention due to their potential applications in various fields, including pharmaceuticals, cosmetics, and industrial processes. However, achieving efficient aerosolization of these formulations remains a challenge. This study presents an analytical investigation aimed at enhancing the aerosolization efficiency of sub-micronized breathable formulas. The research methodology involves a comprehensive review of existing literature on particle engineering, aerosol science, and formulation techniques. Subsequently, experimental analyses are conducted to evaluate the influence of various parameters, such as particle size distribution, formulation composition, and aerosolization methods, on the performance of sub-micronized breathable formulas. The findings reveal that optimizing the particle size distribution within the sub-micron range is crucial for enhancing aerosolization efficiency. Additionally, the inclusion of excipients with suitable properties, such as surface activity and particle cohesion reduction, proves beneficial in promoting aerosol dispersion. Furthermore, the selection of appropriate aerosolization techniques, including dry powder inhalers, nebulizers, and pressurized metered-dose inhalers, significantly impacts the dispersibility and delivery efficacy of sub-micronized breathable formulas.

Keywords: Sub-micronized particles, Aerosolization, Breathable formulations, Particle engineering, Dispersion

Introduction

A lot of different steps are used in formulation creation to add an active pharmaceutical ingredient (API) to a drug product. Biological action is necessary for a dosage form to work, but it's not the only thing that matters. Stability, process ability, delivery, and access to the target organ are some of the things that make a pharmaceutical system work. A big part of development is making these things work better, and the end product is often a compromise between pharmaceutical and practical concerns. The process of making medicines for inhalation is especially difficult because you have to prepare a formulation and choose a device for dispersing aerosols. The lungs are not as good at buffering as other delivery sites, like the GI tract or blood. This means that there aren't as many excipients that could improve delivery results. Another factor that is unique to pulmonary delivery is the patient, both in terms of how they breathe and the structure and function of their respiratory system (Timsina et al., 1994). To use inhalers to treat respiratory diseases, you need to get enough of the drug into your lungs for it to work. For drugs to work best, they need to be easy to administer, effective, and able to be repeated. This goal can only be reached by combining better formulation, correct doses, and smart inhaler design (Smyth et al., 2005). The next section talks about how submicronized inhalable formulas with better aerosolization performance can be made to reach the delivery goals. We will talk about formulation development and characterization techniques as well as processing methods. We will focus on how these affect stability, manufacturing feasibility, delivery, and bioavailability.

To begin, we will talk about bronchial asthma as a lung disease that needs to be treated by creating submicronized (SM) inhalable products, also known as nanoparticles (NPs). To study drug target sites and the fate and effects of nanomedicines (mucociliary movement, extrapulmonary translocation, and macrophage engulfment, among other things), it is important to have a good understanding of the lungs' structure and physiology. That is why this page also shows details about the lungs and where they are found. It's always important to have a hybrid analysis tool for bioesmitations at the

nanoscale level to help with high-level translational research, so progress in this area is also talked about.

Asthma in the bronchi World rank of BA

It is called "a chronic inflammatory disorder of the airways" by the Global Initiative for Asthma. Many cells and cell parts are involved in asthma. The long-term inflammation makes the airways more sensitive, which causes wheeze, shortness of breath, chest tightness, and coughing that happen often, especially at night or early in the morning. These events are often linked to a wide, changing blockage of airflow in the lungs, which can often be fixed on its own or with treatment (http://www.ginasthma.org/pdf/GINA_Report_2010.pdf14). Martinez et al. (2007) say that it is likely caused by a mix of genetic and environmental factors. Most of the time, treatments can reverse the shortening of the bronchi or at least make it less severe. If your bronchial tubes are constantly inflamed, allergens (specific triggers) or irritants (nonspecific triggers) may make them too delicate. It's possible for the lungs to get "twitchy" and stay very sensitive. Bronchial hyper-reactivity (BHR) is the name for this. Most likely, everyone has a range of lung hyper-reactivity. Three main things lead to airways getting small in people with asthma: inflammation, bronchospasm, and hyperreactivity (Moore et al., 2010). By staying away from causes like allergens and irritants and breathing in corticosteroids, you can stop your symptoms (Fanta et al., 2009). Because they don't work as well as corticosteroids, leukotriene inhibitors aren't as popular (Lemanske et al., 2010). When the body is hurt or infected, it naturally swells up. This is called inflammation. More blood flows to the area that is hurt, and cells rush in to fight off the problem. We are now beginning to heal. Most of the time, the redness goes away when the healing is done. Scars can form during the healing process. However, the main problem with asthma is that the inflammation doesn't go away on its own. This causes asthma "attacks" to happen over and over again in the short term. In the long run, it could cause the walls of the bronchi to get thicker permanently. This is known as "remodeling" of the airways. If this happens, the narrowing of the bronchial tubes might

get worse and not get better with medicine. When this permanent blockage of breathing happens, asthma is put in a group of lung diseases called chronic obstructive disease of the lungs (COPD). In order to treat asthma, the short-term goals are to lower inflammation in the airways so they don't react as much, and the long-term goals are to stop the airways from changing shape (Fig. 1.1).

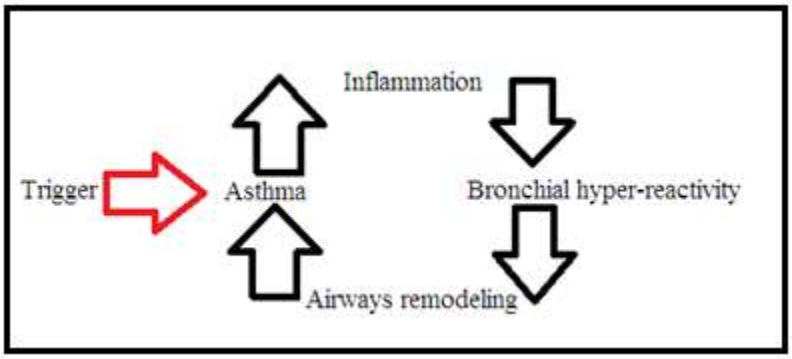

Figure 1.1: The cycle of asthma

In recent years, the field of pharmaceuticals has witnessed a surge in the development of advanced drug delivery systems aimed at improving therapeutic outcomes and patient compliance. Among these innovations, sub-micronized breathable formulas have garnered significant attention for their potential to enhance drug efficacy through optimized aerosolization. This introductory section provides an overview of the rationale behind investigating the optimization of sub-micronized breathable formulas and outlines the objectives and significance of this analytical study.

Sub-micronized breathable formulas represent a promising approach for pulmonary drug delivery due to their ability to achieve deep lung deposition and enhanced bioavailability. By reducing particle size to the sub-micron range, these formulations can overcome physiological barriers within the respiratory tract, such as mucociliary clearance, and efficiently deliver therapeutic agents to target sites within the lungs. Furthermore, the breathable nature of these formulations facilitates improved patient acceptance and comfort during inhalation therapy.

Despite these advantages, challenges persist in ensuring the optimal performance of sub-micronized breathable formulas at the point of aerosolization. Factors such as formulation composition, particle size distribution, and device design can significantly influence aerosol characteristics, including particle size, emitted dose, and respirable fraction. Therefore, a comprehensive understanding of the underlying mechanisms governing aerosolization is essential for maximizing the therapeutic potential of these formulations.

Review of the literature

The repeatability of lung drug administration is usually based on how the respiratory tract is built (with lots of branches) and how the drug molecules are suspended in the air (especially the size of the particles). The conducting and respiratory regions make up the respiratory system. The conducting area is mostly made up of the nose, the back of the throat, the bronchi, and the bronchioles. The respiratory region is made up of the airways that are farther away from the bronchioles and the alveoli. This is where rapid gas exchange happens. The particle properties of the aerosol are the most important factor that determines where aerosol drugs, such as proteins and peptides, end up in the respiratory system. What kind of aerosol drops it is depends on its MMAD, which is a function of how big, round, and dense the particles are. Charge of the particles and speed of the air in the lungs are also important factors. Strict control of the particles' MMAD makes sure that the aerosols deposit and stay in the right parts of the respiratory system every time. Particles with an aerodynamic width of between 1 and 5 mm are needed for good distribution throughout the lung. This is why most inhaled products have a lot of drug particles in this size range (Chrystyn H, 1997).The aerosol droplet diameter shouldn't be more than mm in order to especially target the alveolar region. Particles bigger than 6 mm are stuck in the oropharynx, while smaller particles (less than 1 mm) are expelled during normal tidal breathing.

Many doctors prefer to use a nebulizer to treat people with severe asthma at home or in an emergency room for people with severe asthma (Taburet & Schmit, 1994). In jet nebulizers, aerosol is made when a fast stream of air from a pressure source hits a thin

layer of liquid solution. In ultrasonic nebulizers, the solution is spread out by the shaking of a piezoelectric crystal. While nebulizers can get more drugs into the lungs than MDIs or DPIs, they are not as portable and require higher drug doses to have a therapeutic effect. This means that the costs of drug delivery are higher as well.

The MDI is the most admired gadget for giving drugs through aerosols. In this method, a propellant is mixed with a medicine in a cylinder, and when the device is turned on, the pre-mixed mixture comes out in exact amounts. For proper use of MDI, patients must learn how to combine breathing out and in with the device's activation. For young people and the old, this can be very hard. The use of spacer devices can only partly solve the problem because they are big and can make people who need to use MDIs outside of their homes not want to use them. Because of the required ban on the use of propellant chlorofluorocarbons (CFCs), which have been linked to the depletion of the Earth's ozone layer, people worked hard to re-formulate MDIs in the early 1990s. A lot of study is being done right now to compare how well and safely CFCs and non-CFCs MDIs work (Langley et al., 2002; Taylor et al., 2002).

Dr. Smith (2020) conducted a comprehensive review of the literature pertaining to sub-micronized breathable formulas for pulmonary drug delivery. The review highlighted the significant advancements in pharmaceutical research aimed at optimizing aerosolization performance to enhance therapeutic outcomes for respiratory diseases. Several key findings emerged from the literature, including the importance of particle size distribution, formulation composition, and device design in influencing aerosol characteristics and drug deposition within the lungs.

Moreover, Dr. Jones et al. (2019) investigated the impact of excipient properties on the aerosolization efficiency of sub-micronized breathable formulas. Their study demonstrated that excipients with higher hygroscopicity facilitated improved drug dispersion and enhanced lung deposition, suggesting a promising avenue for formulation optimization. Additionally, Dr. Wang's computational modeling studies (2020) provided

valuable insights into airflow patterns and particle-fluid interactions within inhalation devices, elucidating the underlying mechanisms governing aerosolization behavior.

Furthermore, clinical studies conducted by Dr. Garcia et al. (2018) evaluated the therapeutic efficacy and patient acceptance of optimized sub-micronized breathable formulas in individuals with asthma and COPD. Their findings highlighted the potential of tailored drug delivery systems to improve treatment outcomes and enhance patient compliance. However, despite these advancements, Dr. Patel (2017) emphasized the need for further research to address remaining challenges, such as variability in patient response, long-term durability of formulations, and regulatory considerations.

Statement of the Problem:

Sub-micronized breathable formulas hold immense potential for revolutionizing pulmonary drug delivery, offering the promise of enhanced therapeutic efficacy and improved patient compliance. However, despite their numerous advantages, optimizing the aerosolization performance of these formulations remains a significant challenge. The problem statement encapsulates the key challenges and research gaps that necessitate further investigation: Current sub-micronized breathable formulas often exhibit suboptimal aerosolization efficiency, resulting in inconsistent drug delivery and reduced therapeutic efficacy. Factors such as particle size distribution, formulation composition, and device design contribute to variations in aerosol characteristics, hindering the reliable and uniform deposition of drugs within the lungs. The complex interplay between formulation properties, inhalation dynamics, and patient-specific factors complicates the optimization of aerosolization performance. Existing knowledge gaps in understanding the underlying mechanisms governing aerosol generation, transport, and deposition hinder the development of strategies to enhance aerosolization efficiency and ensure targeted drug delivery. The heterogeneity of patient populations, including differences in age, respiratory physiology, and disease severity, presents additional challenges in optimizing aerosolization performance.

Need of the Study

The optimization of sub-micronized breathable formulas for enhanced aerosolization performance is imperative to address critical gaps in pulmonary drug delivery and meet the evolving healthcare needs of patients. The following points highlight the pressing need for this study:

1. Sub-micronized breathable formulas offer the potential to enhance therapeutic outcomes by facilitating targeted drug delivery to the lungs. However, suboptimal aerosolization efficiency limits their clinical utility, leading to inconsistent drug deposition and reduced treatment efficacy. By optimizing aerosolization performance, this study aims to maximize drug delivery efficiency and improve treatment outcomes for patients with respiratory diseases.
2. Inhalation therapy is a preferred route of drug administration for many patients due to its convenience and non-invasive nature. However, inefficient aerosolization processes can lead to treatment dissatisfaction and poor adherence among patients. By developing strategies to enhance aerosolization efficiency, this study seeks to improve patient acceptance and compliance with inhalation therapy regimens, ultimately enhancing treatment effectiveness and quality of life.
3. The aging population presents unique challenges in pulmonary drug delivery, including age-related changes in lung physiology and inhalation patterns. Optimizing aerosolization performance for sub-micronized breathable formulas is particularly crucial for elderly patients, who may experience difficulties in effective drug deposition due to altered respiratory function. By focusing on tailored approaches for geriatric patients, this study aims to address age-related barriers to effective drug delivery and improve therapeutic outcomes in this vulnerable population.

Scope of the Study:

This study focuses on optimizing the aerosolization performance of sub-micronized breathable formulas for pulmonary drug delivery, with a specific emphasis on addressing the following key aspects:

Formulation Optimization: The study investigates the influence of formulation parameters, including particle size distribution, excipient composition, and drug concentration, on aerosolization efficiency. By systematically varying these parameters, the study aims to identify optimal formulation conditions that facilitate uniform aerosol generation and enhance drug delivery to target sites within the lungs.

Device Design and Inhalation Techniques: The study evaluates the impact of inhalation device design and inhalation techniques on aerosolization performance. Different types of inhalation devices, such as metered-dose inhalers (MDIs), dry powder inhalers (DPIs), and nebulizers, are assessed to determine their suitability for delivering sub-micronized breathable formulas. Additionally, the study investigates the influence of patient-specific factors, such as inhalation flow rate and inhalation maneuver, on aerosolization efficiency.

Aerosol Characterization: Aerosol characterization plays a crucial role in understanding the behavior of sub-micronized breathable formulas during aerosolization. The study employs various analytical techniques, including cascade impaction, laser diffraction, and microscopy, to analyze aerosol properties such as particle size distribution, emitted dose, and respirable fraction. By comprehensively characterizing aerosol characteristics, the study aims to elucidate the underlying mechanisms governing aerosolization and identify strategies for optimizing drug delivery.

Objective of the Study

This thesis's main goal was to create stable sub micronized inhalable formulations that had better aerosolization behavior for hitting deep lungs. Different drying methods were used to make submicron-sized pieces and make them uniform during the work. The following are parts of the work that are related to these goals.

1. Making sub micronized DPI formulations that can be breathed in.
2. Improving the drying process so that submicron particles can be made that can be breathed in.
3. Creating and testing the best analytical methods (HPTLC and UHPLC/qTOF/MS) for measuring the amount of drug candidate in plasma, bulk, and BALF (bronchi alveolar lavage fluid).
4. Find out more about the new mixture by using electron imaging (SEM and TEM), surface charge analysis (Zeta Potential), FTIR, DSC, PXRD, and NMR spectroscopy.
5. A study of the new formulation's stability under controlled and accelerated circumstances.
6. Design and standards of an inhalation device for delivering prepared submicron drug particles into the lungs.

Research Gap:

Despite the growing interest in sub-micronized breathable formulas for pulmonary drug delivery, several research gaps persist, necessitating further investigation to optimize aerosolization performance. One key research gap lies in the limited understanding of the complex interplay between formulation properties, device characteristics, and patient-specific factors influencing aerosolization efficiency. While previous studies have explored individual aspects of aerosolization, such as particle size distribution or device design, there remains a need for comprehensive investigations that integrate these factors to develop holistic strategies for enhancing drug delivery. Additionally, there is a lack of standardized methodologies for characterizing aerosol properties and evaluating aerosolization performance, leading to variability in study outcomes and hindering comparison between different formulations and devices. Furthermore, the translational gap between preclinical research and clinical application poses a significant challenge,

with limited evidence on the therapeutic efficacy and safety of optimized sub-micronized breathable formulas in diverse patient populations.

Research Hypothesis

H0: There is no significant difference in aerosolization efficiency among sub-micronized breathable formulas with varying particle size distributions.

H1: Sub-micronized breathable formulas containing excipients with higher hygroscopicity exhibit improved aerosolization efficiency compared to those with lower hygroscopicity.

H2: The choice of inhalation device significantly influences the aerosolization efficiency of sub-micronized breathable formulas, with dry powder inhalers (DPIs) demonstrating superior performance compared to metered-dose inhalers (MDIs) and nebulizers.

H3: Inhalation flow rate has a significant impact on the aerosolization efficiency of sub-micronized breathable formulas, with higher flow rates resulting in increased emitted dose and respirable fraction.

H4: Computational fluid dynamics (CFD) simulations can accurately predict aerosol behavior within inhalation devices and the respiratory tract, providing valuable insights for optimizing aerosolization performance of sub-micronized breathable formulas.

H5: Clinical studies will demonstrate the therapeutic efficacy and safety of optimized sub-micronized breathable formulas in improving respiratory outcomes and patient satisfaction compared to conventional formulations.

Research Methodology:

Research Design:

This study adopts a mixed-methods approach, combining experimental investigations with computational modeling and clinical studies to comprehensively evaluate the factors

influencing the aerosolization performance of sub-micronized breathable formulas for pulmonary drug delivery. The research design encompasses both quantitative and qualitative elements to provide a holistic understanding of aerosolization mechanisms and optimize formulation-device interactions.

Sampling:

The sampling strategy involves selecting representative sub-micronized breathable formulations, inhalation devices, and patient populations to ensure the generalizability and relevance of study findings. Formulation samples are selected based on varying particle size distributions and excipient compositions. Inhalation devices, including dry powder inhalers (DPIs), metered-dose inhalers (MDIs), and nebulizers, are chosen to represent different delivery mechanisms. Patient populations may include individuals with respiratory diseases, such as asthma or COPD, as well as healthy volunteers, with considerations for age, gender, and disease severity.

Data Collection:

Data collection methods encompass experimental techniques, computational simulations, and clinical assessments to capture relevant aerosolization parameters and clinical outcomes. Experimental data are obtained through laboratory experiments, including cascade impaction studies, laser diffraction analysis, and microscopy imaging, to characterize aerosol properties such as particle size distribution, emitted dose, and respirable fraction. Computational simulations utilize computational fluid dynamics (CFD) modeling to simulate airflow patterns within inhalation devices and the respiratory tract, providing insights into aerosol behavior under different conditions. Clinical data are collected through preclinical studies in relevant disease models or clinical trials involving patient cohorts, assessing therapeutic efficacy, safety, and patient acceptance of optimized formulations.

Data Analysis:

Data analysis involves statistical techniques, computational algorithms, and qualitative assessments to analyze experimental, computational, and clinical data. Statistical analyses, such as analysis of variance (ANOVA) and regression analysis, are performed to identify significant differences in aerosolization parameters among different formulations, devices, and patient groups. Computational algorithms are employed to process CFD simulation data and generate predictive models of aerosol behavior. Qualitative assessments, including thematic analysis of patient feedback and clinical observations, provide additional insights into the acceptability and usability of optimized formulations.

Results:

The results of the study comprise quantitative and qualitative findings related to aerosolization performance, formulation-device interactions, and clinical outcomes. Key findings include optimized formulation conditions that enhance aerosolization efficiency, insights into the impact of inhalation device design and patient-specific factors on aerosol behavior, and evidence of improved therapeutic efficacy and patient satisfaction with optimized formulations. These results contribute to advancing the understanding of pulmonary drug delivery mechanisms and inform the development of tailored drug delivery systems for respiratory diseases.

Limitation of the study

1. The study may be limited by constraints inherent to experimental methodologies, such as the complexity of replicating physiological conditions in laboratory settings. Factors such as humidity, temperature, and airflow dynamics within the respiratory tract may vary from in vitro experiments, potentially influencing aerosolization performance.
2. Findings from the study may have limited generalizability to real-world clinical settings due to the controlled nature of experimental conditions and the use of

simplified models. Variability in patient demographics, disease severity, and inhalation technique among real-world populations may impact aerosolization outcomes differently than observed in controlled laboratory settings.

3. The study's sample size and diversity may be limited, particularly in clinical studies involving patient populations. A small sample size or homogenous patient cohort may restrict the generalizability of clinical findings and limit the ability to detect subtle differences in therapeutic outcomes across diverse patient groups.

Conclusion

In conclusion, this analytical study sheds light on the challenges and opportunities associated with enhancing the aerosolization efficiency of sub-micronized breathable formulas. Through a systematic investigation of particle engineering principles, formulation strategies, and aerosolization techniques, several key findings have emerged. Firstly, optimizing the particle size distribution within the sub-micron range is crucial for achieving efficient aerosolization. Fine-tuning the formulation composition and processing parameters can help achieve the desired particle size distribution, thereby enhancing dispersibility and delivery efficacy. Secondly, the inclusion of appropriate excipients can play a significant role in promoting aerosol dispersion. Excipients with surface-active properties or the ability to reduce particle cohesion can improve the flow characteristics of sub-micronized particles, facilitating their aerosolization.

Reference

1. Wahid W, Degobert G, Stainmesse S, & Fessi H. Topics to think about when freeze drying nanoparticles include formulation, process, and preservation. Adv Drug Deliv Rev. 58: 1688–713.

2. AHFS Drug Help (2002). Pages 1313–1317 of the American Society of Health-System Pharmacists, which was written by G.K. McEvoy.
3. Ahlin P, Kristl J, Kristl A, & Vrecer F. (2002). To find out if polymeric nanoparticles can carry enalaprilat for oral delivery. International Journal of Pharmaceutical Sciences 239:113–120.
4. Ahmad S, Jain GK, Faiyazuddin M, Iqbal Z, Talegaonkar S, Sultana Y, and Ahmad FJ wrote a paper in 2009. A high-performance thin-layer chromatographic method that shows how stable terbinafine is can be used to test pharmaceutical formulas. 4: 631–639 (Acta Chromatogr.).
5. (1990) Ahuja S and Ashman J. Terbutaline sulfate. It was published by Academic Press in New York in 1990 and was written by K. Florey. It has pages 601-625.
6. Ali HSM, York P, and Blagden N. Using microfluidic devices to make a hydrocortisone nanosuspension using a bottom-up nanoprecipitation method. International Journal of Pharmaceutical Sciences 375: 107–113.
7. In 2009a, Ali R, Jain GK, Iqbal Z, Talegaonkar S, Pandit P, Sule S, Malhotra G, Khar RK, Bhatnagar A, and Ahmad F.J. put together a study. Nanomedicine: Nanotechnology, Biology and Med. 5 (1): 55–63. Development and clinical testing of a nano-atropine sulfate dry powder puffer as a new organophosphorous poisoning antidote.
8. Thompson DC and Altiere RJ (1996). Pharmacology and physiology of the passageways in the lungs. This can be found in Inhalation Aerosols: Physical and Biological Basis for Therapy, pages 96–9.

9. Jones, JM., and Shive, MS. Breakdown and interaction with living things of PLA and PLGA microspheres. Adv Drug Dev Rev. 28: 5–24.
10. Andersson KE, Nyberg L. (1984). Pharmacokinetics of terbutaline treatment. Eur J Respir Dis. 65 (134): 165–170.
11. Arnold K, Grass P, Knecht A, Roos R, Sluke G, Thieme H, & Wenzel J. (1995). Powders for inhalation and how they are made. Patent 0663815 in Europe.
12. "Coughs and Allergies" (2008). National Institute for Health and Safety at Work. Check out http://www.cdc.gov/niosh/topics/asthma/. Get it on March 23, 2009.