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Review Article

A Review On Pharmaceutical Aerosol

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ABSTRACT

The effectiveness of inhaling medications isn't solely determined by the drugs themselves; it also relies on where and how much of the medication is deposited in the respiratory system. This article examines the primary factors influencing how inhaled aerosols are transported and deposited in the human lung. It discusses the deposition of aerosols in both healthy and diseased lungs, drawing mainly from human studies utilizing non-imaging methods. Additionally, it delves into how the flow pattern impacts aerosol deposition. The article briefly touches on the connection between the therapeutic effects of inhaled drugs and where they are deposited in the lungs. Research indicates that the overall deposition in the lungs is not a reliable indicator of clinical effectiveness. Instead, evaluating the distribution of deposited particles and their sizes is crucial in predicting how well a drug will work.

INTRODUCTION

In recent years, pharmaceutical aerosolized dosage forms have gained significant traction due to their rapid technological advancements. This surge in interest has driven the development of inhaled drug delivery for treating both pulmonary and nonpulmonary diseases [1]. The term "aerosol" typically refers to a pressurized system that dispenses a continuous or metered dose of fine mist spray via a valve system. These pharmaceutical aerosols contain the active pharmaceutical ingredient (API), either dissolved or dispersed in a propellant within a pressurized container. They serve various purposes, from topical application on the skin to lung inhalation, lingual application in the mouth, and nasal application for local effects(Figure 1);[2]. Pharmaceutical aerosols offer a localized effect by delivering small amounts of aerosolized drug particles directly to the airway surface, resulting in a rapid clinical response. However, they may also cause undesirable systemic effects when the drug particles are absorbed systemically, as seen with inhaled corticosteroids [1]. Lungs are an ideal site

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for targeted drug delivery due to their large surface area, high drug absorption potential, thin mucous membrane, and rich blood supply. This noninvasive route of administration, bypassing hepatic first-pass metabolism, has garnered attention for developing inhaled medicines to treat various pulmonary conditions [3]. Pulmonary drug delivery systems provide adjustable advantages and allow direct application of medications to the lungs. This facilitates treating respiratory conditions like pulmonary arterial hypertension (PAH) with lower drug quantities compared to other administration routes. For example, Iloprost (Ventavis) aerosol, an analog of prostacyclin used globally for PAH treatment, minimizes side effects associated with intravenous medication strategies due to its relative pulmonary selectivity when administered through inhalation (Figure 2);[4].Looking ahead, in about 70 years from now, various devices for delivering inhaled drugs to treat respiratory conditions will likely have evolved. Ultrasonic nebulizers were developed in the late 1940s, followed by pressurized metered-dose inhalers (pMDIs) in the late 1950s. These two delivery systems dominated inhaled medications until the late 1970s when dry-powder inhalers (DPIs) were introduced [5]. This chapter discusses pharmaceutical aerosol manufacturing, formulation considerations, marketed inhalers, their formulations, advantages, disadvantages, the current clinical status of aerosolized medications, and recent developments in this field

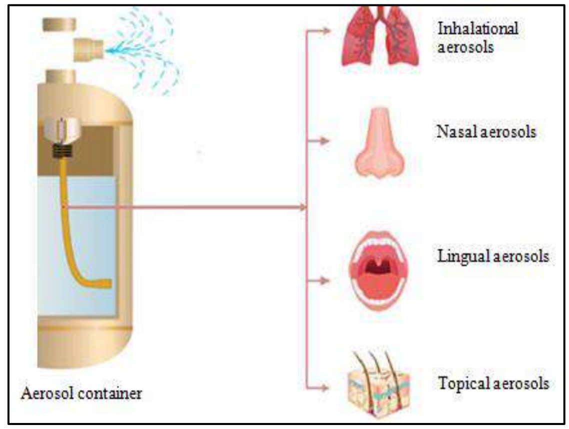

Figure 1: The four types of aerosolized pharmaceutical products are classified based on the site of action.

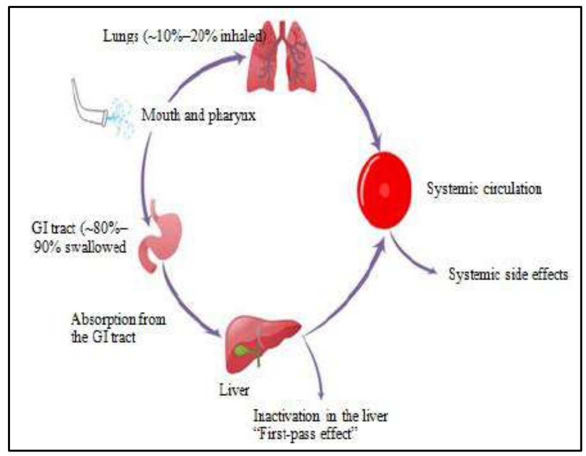

Figure 2: A Schematic representation showing the pharmacokinetics of inhaled drug.

AEROSOL DELIVERY SYSTEM:

Inhalation therapies and systems for treating medical conditions have been in use for thousands of years, even though the term "aerosol" wasn't coined until 1920. Traditional cultures, like Ayurvedic medicine in ancient India around 2000 BCE, utilized inhalation therapy to address respiratory issues [6]. Historical records mention the use of vapor from Hyoscyamus muticus, an herb with anticholinergic properties, inhaled for therapeutic purposes in ancient Egyptian culture. Ibn Sina, also known as Avicenna, a Persian physician from centuries ago, employed pine and eucalyptus essential oils for inhaled therapy to treat certain respiratory disorders [7].

Respiratory conditions continue to be prevalent, and many medically prescribed treatments for these conditions are administered as inhalation therapeutics. Therefore, these medications require specialized delivery systems to ensure precise dosing and efficient deposition of drug particles [5].Inhaled drugs used to treat respiratory infections are highly effective as both preventive measures and treatments. Aerosolized drug administration is believed to be particularly effective due to its direct delivery of anti-infective agents to the infection site, providing the necessary concentrations to eliminate pathogens. This method has demonstrated a significant reduction in the toxicity commonly associated with systemic exposure to the drug [8]. Aerosol dosage forms can be formulated as solutions or suspensions, and in recent decades, innovative delivery systems, like soft mist inhalers, have shown improved efficiency. However, each delivery system has its own set of pros and cons. Inhalers differ in their efficiency of drug delivery, influenced by factors such as device design, formulation, particle size, and more, which are thoroughly discussed in subsequent sections. Advancements in inhalation therapeutics rely heavily on developing new formulations, specialized delivery devices, and optimizing the pulmonary pharmacokinetics and pharmacodynamics of inhaled drugs [9].

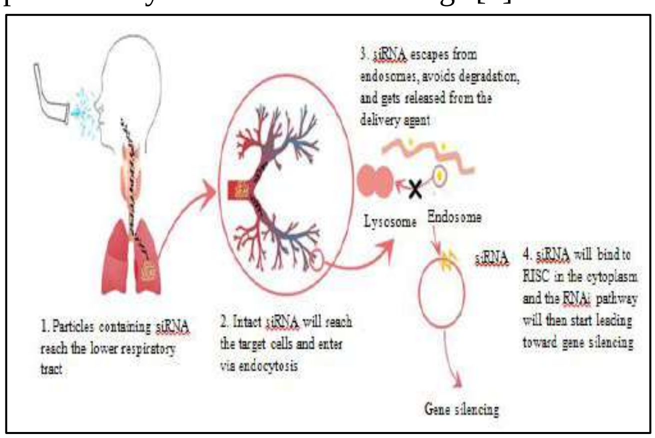

Figure 3: siRNA as a new technology for an inhalational drug targeted delivery. siRNA, Small interfering ribonucleic acid.

Types of aerosol systems:-

The aerosol, functioning as a dosage form, consists of both the propellant and the product concentrate, which houses the pharmaceutically active ingredients, cosolvents, and any other necessary filler materials crucial for the product's efficacy and stability enhancement. This product concentrate can take various forms solution, semisolid, or suspension resulting in aerosol systems that exist as solutions, dispersions, dry powders, emulsions, or pastes [10]. Several formulation factors influence the release of the aerosol content from the inner container to the external environment. Viscosity and the solvent properties of the concentrate mixture are significant factors to consider, especially when employing different valve systems and propellants [11]. The following sections will delve into and briefly discuss the primary types of aerosol systems commonly manufactured in the pharmaceutical industry.

1. **Water-based system:-**

The water-based aerosol system is comprised of three phases: a water phase, a propellant, and a vapor phase. Water is typically added in a significant amount to dissolve the contents. The propellant used in this system is usually immiscible with water, hence the recommendation to include cosolvents like ethanol and surfactants at a range of 0.5% to 2.00%. These surfactants work by reducing the interfacial tension between the water and the propellant [12].Commonly used propellants for these systems include hydrofluorocarbons (HFC), hydrocarbon (HC) blends, pure HCs, nitrogen, and dimethyl ether. However, a drawback of these systems is the potential corrosion of the container due to the production of carbonic acid by the added propellants. This corrosion can alter the product's pH and stability. Additionally, the inclusion of ethanol, which increases the flammability of the product, is considered a major disadvantage of water-based aerosols. To mitigate corrosion, corrosion inhibitors are often added to the formulation, and these water-based products are typically filled in phenolic, urethane, or epoxy-lined containers [10].

2. Solution system:-

Achieving a homogeneous solution between the product concentrate and the propellant is crucial for expelling the formulation in spray form. Specific formulation techniques involve using solvents like alcohol, glycols, and acetone [11]. However, most propellants or propellant-solvent blends are nonpolar, which can limit their ability to dissolve all components in the product concentrate, particularly with widely used hydrocarbon (HC) propellants. This limitation often leads to the formation of a two-phase system when the product concentrate and propellant are combined [10, 11]. Several factors impact the spray rate in experiments, including the solvent used, propellant concentration, vapor pressure, and valve characteristics. Maintaining adequate pressure is essential to expel the formulation at an appropriate rate under the desired operating conditions. Propellant concentration plays a role in determining droplet size and the wetness or dryness of the spray. Adjusting these factors is crucial to achieving the desired spray characteristics [11].

3. Foam/emulsion system

This system is often referred to as a three-phase system where the product concentrate is emulsified with the propellant. When the valve is actuated, the emulsion is dispensed, and bubbles form within the formulation as the propellant evaporates [10]. Typically, an oil-in-water (o/w) emulsion system expels the product as foam. Hydrocarbon (HC) propellants, added in small ranges like 3% to 4% in a 90% to 97% emulsion concentrate, help create the desired foam [11]. Depending on the formulation content, the resulting foam can be either stable or rapidly collapsing [11]. Emulsifiers and surfactants play crucial roles in facilitating component mixing and enhancing emulsification [13]. Generally, when the propellant is added to the immiscible internal phase, the formulation is expelled as foam, while adding the propellant to the external phase emits the formulation as a spray [11]. As the formulation reaches the atmosphere, the propellant vaporizes rapidly, and the product concentrate is expelled as foam (Figure 4);[13]. For these aerosol systems, it's recommended to shake the container before use to disperse the propellant throughout the concentrate, aiding foam generation. Holding the device upright is advised when the dip tube is part of the valve assembly. However, if the dip tube is not part of the assembly, inverting the containers before use delivers the content directly to the valve. Propane/isobutane blends, difluoroethane, low-flammability isobutene, and certain compressed gases like nitrous oxide and carbon dioxide are commonly used propellants in foam systems [10].

4. Suspension or dispersion system:-

These systems involve adding components in solid form, as seen in powder aerosols. Suspending agents are commonly included to enhance the susceptibility or dispersibility of solid particles within the propellants. It's crucial to consider factors like moisture, agglomeration, sedimentation, and compaction of particles. Moisture content is typically kept below 300 parts per million (ppm), while measures are taken to control agglomeration, sedimentation, and compaction to prevent fine particles from clogging the valve [11]. This type of aerosol system is often used when the product concentrate is relatively insoluble in the propellant. Different propellants, either a single type or a mixture, can be added in this system. Examples of products using suspension aerosols include antibiotics, steroids, and anti-asthmatic drugs [10].

Adjusting the density of both the powder and the propellant helps reduce the rate of sedimentation. Additionally, particle size control is essential, usually aiming for particles smaller than 40 micrometers to efficiently pass through the valve orifice [11]. When the valve is activated in this system, the suspension is expelled from the aerosol, and the propellant rapidly vaporizes, leaving behind a fine dispersion of the product concentrate [10]. For topical applications, it's recommended to use larger particles, typically ranging from 3 to 6 micrometers, to minimize potential inhalation adverse effects. This size range helps prevent the particles from being easily inhaled during application [11].

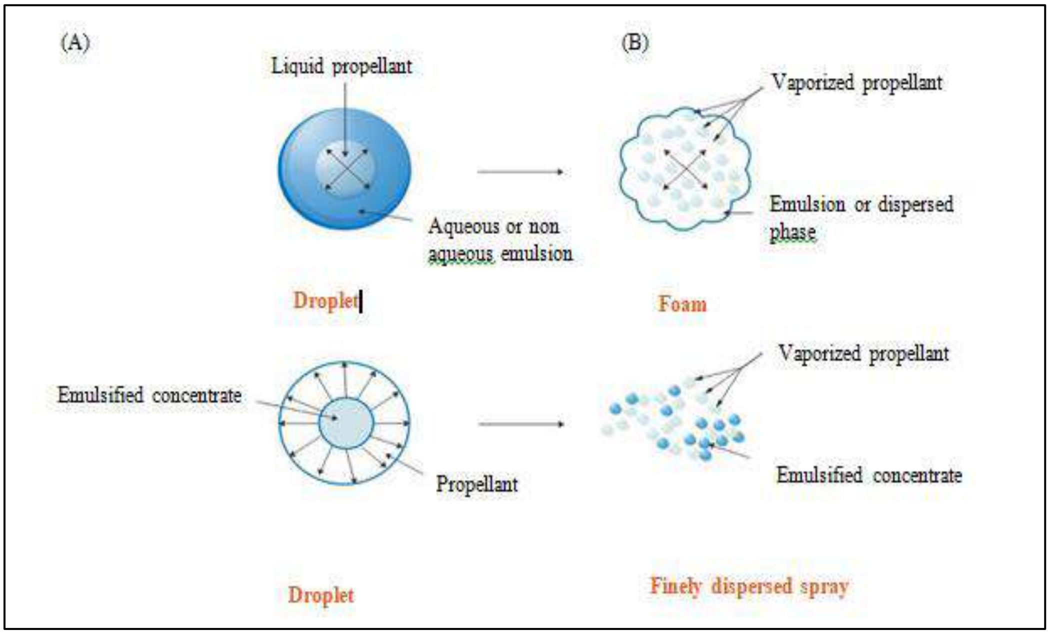

Figure 4: Aerosol emulsion droplets containing propellant (A) in the internal phase with subsequent formation of aerosol foam and (B) in the external phase with subsequent formation of wet spary.

DESIGNING PHARMACEUTICAL AEROSOL:

FORMULATION PREREQUISITES:

Absolutely, there are numerous factors that influence aerosol delivery systems. Here are some of the common factors that significantly impact aerosol formulation:

1. Particle Size: The size of aerosol particles plays a crucial role in their deposition within the respiratory tract. Smaller particles tend to reach deeper into the lungs, while larger particles may deposit in the upper airways [17].
2. Physical Properties of Ingredients: The properties of the active pharmaceutical ingredients (APIs), propellants, and other components such as solvents and suspending agents affect the stability, dispersion, and efficacy of the aerosol.
3. Formulation Stability: The stability of the formulation over time, including resistance to changes in temperature, pressure, and moisture, is vital to maintain effectiveness.
4. Propellant Selection: The choice of propellant impacts the aerosol's dispensing characteristics, stability, and safety. Factors like flammability, solubility, and compatibility with the formulation are considered.
5. Valve Design and Actuation: The design and functioning of the valve significantly impact the spray pattern, droplet size, and consistency of aerosol delivery.

6. Surfactants and Emulsifiers: These additives influence the interfacial tension between phases, aiding in emulsification and dispersion of components.
7. Container Material: The material of the container can affect the stability of the formulation and its interaction with the propellant or other ingredients.
8. Moisture and Environmental Factors: Moisture content in the formulation, exposure to light, heat, and other environmental factors can impact the stability and performance of the aerosol.
9. Dose Consistency: Ensuring uniform dosing with each actuation is crucial for effective and safe drug delivery.
10. Regulatory Compliance: Meeting regulatory standards and guidelines concerning aerosol formulations, labeling, and safety is essential for commercialization and use.

These factors, among others, are carefully considered and optimized in the development and formulation of aerosol delivery systems to ensure their efficacy, safety, and reliability in delivering medications.

Properties and factors affecting aerosols:-

Several other properties also affect particle behavior. For pharmaceutical inhalers, particle size plays a critical role in various aspects:

- Rate of Absorption and Dissolution: Smaller particles may dissolve or be absorbed more rapidly due to their increased surface area.
- Bioavailability: The extent to which a drug is available for use by the body can be impacted by the particle size and its deposition site.
- Deposition and Distribution in Vivo: The location within the respiratory system where particles deposit influences their distribution and subsequent absorption.
- Clearance Time: Particles' residence time within the lungs is influenced by their size, affecting their clearance rate.
- Flow Packing Properties: The flow and packing of particles affect their behavior during aerosolization and deposition.
- Content Dose Uniformity: Ensuring consistent dosing is crucial for achieving predictable therapeutic outcomes.

Investigating how lung deposition is affected by these physicochemical properties of particles is essential for optimizing inhalation therapies and ensuring effective drug delivery to the targeted areas within the respiratory system.

A. Aerodynamic size distribution:-

Understanding the aerodynamic size distribution of aerosol particles is crucial in designing inhalers and evaluating their dynamics for medical purposes. The aerodynamic diameter, specific to spherical particles with a density of 1 mg/cm³ and similar settling velocity under defined conditions, is a key metric used in these assessments [16].The size distribution of aerosol particles significantly influences their delivery through the airways. Instruments like cascade impactors, which use inertial impaction, are employed to measure the aerodynamic size distribution of inhalers produced for medical use. They directly measure aerodynamic diameters and help characterize the particle sizes [15].Determining ambient particle diameter can be accomplished through various methods, including assessing aerodynamic resistance, measuring settling velocity or electrical mobility, and employing light-scattering measurement techniques. Pharmaceutical aerosols typically consist of polydispersions with various aerodynamic sizes, necessitating dispersion between upper, peripheral, and central airways. Smaller aerodynamic diameter particles exhibit lower inertia and momentum than larger ones, leading to a lower likelihood of deposition on impaction plates [15].The diverse geometries of patients' airways, influenced by respiratory conditions, affect the efficiency of regional deposition. At a given aerodynamic size, factors like different inhalation flow rates impact regional deposition. However, relying solely on aerodynamic size for targeting particle deposition has limitations. These limitations could impact the clinical success of aerosolized medicines, especially those with a narrow therapeutic index. Therefore, considering additional factors beyond aerodynamic size becomes critical for effective and targeted particle deposition [18].

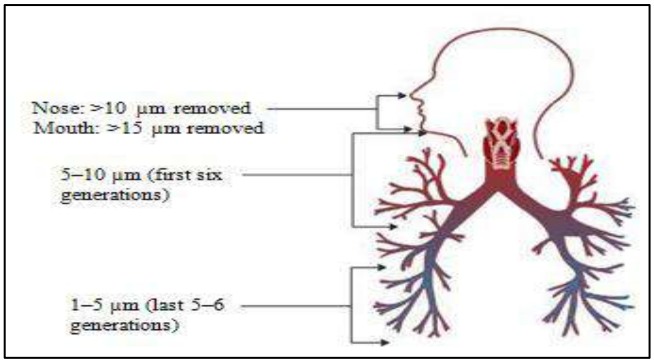

Figure 5: The effect of aerosol particle size on the site of prefential deposition in the airways

B. Emitted dose uniformity:-

Measuring aerosol mass during the manufacturing of aerosolized medicines is crucial for assessing their pulmonary availability. This measurement helps evaluate the uniformity of the emitted dose and the distribution of its aerodynamic size [16]. Calculating the mean of delivered doses resulting from testing the drug uniformity and exact quantity expelled per actuation is vital. During these tests, the accepted limit for emitted dose uniformity required by regulations is typically set at ±15% [2]. For devices using a filter house to collect the emitted dose from the inhaler, testing the uniformity of this emitted dose is necessary. Factors like breathing frequency and tidal volume have been observed to affect the emitted dose of nebulizer inhalers. Conversely, the emitted dose delivered by passive dry powder inhalers (DPIs) is influenced by the patient's inhalation technique. This necessitates the application of specific methods to standardize the emitting operation across different inhalers. Ensuring uniformity in the emitted dose is critical for consistent and reliable drug delivery, especially in inhalation therapies where precision in dosing is essential for effective treatment. Therefore, manufacturers employ rigorous testing and assessment protocols to meet regulatory standards and ensure the quality and performance of aerosolized medicines [16].

C. Hygroscopicity

Hygroscopicity refers to the capacity of certain substances to absorb or release moisture based on their environmental conditions. Aerosolized particles can exhibit varying degrees of hygroscopicity, which means they can become more or less prone to moisture absorption upon reaching the respiratory tract. This property can significantly impact their deposition patterns within the airways. Several factors contribute to determining the size of particles after they undergo hygroscopic growth [19]. These factors include the environmental conditions within the airways, intrinsic properties of the particles, and their initial size. Hygroscopicity can aid in the deposition of aerosolized drugs by minimizing extrathoracic loss and enhancing particle deposition in the lungs through the growth of particles caused by moisture absorption. Studies on inhalers with nanometric and submicrometric median mass aerodynamic diameter (MMAD) have shown an increase in MMAD due to factors such as the presence of water vapor in the respiratory tract [20]. Particles with an MMAD smaller than 0.1 μm are less affected by hygroscopic growth, while those larger than 0.5 μm are significantly impacted [19]. The condensation of vapor resulting from the humid respiratory environment or carrier solvent evaporation can cause size changes in inhaled particles, unlike particles used in stable laboratory experiments of deposition [21]. Understanding these effects is crucial in adjusting aerosolized particle size to enhance their deposition in specific lung regions [22]. Additionally, condensational growth has shown improved accuracy in targeting particle deposition to peripheral airway sites compared to traditional approaches. This knowledge helps in optimizing drug delivery systems for more effective and targeted treatment [18].

D. Stability:-

In pharmaceutical development, assessing drug stability is a crucial aspect during clinical trials. Stability studies are conducted to determine the drug product's shelf life or the expiration date for the active pharmaceutical ingredients (APIs). These studies also identify appropriate storage conditions by examining how the quality of APIs changes over time under specific environmental conditions [23]. Ensuring proper physical stability is essential for the dosage form to perform adequately throughout its shelf life [24]. For a long time, regulatory guidelines and industrial practices have emphasized the importance of microbiological, chemical, and physical stability assessments [3]. Physical stability changes are often challenging to predict and quantify compared to chemical stability changes. Developing a stable drug formulation involves understanding both the chemical and physical mechanisms responsible for any physical alterations. Implementing a drug development strategy that systematically assesses APIs, additives, and manufacturing processes is part of the quality by design approach. This comprehensive strategy aims to enhance product quality, reliability, and consistency throughout the drug development lifecycle [24].

ADVANTAGES OVER CONVENTIONAL DELIVERY SYSTEMS:

The scientific focus on aerosol therapy has surged lately, prompting advancements in technologies for developing innovative inhalation treatments. Inhalation as a drug delivery route has gained attention for treating both pulmonary and nonpulmonary conditions. As mentioned earlier, delivering minute doses through inhalation enables targeted effects at specific sites, ensuring swift clinical responses with minimal systemic side effects [1]. Lungs offer significant advantages for delivering noninvasive drugs that aim for localized effects [25]. Compared to oral or intravenous routes, pulmonary delivery enhances drug bioavailability in the lungs due to limited metabolic activity, leading to improved drug availability and effectiveness [26]. Higher absorption rates, lower required doses, and rapid onset of action stand as common benefits associated with inhalation as a drug administration route [27].

TYPES OF PROPELLANTS: MECHANISM OF RELEASING THE CONTENT

Certainly, various propellants are employed in the formulation of pharmaceutical aerosols, falling into two primary categories: liquefied gases and compressed gases.

Different classes of propellants have distinct properties and applications in aerosol formulations, each offering specific advantages and considerations in pharmaceutical manufacturing. Subsequent sections will likely delve into the characteristics, uses, and considerations surrounding these different propellant classes in pharmaceutical aerosol formulations (Figure 6);[10].

1. Chlorofluorocarbon propellants:-

CFCs, or chlorofluorocarbons, were first synthesized in 1890 and were composed of carbon, fluorine, and chlorine. By the 1930s, they found widespread use in various applications, such as air conditioners, refrigerators, fire suppressants, and as propellants in various aerosol types. In pressurized metered-dose inhalers (pMDIs), commonly used CFCs included CFC-11 (CCl_3F), CFC-12 (CCl_2F_2), and CFC-114 (CCl_2F_4) [28].

CFC propellants demonstrated a higher rate of expansion compared to compressed gases and could be liquefied either by applying high pressure at room temperature or by cooling them below their boiling points[10]. They were highly stable molecules with strong carbon-fluorine and carbon-chlorine bonds, making them resistant to However, their extensive use in pharmaceutical aerosols continued until the 1980s when they were gradually phased out due to their detrimental impact on the ozone layer. Scientific evidence revealed that CFCs contributed to ozone depletion in the atmosphere. As a result, environmental concerns led to the search for more metabolism by biological and environmental systems [28].

environmentally friendly propellants to replace CFCs in aerosol products, including pharmaceutical inhalers like MDIs. This transition aimed to mitigate environmental harm while maintaining the safety and efficacy of aerosolized medications [10].

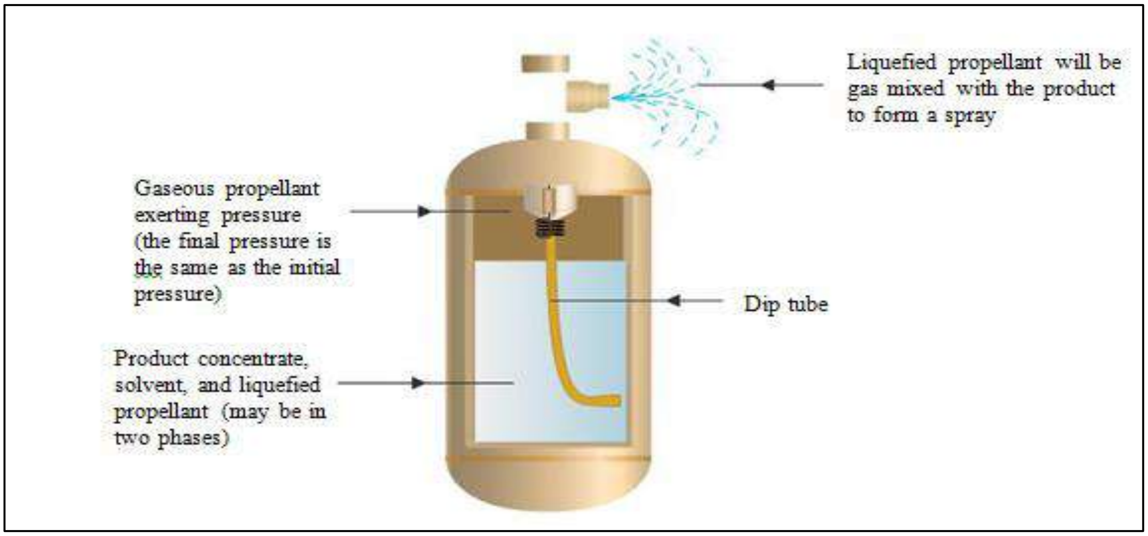

Figure 6: The mechanism of activation of aerosols.

2. Hydrocarbon propellants:-

HC propellants, also known as hydrocarbon propellants, operate as double-phase propellants within aerosol containers. These propellants work with the product concentrate in a liquid state, compressed alongside the propellant at a pressure equal to or slightly higher than the propellant vapor pressure[29]. Common examples include propane (C3H8; propellant A-108), butane (C4H10; propellant A-17), and isobutane (C4H10; propellant A-31). These hydrocarbon propellants can be used individually or as mixtures. With densities approximately lower than 1 mg/cm3 and being relatively immiscible in water, HC propellants usually form two layers or three phases in a container. The hydrocarbon layer sits above the aqueous layer, generating the necessary force to expel the content from the container [10]. Upon pressurized compression, most of the propellant becomes liquefied, with only a small portion remaining in the vapor state. When the product is dispensed, the pressure within the container decreases, leading to more liquid propellant converting into vapor. These hydrocarbon propellants are favored for their low toxicity, inertness, and environmentally acceptable nature, making them commonly used in topical pharmaceutical aerosols [29]. Their stability against hydrolysis, as they lack halogens, makes HC propellants suitable for water-based aerosols. However, their flammability poses an explosion risk, a characteristic that needs careful handling and consideration during manufacturing and usage [10].

3. Compressed gas propellants:-

Indeed, the dynamics of compressed gas propellants differ from liquefied gas propellants in aerosol containers. Unlike liquefied gas propellants, the amount of compressed gas propellants added correlates with the pressure inside the container [29]. As a result, there are restrictions on the quantity of these propellants used. These compressed gas propellants occupy the headspace within the container, supplying the necessary pressure to expel the drug concentrate from the aerosol container [10]. However, compressed gas propellants have limited shelf lives due to a combination of factors, including low usage levels and permeation. Ensuring a suitable shelf life requires costly bottle improvements [29]. During aerosol activation, the pressure decreases, causing the gas to expand and fill the empty space. This process indicates that the initial pressure required for compressed gas propellants is higher than that required for liquefied gas propellants. Devices containing compressed gas propellants lack a propellant reservoir. Consequently, higher initial pressure is necessary, and this pressure decreases as the product is administered [10].

4. Advanced propellants:-

Pharmaceutical companies are actively exploring alternatives to CFCs used in MDIs, aiming for safer propellants. Nonchlorinated HFAs like HFA-134 and HFA-227 have successfully replaced CFCs [30]. These transitions have sparked competition among companies to secure patents, fostering collaboration to demonstrate the non-toxic profiles of HFA propellants [31]. The shift to HFAs necessitated the development of new components for MDI aerosols. For instance, elastomeric components in MDI valves designed for CFCs weren't suitable for HFA propellants. Cleaner elastomers like ethylene propylene diene monomer (EPDM) were developed, offering lower leachable levels and compatibility with HFA-containing MDIs. Additionally, coated canisters were produced to reduce chemical degradation of the product concentrate and minimize drug deposition, particularly in ethanol-free HFA suspension dosage forms. To improve lung deposition, more effective actuator devices were developed to control the plume [32]. Compared to CFC-beclomethasone suspension, solution formulations exhibited a smaller mass median aerodynamic diameter [30]. The extrafine nature of Qvar resulted in enhanced deep lung deposition, contributing to improved therapeutic outcomes [33].

CONTAINER TYPE: PRODUCT FEASIBILITY AND COMPATIBILITY:-

Aerosol containers come in varying sizes and materials, engineered to withstand specific pressures. Common materials used in manufacturing include plastic (such as polyethylene naphthalate and polyethylene terephthalate), metals like aluminum, stainless steel, and tin-plated steel, as well as uncoated or plastic-coated glass. Selecting the appropriate container involves considerations like pressure resistance during production, compatibility with formulation components, cost-effectiveness, adaptability to production methods, and alignment with the manufacturer's design and appearance preferences [13]. Plastic materials used in metal canister coatings bolster formulation stability by improving corrosion resistance, while in glass container coatings, they enhance safety features. The containers are meticulously designed to endure maximum pressure while ensuring safety and impact resistance [34]. Among aerosol canisters, three-piece tin-plated steel containers are the most widely used. The efficacy of pharmaceutical aerosols heavily relies on the proper formulation, valve assembly, and container. It's crucial for the formulation to remain chemically stable without compromising the integrity or operation of the valve assembly and canister. The choice of valve should be well-suited to the content being dispensed, while the canister must resist corrosion [13].

A. **Glass:-**

Glass containers are a preferred choice for pharmaceutical products due to their non-reactive nature, transparency or opacity options, and resistance to potential leaks (except for valve joints) [11]. They're commonly used for medicinal products administered locally or orally, such as injection syringes for unit- or multi-dose administration and tablet bottles. However, they are generally limited to sizes up to 120 mL in pharmaceutical and cosmetic aerosols [35]. In terms of manufacturing, conventional glass bottles typically have thinner walls compared to plastic-coated glass containers [11]. Various types of glass containers are available, chosen based on the product's characteristics and intended application. Suppliers typically provide packaging and raw materials based on industrial specifications. Different pharmacopeias, such as the US and European Pharmacopoeias, classify permissible types of glass containers. These standards may vary, with tests for light transmission and hydrolytic resistance commonly included for most glass containers in the US and European Pharmacopeias. However, in the Japanese Pharmacopoeia, these tests are primarily for glass containers used in injectable products [35].

Despite their advantages, glass containers have some drawbacks:

1. They are prone to breakage during usage, shipping, and manufacturing.
2. Their weight contributes to higher transportation costs.
3. Their manufacturing process is slower, leading to a higher scrap rate.
4. They are suited for low-pressure product systems. To mitigate breakage risks, thick vinyl coatings can be applied.

These limitations have led to the consideration of alternative packaging materials in certain contexts to address safety and cost concerns [11].

B. Metals:-

Metal containers, particularly stainless steel and aluminum, are commonly used for nonparenteral dosage forms in pharmaceutical packaging. These materials offer strength, durability, and impermeability to gases, making them ideal for pressurized containers [35]. Stainless steel containers typically have a cylindrical design with separate body, top, and bottom pieces that are joined together during manufacturing. These containers can be coated for corrosion prevention and to minimize interactions with the contents [11]. Aluminum containers, on the other hand, are often constructed as one-piece units and come in various diameters, heights, and shapes. They are widely utilized due to their corrosion-resistant oxide coating and overall hardness. Manufacturers often employ extrusion processes and other techniques to create seamless aluminum containers, ensuring greater safety, compatibility, and reduced leakage compared to seamed containers. However, if the protective coating of aluminum is compromised, corrosion can be accelerated [13].While stainless steel containers offer excellent properties, their relatively high cost limits their widespread use. Conversely, aluminum containers are extensively used due to their corrosion resistance and durability, although they can be prone to corrosion if the protective layer is breached. These factors influence the choice of metal containers for pharmaceutical packaging in different scenarios [11].

C. Plastics:-

Plastic containers have gained popularity in aerosol container design due to their ease of manufacturing, cost-effectiveness, and appealing appearance. They are increasingly utilized in various applications, including parenteral solutions. Plastic containers offer several advantages over glass, such as being lightweight, shatter-resistant, and collapsible, making them less prone to breakage. Detailed specifications and tests for medicinal product use and administration routes are outlined in the European Pharmacopeia [35].However, plastic containers can pose challenges related to drug-plastic interactions, potentially impacting the product's stability, efficacy, and release mechanisms. Vapor permeation is another concern associated with plastic containers, leading to variable packaging quality. Despite their advantages, these limitations prompt careful consideration and testing when using plastic containers for pharmaceutical aerosols [13].

CONCLUSION

The development of pharmaceutical aerosols has seen rapid progress in recent years, offering advantages over conventional drug administration routes. These pressurized systems release fine mist sprays, delivering medication through inhalation. The unique anatomical features of the respiratory system make it an attractive target for drug delivery, particularly for conditions that are challenging to treat via other routes. Over the past 70 years, various devices have been developed for delivering inhaled drugs to address respiratory conditions. Advancements in charging technologies are enhancing drug deposition, optimizing therapeutic effectiveness.The efficient deposition of aerosolized particles significantly impacts the effectiveness of these therapies. Inhalational therapeutics can deposit in the airways through different mechanisms, influencing their distribution and action within the respiratory tract. Propellants are crucial components of aerosol formulations, and various classes of propellants are employed in these dosage forms. Multiple technologies exist for manufacturing pharmaceutical aerosols, each offering distinct characteristics and advantages. Testing the efficiency and deposition of pharmaceutical aerosols is a critical process, often carried out using specialized deposition models designed for this purpose. Continuous updates in aerosol technology through research and reports facilitate ongoing advancements in this field, fostering further studies and improvements.

REFERENCES

1. Dolovich, Myrna B., and Rajiv Dhand. "Aerosol drug delivery: developments in device design and clinical use." The Lancet 377.9770 (2011): 1032-1045.
2. Uddin, Md, et al. "Pharmacopoeial standards and specifications for pharmaceutical aerosols: In-process and finished products quality control tests." Advances in Research 6.3 (2016): 1-12.
3. Shetty, A. D. V. A. I. T., and G. A. N. G. A. Srinivasan. "Advancements in dry powder inhaler." Asian J Pharm Clin Res 10.2 (2017): 8-12.
4. Tiwari, Gaurav, et al. "Drug delivery systems: An updated review." International journal of pharmaceutical investigation 2.1 (2012): 2.
5. Myers, Timothy R. "Year in review 2014: aerosol delivery devices." Respiratory Care 60.8 (2015): 1190-1196.
6. Cazzola, Mario, et al. "Tiotropium formulations and safety: a network meta-analysis." Therapeutic Advances in Drug Safety 8.1 (2017): 17-30.
7. Usmani, Omar S. "Treating the small airways." Respiration 84.6 (2012): 441-453.
8. Andrade, Fernanda, et al. "Nanotechnology and pulmonary delivery to overcome resistance in infectious diseases." Advanced drug delivery reviews 65.13-14 (2013): 1816-1827.
9. Lavorini, Federico. "The challenge of delivering therapeutic aerosols to asthma patients." International Scholarly Research Notices 2013 (2013).
10. Kulkarni, Vitthal S., and Charles Shaw. Essential chemistry for formulators of semisolid and liquid dosages. Academic Press, 2015.

11. Sciarra, John J., Christopher J. Sciarra, and Updated by Staff. "Aerosol technology." Kirk‐Othmer Encyclopedia of Chemical Technology (2000): 1-20.
12. Shinde, Namdeo G., et al. "Pharmaceutical foam drug delivery system: General considerations." Indo Am. J. Pharm. Res 3 (2013): 1322-1327.
13. Allen Jr, Loyd V. "Dosage form design and development." Clinical therapeutics 30.11 (2008): 2102-2111.
14. Hinds, William C., and Yifang Zhu. Aerosol technology: properties, behavior, and measurement of airborne particles. John Wiley & Sons, 2022.
15. Wang, Hui, et al. "Design and pharmaceutical applications of a low-flow-rate single-nozzle impactor." International Journal of Pharmaceutics 533.1 (2017): 14-25.
16. Colbeck, I., and Mihalis Lazaridis. Aerosol Science. Wiley Online Library, 2014.
17. Usmani, Omar S., Martyn F. Biddiscombe, and Peter J. Barnes. "Regional lung deposition and bronchodilator response as a function of β2-agonist particle size." American journal of respiratory and critical care medicine 172.12 (2005): 1497-1504.
18. Darquenne, Chantal, et al. "Bridging the gap between science and clinical efficacy: physiology, imaging, and modeling of aerosols in the lung." Journal of aerosol medicine and pulmonary drug delivery 29.2 (2016): 107-126.
19. Tena, Ana Fernández, and Pere Casan Clarà. "Deposition of inhaled particles in the lungs." Archivos de Bronconeumología (English Edition) 48.7 (2012): 240-246.
20. Worth Longest, P., and Michael Hindle. "Numerical model to characterize the size increase of combination drug and hygroscopic excipient nanoparticle aerosols." Aerosol Science and Technology 45.7 (2011): 884-899.
21. Martin, Andrew R., and Warren H. Finlay. "The effect of humidity on the size of particles delivered from metered-dose inhalers." Aerosol science and technology 39.4 (2005): 283-289.
22. Javaheri, Emadeddin, and Warren H. Finlay. "Size manipulation of hygroscopic saline droplets: Application to respiratory drug delivery." International Journal of Heat and Mass Transfer 67 (2013): 690-695.
23. Guo, Yushen, Evgenyi Shalaev, and Scott Smith. "Physical stability of pharmaceutical formulations: solid-state characterization of amorphous dispersions." TrAC Trends in Analytical Chemistry 49 (2013): 137-144.
24. Huang, Jun, Chimanlall Goolcharran, and Krishnendu Ghosh. "A quality by design approach to investigate tablet dissolution shift upon accelerated stability by multivariate methods." European Journal of Pharmaceutics and Biopharmaceutics 78.1 (2011): 141-150.
25. Karathanasis, Efstathios, et al. "Preparation of in vivo cleavable agglomerated liposomes suitable for modulated pulmonary drug delivery." Journal of Controlled Release 103.1 (2005): 159-175.
26. Loira-Pastoriza, Cristina, Julie Todoroff, and Rita Vanbever. "Delivery strategies for sustained drug release in the lungs." Advanced drug delivery reviews 75 (2014): 81-91.
27. Lee, Wing-Hin, et al. "Inhalation of nanoparticle-based drug for lung cancer treatment: Advantages and challenges." Asian journal of pharmaceutical sciences 10.6 (2015): 481-489.
28. Leach, Chet L. "The CFC to HFA transition and its impact on pulmonary drug development." Respiratory care 50.9 (2005): 1201-1208.

29. Shieh, D., Huitt, D., Kennedy, T., Gopegui, R., 2008. US 7,448,517 B2. US 7,448,517 B2.
30. Stein, Stephen W., and Charles G. Thiel. "The history of therapeutic aerosols: a chronological review." Journal of aerosol medicine and pulmonary drug delivery 30.1 (2017): 20-41.
31. Rogueda, Philippe, et al. "Twenty years of HFA pMDI patents: facts and perspectives." Journal of Pharmacy and Pharmacology 64.9 (2012): 1209-1216.
32. Stein, Stephen W., et al. "Advances in metered dose inhaler technology: hardware development." Aaps Pharmscitech 15 (2014): 326-338.
33. Van den Berge, M., et al. "Treatment of the bronchial tree from beginning to end: targeting small airway inflammation in asthma." Allergy 68.1 (2013): 16-26.
34. Kadam, Praful, Hema Kanekar, and Anubha Khale. "Pulmonary drug delivery system: current practices and applications." World J. Pharm. Res 3.6 (2014): 204-229.
35. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, International Agency for Research on Cancer, and World Health Organization. Some traditional herbal medicines, some mycotoxins, naphthalene and styrene. Vol. 82. World Health Organization, 2002.

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