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DESIGN AND FORMULATION OF NEXT GENERATION DRY POWDER INHALERS: OPPORTUNITIES AND CHALLENGES

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ABSTRACT

Dry powder inhalers (DPIs) have become a significant system for pulmonary drug delivery, attributed to their breath-actuated mechanism, portability, and stability of formulation. In recent decades, notable progress in DPI technology has tackled major challenges related to inadequate powder flow, variability in dosing, and inhalation performance that depends on the patient. The development of advanced DPIs emphasizes innovative particle engineering techniques such as spray drying, supercritical fluid technology, and formulations without carriers to improve aerosolization efficiency and deep lung deposition. The incorporation of new excipients, techniques for surface modification, and engineered porous particles has further enhanced the dispersibility of powders and consistency in dosing. Additionally, innovations in devices, including low-resistance inhalers, active dispersion mechanisms, and smart inhalers with digital sensors, are revolutionizing patient adherence and therapeutic monitoring. Future advancements in DPIs are anticipated to focus on personalized medicine, integrating patient-specific inhalation profiles and connectivity with digital health platforms. Furthermore, the expanding use of DPIs for systemic delivery, vaccines, biologics, and gene therapies underscores their increasing clinical importance beyond just respiratory conditions. Despite these advancements, challenges such as scalability in manufacturing, regulatory demands, and long-term stability persist. Ongoing interdisciplinary research that merges formulation science, device engineering, and clinical assessment will be vital in progressing the next generation of dry powder inhalers to achieve better therapeutic results.

INTRODUCTION

For the pulmonary delivery of therapeutic agents, particularly synthetic biomolecules like proteins, peptides, and nucleic acids, DPIs are becoming a game-changing platform. The pulmonary route has special benefits, such as systemic administration of biomolecules with high bioavailability and direct access to the lungs vast surface area and vascular network, which permits localized therapy of respiratory disorders. DPIs offer a non-invasive, patientfriendly alternative for biomolecule administration by avoiding the problems associated with conventional parenteral routes, including patient pain, infection risk, and poor compliance [1].

DPIs' applicability for the delivery of synthetic biomolecules has been further increased by their combination with state-of-the-art technologies including particle engineering, SD, and nanocarrier systems. DPIs are especially useful in treating complex ailments such respiratory infections, genetic abnormalities, and chronic inflammatory diseases because of their capacity to deliver medication locally or systemically [2].

Furthermore, compared to other inhalation devices like nebulizers and pressurized metered-dose inhalers (pMDIs), DPIs have clear advantages. These characteristics make DPIs scalable solutions for the world's healthcare needs, improve patient adherence, and simplify manufacturing [3].

1. OVERVIEW OF DPI PRODUCTS

DPIs are widely used medications with particularly made delivery systems for contemporary inhalation treatment of respiratory conditions [4].

1.1. Drug Formulation as a Powder

The formulation of a DPI is usually a complex dry powder mixture of inactive excipient components and one or more active pharmaceutical ingredients (API). In addition to improving the API's chemical and physical stability, the usage of excipients in formulation creation may also affect the product's performance [5].

1.2. Drug Delivery and the Device Landscape

Due to optimization for formulation delivery and patient use, DPI device designs occur in a wide range of variations. have a resistance suitable to reach the specified flow rate; and be able to shield the drug formulation from environmental influences (such as humidity, light, and dust).

The airflow resistance of the HandiHaler® is somewhat greater than that of the Cyclohaler®. Though this isn't always the case for all devices with high, medium, or low airflow resistance [6]. Podhaler: In 2013, the TOBI® Podhaler® (Figure 2) received approval to treat Pseudomon infections in patients with cystic fibrosis. The Novartis Pharmaceuticals Corporation's Podhaler® was seen more favorably than nebulizers, which were cumbersome to travel and prone to contamination. Asthma and the symptoms of chronic obstructive pulmonary disease (COPD) are treated with the Ellipta® family of DPIs (Figure 3). The patient is said to find the device's design intuitive, and it has mild resistance.

As part of the Asmanex® Twisthaler® medication product, which contains mometasone furoate and is prescribed to treat asthma, the Twisthaler® (Figure 4) is an example of a reservoir-based DPI for distribution. The gadget is a member of the higher-resistance device class and is utilized by both adults and children. The TwinCaps® is a single-use, disposable, multi-unit dose inhaler that is intended to be sold as an inexpensive, pre-filled inhaler that can provide high dosages of medication. The systemic distribution of laninamivir (laninamivir octanoate hydrochloride), a new neuraminidase inhibitor, for the treatment and postexposure prevention of influenza through pulmonary administration was its primary usage in Japan [7].

2. OVERVIEW OF DPI TECHNOLOGY AND APPILICATION

2.1. Methods of Application for DPIs

DPIs are non-invasive drug delivery methods that avoid hepatic first-pass metabolism and gastrointestinal breakdown by focusing on the respiratory tract. DPIs improve efficacy and patient comfort by ensuring both localized and systemic therapeutic effects [8].

2.2. Pulmonary Delivery of Therapeutics

DPIs are excellent at delivering medicinal substances straight to the lungs, providing targeted therapy with little exposure to the rest of the body. For example, when administered by DPIs. Circumventing pulmonary obstacles such alveolar macrophage activity and mucociliary clearance. DPIs enable targeted pulmonary gene delivery for localized treatment, as demonstrated by polyethyleneimine (PEI)-based siRNA carriers [9].

2.3. Advances in DPI Formulations

Carrier-Based Systems for Improved Delivery: To maximize the aerodynamic qualities of DPI formulations, carriers such lactose, mannitol, and trehalose are essential. Advances in needle-shaped carriers, tailored mannitol crystals, and nanoporous microparticles maximize therapeutic results by improving tiny particle deposition in deep lungs [10].

2.4. Specialized Applications of DPIs

Antimicrobial and Gene Therapy: DPIs play a key role in gene therapy by delivering plasmid DNA and siRNA while maintaining bioactivity.

Inhalable Mannitol for the Treatment of Infectious and Chronic Diseases: DPIs have been proven to improve lung function and lower exacerbation rates in patients with cystic

Fibrosis [11].

3.ADVANTAGES OF PULMONARY DRUG DELIVERY SYSTEM

1. The onset of effect of drugs administered by the pulmonary route is rapid.
2. Because medications are not administered to the rest of the body, pulmonary drug delivery systems have extremely few adverse effects.
3. The pulmonary medication delivery mechanism does not require needling.

Three main categories can be used to classify inhaled medication delivery systems:

*DPIs *Nebulizers *pMDIs

4. GENERAL REQUIREMENTS OF DPI

DPIs must meet the following requirements.

4.1. Drug content uniformity

Each capsule or blister in a single-dose system must have the same amount of powder and medication in order to ensure that the patient receives the same dose each time

4.2. Flowability

This feature must be adequate to ensure that the proper quantity of powder is used to generate a DPI

4.3. Particle Size of API

The active ingredient needs to be inhaled. It needs to be present in particles that are between one and five micrometers in size in order to enter the lungs

5. PRINCIPLE OF DRY POWER INHALER DESIGN

An aerosol of dry powder is dispersed using a static powder bed. To create the aerosol, the particles must be moved. Movement can be caused by a variety of causes, including active and passive ones. For aerosol production, a number of power-assisted devices-pneumatic, impact force, and vibratory-have been developed or are in the process of being developed.

These DPIs, referred to as active-dispersion DPIs, are not available for purchase [12].

6. FORMULATION STRATEGIES FOR DRY POWDER INHALERS

The flow characteristics of the powder, which are primarily influenced by strong interparticle forces that cause the cohesive bulk powder to agglomerate, are what determine the effectiveness of DPI. The three distinct interparticle forces are the van der Waals force, electrostatic force, and capillary force [13]

6.1. Carrier Free

In the carrier-free approach, the active therapeutic element may be housed in tiny particles, a composite consisting of many chemicals, or a single molecule. The drug particle that is meant to be inhaled must be less than five micrometers.

6.2. Drug Carrier

For dry powder inhalers, it is challenging to deliver 1g or 1mg of pharmacological dosages into the tiny blisters. Inhaling powder is also challenging because the optimal particle distance is between 1 and 5 meters. [14]

7. PHYSICOCHEMICAL CHARACTERIZATION FOR OPTIMIZED DPI DELIVERY

Accurate physical-chemical description is essential for DPIs to transport synthesized biomolecules. For efficient drug deposition in the lungs, methods like laser diffraction and scanning electron microscopy (SEM) provide precise particle size and even distribution. As a result, many techniques have been found to describe these characteristics, which might be useful when trying to improve the formulation and functionality of a DPI. Inverse gas chromatography (IGC) measurements of powder surface energy have been linked to pow der dispersion [15].

8. DRY POWDER INHALATION: PRESENT INHALERS

The use of metered dosage inhalers (MDIs) and nebulizers has drastically decreased with the advent of DPIs. However, it is noteworthy that in the UK, where it was born, DPIs still made up less than 30% of all respiratory retail units in 2017, compared to 70% for MDIs. The quick capture of a sizable portion of the inhalation market demonstrates that DPIs are superior to MDIs and nebulizers in a few ways.

1.First generation capsule inhalers
2.Multiple unit-dose inhalers
3. multi-dose reservoir inhalers

9. THE MAIN CLASSES OF DPIS, BASED ON THEIR INTRINSIC RESISTANCE, AND

Pressure Drop across the Device

Device based on a capsule: These DPI devices frequently feature a chamber where a capsule is placed. Pins or twists placed inside the capsule cause it to shatter with external force when the patient hits the button. After the powder has been released, the patient inhales it.

Capsule-based devices listed below.

*Aerolizer *Rotahaler *ARCUS *Flow Caps *DOTT DPI *Breeze haler *Aerohaler, and

*Podhaler Redihaler.

Device based on a cartridge**:** These devices contain a chamber to store medicine powder. The device releases drugs when inhaled via a special mechanism. It has a push lever attached to a bar that is attached to the powder chamber, and a button that is connected to it. It has multiple applications [16].

10. ADVANCEMENTS IN DPI DEVICE TECHNOLOGIES

The Digihaler® used with ProAir®, AirDuo®, and Armonair® products are among the digital DPIs that are now FDA-approved; they received approval in 2018, 2019, and 2020, respectively. An electronic module (eModule) on the top part of the inhaler houses the Digihaler®'s integrated digital sensor, which can store usage information (date and time), inhalation statistics pertinent to the inhalation technique (such as PIF and flow volume), and send out medication reminders [17].

11. FACTORS INFLUENCING DPI PERFORMANCE

11.1. Characterizing Particle Properties and Aerodynamic Performance

The efficiency of aerosolization and lung deposition is determined by particle properties such size, shape, density, and surface roughness. These characteristics are optimized using sophisticated analytical methods including as SEM, NanoXCT imaging, and laser diffraction.

11.2. In Vitro, Ex Vivo, and In Vivo Testing

A thorough strategy that incorporates in vitro, ex vivo, and in vivo testing techniques is needed to link preclinical discoveries with clinical applications. confirm systemic effects and lung deposition patterns, guaranteeing the successful transfer of aerosol treatments from lab to clinical settings [18].

12. BIOEQUIVALENCE AND BIOAVAILABILITY ISSUES OF DPI PRODUCTS

One of the most important tasks for pharmaceutical businesses is to address the bioavailability/bioequivalence (BA/BE) difficulties of pharmaceutical products. The problem of BA/BE assessment has only recently been brought back to life for orally inhaled and nasal drug products (OINDPs), despite being well established for the majority of oral products for which the growth of the generics market has permitted the exclusivity extension for wellknown blockbuster drugsdue to the patent expirations of several important inhalation products [19].

13. REGULATORY CONSIDERATION

The European Medicines Agency (EMA), which recently released a draft guideline on the quality standards for drug-device combinations, views DPIs as drug-device combination products. This is why it's critical to differentiate between integral and non-integral devices. The first one must be (i) a single integral product consisting of the equipment and the medication, (ii) designed for use in the specified combination, and (iii) non-reusable [20].

14. LIMITATIONS OF CURRENTLY AVAILABLE DPIS

The fraction of delivered dose in the lungs varies from around 9% to 80%, and the aerosolization performance of the DPIs currently on the market varies as well. Two main factors may be responsible for this high variability and occasionally low lung deposition: (a) the patient's incapacity to obtain adequate inspiratory airflow, and (b) the strong cohesive forces of the particles and poor device design, both of which may impede powder deagglomeration [21].

15. CHALLENGES AND FUTURE DIRECTIONS IN DPI DEVELOPMENT FOR BIOMOLECULES

15.1. Challenges in DPI Formulation and Delivery

Because synthetic biomolecules including proteins, peptides, and nucleic acids are delicate medicinal agents, developing DPIs for them presents several difficulties. Bioavailability and therapeutic efficacy can be impacted by denaturation and aggregation that occurs during production, storage, or aerosolization [22].

15.2. Patient Factors and Safety Concerns

The performance of DPIs is significantly impacted by patient-related variables, including inspiratory flow rates and inhalation technique. Drug deposition and dispersion can be greatly impacted by patient effort variability, especially when using passive DPIs. [23].

15.3. Emerging Applications and Complexity in Formulation.The development of DPI is made more difficult by the emergence of medicinal applications including gene and RNA delivery. These biomolecules need carriers that minimize off-target effects, ensure efficient pulmonary deposition, and preserve their structural integrity during aerosolization. [24].

16. CONCLUSION

This review has provided a discussion of the FDA's current understanding of the principles and contributions that a DPI's formulation and device provides to its performance, as well as a brief overview of performance characterization methods that can be used during drug development and establishing BE. With the challenges that novel DPI formulations, manufacturing approaches, and device designs can present for evaluating potential generic DPIs, the FDA has funded research initiatives to better understand what factors.

17. AUTHOR CONTRIBUTIONS

All authors are contributed equally.

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The authors have no conflicts of interest to declare.

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