Pharmaceutical Sciences, 2024, 30(3), 279-281
doi:10.34172/PS.2024.16
https://ps.tbzmed.ac.ir/

Editorial

Future of Carrier-Free Dry Powder Inhaler Formulations

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Article History: Received: 9 May 2024 Accepted: 18 May 2024 ePublished: 28 May 2024

Pulmonary drug delivery, which involves administering medications via oral inhalation, is gaining increasing prominence as a promising alternative to conventional drug delivery methods. In 2021, the global market for inhaled medicinal products surged to a record high of $13.4 billion, and it has been projected to grow further, reaching $54.1 billion by 2030.[1]

Pulmonary drug delivery through carrier-based dry powder inhaler (DPI) formulations is a common practice,[2-4] with the formulations typically consisting of micronized drug particles (ranging from 6 to 500 μg) and lactose monohydrate as the carrier. This drug-excipient blend effectively prevents the agglomeration of cohesive drug particles.[5,6] Though, it necessitates aerosolization to separate the drug from the carrier, allowing it to reach the deeper regions of the lungs. Within this formulation, the efficiency of drug delivery is heavily dependent on the balance of the adhesive inter-particulate forces (between the drug and excipient particles) compared to the cohesive forces among drug particles.[7,8]

Challenges such as improper mixing, non-uniform doses, and incompatibility between the drug and lactose monohydrate are the main complications associated with carrier-based DPI formulations.[6,9-12] For example, research has demonstrated that drugs containing active functional groups (such as -NH, -OH, -COOH) can interact with the free carbonyl group of lactose monohydrate, leading to undesired chemical reactions and incompatibility.[12-14] Additionally, lactose intolerance in some individuals renders lactose monohydrate an unsuitable excipient for DPI formulations, as it can trigger hypersensitivity reactions.[15] Moreover, developing carrier-based formulations is difficult for high-dose drugs (> 10–250 mg) such as antibiotics and other drugs used in chronic obstructive pulmonary disease, cystic fibrosis, and tuberculosis.[16-17] Consequently, there is a pressing need for alternative methods to address these limitations. One such method is carrier-free high-drug dose DPI systems.

Despite challenges such as potential agglomeration, handling issues, and limited flexibility in formulation options, these carrier-free DPI formulations are viable alternatives for some drugs. These formulations can be useful when enhanced drug loading is required, while they reduce the inhaler volume and potentially improve the drug deposition. Careful consideration and optimization of the formulation content and the manufacturing processes are necessary to realize the full potential of carrier-free DPIs while addressing the potential pitfalls, especially the potential agglomeration issues that may affect some drugs.

Over the past 20 years, advancements in pharmaceutical powder processing and manufacturing technology have facilitated the growth of DPI formations. In particular, the new technology can assist in developing the more challenging carrier-free DPIs. Various particle engineering techniques,[18,19] process-controlled crystallizations,[20] spray drying,[21] spray freeze drying,[22] jet milling methods,[23] and supercritical fluid technology[24] to produce micro and nanoparticles can allow a diversity of drug particle morphology, size, and surface energy. The diversity of the engineered powder products may be explored to overcome the formulation challenges and to enhance the performance of the carrier-free DPIs. A prevalent objective in designing carrier-free products is to diminish the inherent cohesion of particles while optimizing their dispersion and delivery from the inhaler. An additional consideration with particle designs is the physical stability of the powders which is also highly dependent on the choice of a particle manufacturing method. Concurrently, alongside the exploration of alternative formulations, strides have been made in engineering devices tailored to facilitate the effective delivery and dispersion of carrier-free powder upon inhalation. Innovative inhaler device designs can enable ever-improving dose uniformity of the new carrier-free DPIs.

A key advantage of carrier-free DPI formulations lies in their potential to address the challenges associated with the carrier, such as its potential allergenic reactions, inconsistent dosing due to drug-carrier interactions, and limitations in drug loading capacity. By eliminating carrier(s), carrier-free DPI formulations offer the possibility of delivering higher concentrations of API per dose, reducing the overall volume of powder required

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for effective treatment. This can lead to more compact and portable devices, enhancing convenience and patient adherence to therapy. Furthermore, carrier-free DPIs may improve drug deposition efficiency in the lungs, as they preclude carriers that may interfere with the dispersion and delivery of the API. Improved drug deposition results in more targeted and efficient drug delivery to the desired regions of the respiratory tract, leading to improved therapeutic outcomes.

In addition to these benefits, carrier-free DPIs are amenable to customization by fine-tuning the properties of the API particles, such as particle size, morphology, and surface characteristics. As a result, formulations can be tailored to specific patient needs and disease states. This also allows for personalized drug delivery that holds promise for optimizing treatment efficacy and minimizing adverse effects.

In conclusion, the future of carrier-free dry powder inhaler (DPI) formulations holds significant promise and potential for revolutionizing respiratory drug delivery. Unlike traditional DPI formulations, which rely on carriers such as lactose to disperse and deliver the active pharmaceutical ingredient (API), carrier-free DPI formulations can deliver the drugs without the need for such additives. The future of carrier-free DPI formulations is bright, given the availability of advanced particle design and manufacturing technology, and, with continued research and innovation, it is poised to unlock new possibilities for improved respiratory drug delivery. As technology advances and our understanding of pulmonary drug delivery deepens, it can be expected to see increasingly sophisticated and effective carrier-free DPI formulations that offer enhanced therapeutic benefits and improved patient outcomes.

Author Contributions

Ali Nokhodchi: Conceptualization, Investigation, Writing - Original Draft. Ghafourian: Investigation, Writing - Review & Editing.

Conflict of Interest

The authors report no conflicts of interest.

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