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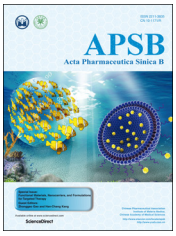

REVIEW

Influence of physical properties of carrier on the performance of dry powder inhalers

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Abstract Dry powder inhalers (DPIs) offer distinct advantages as a means of pulmonary drug delivery and have attracted much attention in the field of pharmaceutical science. DPIs commonly contain micronized drug particles which, because of their cohesiveness and strong propensity to aggregate, have poor aerosolization performance. Thus carriers with a larger particle size are added to address this problem. However, the performance of DPIs is profoundly influenced by the physical properties of the carrier, particularly their particle size, morphology/shape and surface roughness. Because these factors are interdependent, it is difficult to completely understand how they individually influence DPI performance. The purpose of this review is to summarize and illuminate how these factors affect drug–carrier interaction and influence the performance of DPIs.

Abbreviations: API, active pharmaceutical ingredient; CLF, coarse lactose fines; d_{ae}, aerodynamic diameter; DPI, dry powder inhaler; ED, emission dose; ER, elongation ratio; FLF, fine lactose fines; FPF, fine particle fraction; FR, flatness ratio; F_{shape}, shape factor; $F_{surface}$, surface factor; MFV, minimum fluidization velocity; PDD, pulmonary drug delivery; pMDI, pressurized metered-dose inhaler; RO, roundness

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1. Introduction

With increases in our understanding of the physiology of the lung and related diseases, pulmonary drug delivery (PDD) is becoming an alternative choice to treat local and systemic diseases. PDD systems take a variety of forms ranging from nebulizers to inhalers[1] and deliver drug directly to the site of action in the lung or to a distant site *via* the bloodstream. PDD possesses several distinct advantages. First, due to the high permeability, large surface area (about 100 m^2) and thin adsorption membrane (0.1–0.2 μm) of the lung, and because of its excellent blood supply (5 L/min), inhalation produces rapid systemic onset almost comparable to intravenous injection[2]. Secondly, because the lung exhibits relatively low metabolic activity, drugs delivered *via* the lung are not susceptible to first pass metabolism making the lung an attractive administration route for proteins and peptides[3]. For these reasons, PDD is highly desirable for the treatment of patients with pulmonary diseases such as pneumonia, asthma, cystic fibrosis, chronic obstructive pulmonary disease and lung cancer.

PDD systems can be divided into three major categories *viz* nebulizers, pressurized metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs). Nebulizers, the first type of device developed for inhalation therapy, utilize an air jet or ultrasound to convert a drug solution or suspension into fine droplets which are then inhaled by the patient over a couple of minutes[4]. However, nebulizers are not portable, suffer from poor reproducibility in delivering an accurate dose and are only commonly used in hospitals. Since the 1950s, portable pMDIs have been developed and have become the mainstay of asthma therapy with good patient compliance. Nevertheless, they require good coordination between actuation and inhalation and only a small fraction of drug reaches the patient's lungs due to the high particle exit velocity. They are also environmentally unfriendly because they require a chlorofluorocarbon propellant that depletes the ozone layer. In contrast, the DPI is propellant-free, portable, easy to operate, low-cost, and provides better formulation stability than liquid dosage forms. In particular, the development of DPIs was stimulated by the Montreal Protocol (1987) which recommended the removal of chlorofluorocarbon propellants[5,6].

DPIs consist of an active pharmaceutical ingredient (API) of suitable aerodynamic size (usually 1–5 μm) for inhalation[7], contained within a device which, upon inhalation, provides sufficient deagglomeration of particles to deliver a therapeutic dose to the lungs. The main problem with particles of this small micron size is that their high surface free energy makes them stick to each other (*via* cohesive forces) or to any surface they encounter (*via* adhesive forces). As a result, they exhibit poor flowability and aerosolization performance and have a propensity to remain within the inhaler. In addition, many APIs used for treating local diseases such as asthma are highly potent and require only a low dose (200–400 μg for salbutamol and 6–12 μg for formoterol)[8] which poses significant problems in relation to powder handling and accurate metering of doses. Recently, a DPI containing carrier particles as well as drug has been developed to overcome these limitations. The functions of the carrier include (1) improving flowability of drug particles to facilitate filling the DPI, (2) increasing dispersion of drug particles during emission and (3) diluting the drug to improve accurate dose delivery[7].

Aerodynamic diameter (d_{ae}) is the best parameter to evaluate the ability of fine drug particles to deposit deep within the lung. It is defined (Eq. (1)) as the diameter of spherical particles of unit density that reach the same terminal velocity and deposition as the particles under investigation[9]:

$$d_{ae} \cong d_g \sqrt{\frac{\rho_p}{\rho_0 \chi}} \quad (1)$$

where d_g is the geometric diameter of the spherical particle, ρ_p and ρ_0 represent the particle density and unit density respectively and χ is the shape factor.

This equation indicates that d_{ae} is influenced by particle size, morphology/shape and density. For porous particles with low density, $d_{ae} \ll d_g$[10], and particle size has a greater effect on drug deposition than particle density. Since the amount of API in a DPI is relatively low (0.05%–10%)[11], a slight change in the physical properties of the carrier has a considerable effect on DPI performance. It was also reported that carrier surface properties (*e.g.*, surface area, morphology and roughness) play a significant role in determining interparticulate interactions, stability, ease of dispersion, and de-agglomeration[12]. Therefore, considerable researches have focused on particle characteristics of carriers to investigate their influence on the performance of DPIs. These important carrier characteristics are discussed below.

2. Approaches to produce DPI formulations

As shown in Fig. 1, there are commonly two approaches to produce a DPI formulation. One approach is to dissolve drug and carrier in a solvent and then remove solvent by spray drying or other methods (Fig. 1A). The size of the resulting particles is in the range 1–5 μm which, on inhalation, ensures the drug is deposited deep in the lung. The second approach is to combine drug and carrier *via* particle interactions (Fig. 1B) so that, on inhalation, drug is carried past the respiratory tree and released deep in the lung. Carriers used are commonly coarse particles with a size range of 50–200 μm[13] which are designed to be swallowed after impact with the upper respiratory tract[14] so that only fine drug particles are deposited deep in the lung. Due to the lack of toxicological data concerning the potential hazard of carriers to lung tissue, the number of carrier materials currently approved or certified safe by the U.S. Food and Drug Administration (FDA) remains limited so much so that most commercially available DPI formulations rely on lactose as the carrier[15]. Therefore, DPIs in which the API is physically combined with carrier are superior in reducing lung deposition and adverse effects of the carrier while retaining lung deposition of drug. Section 3 focuses on such physically combined DPI formulations.

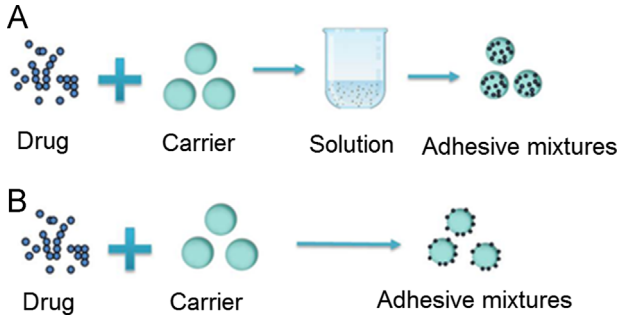

Figure 1 Two methods of combining drug and carrier for use in dry powder inhalers.