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Review article

Modeling the performance of carrier-based dry powder inhalation formulations: Where are we, and how to get there?

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ABSTRACT

Development of carrier-based dry powder inhalation formulations follows till date empirical approaches. This is mainly underlain by numerousness of interplaying determinants of performance and complexity of involved interactions. Mathematical modeling helps elucidate such interactions and aids rational development of formulations. This article provides a critical overview of attempts made to model the performance of carrier-based dry powder inhalation formulations. The complex dependence of the performance on formulation properties is comprehensively discussed. A potential microstructure-based model is ultimately introduced.

1. Introduction

The therapeutic potential of drug delivery via the pulmonary route is developing and expanding [1]. Its efficacy in management of asthma, chronic obstructive pulmonary disease, and pulmonary infections is widely acknowledged. The pulmonary route also offers several pharmacokinetic advantages for systemic drug delivery [2]: the immense surface area ($> 100\ m^2$), the low metabolic activity, the rich blood flow (approx. $5\ L\ min^{-1}$), and the submicron thickness of the alveolar epithelium [3] allow rapid onset of action and offer a portal for non-invasive delivery of hydrophilic macromolecules, e.g. polypeptides and proteins. Drug delivery via the pulmonary route can provide immediate and/or controlled drug release [4–6]. Among inhalation technologies, dry powder inhalation (DPI) exhibits advantageous portability and stability [7], on account of being a solid dosage form. Breath actuation eliminates treatment failure due to poor inspiration-actuation coordination.

A DPI system is composed of a DPI formulation, an inhalation device, and a dose-metering system. A typical carrier-based DPI formulation (Fig. 1) is composed of coarse (diameter ≈ 50–200 μm) excipient (carrier) particles over which respirable (micronized; aerodynamic diameter = 1–5 μm) drug particles are distributed. A ternary, fine excipient material is often added to modulate and improve the formulation performance. Although development of DPI excipients is expanding, the number of excipients accepted for inhalation is yet limited [5]. Lactose monohydrate remains the most studied and the most used DPI excipient. The performance of a DPI system is determined by the balance between inter-particulate adhesion forces in the DPI formulation and dispersion forces generated by the inhalation device.

Inter-particulate adhesion forces in DPI formulations include van der Waals forces, mechanical interlocking, capillary forces, and electrostatic forces [8–12]. Inter-particulate adhesion forces are governed not only by physicochemical properties of formulation components but also by processing and storage conditions. The roles of processing conditions are exemplified by the influences of milling and mixing. The influences of milling result mainly from alterations of the size distribution and the surface structure of particles [13,14]. Molecular disorder resulting from milling moreover lead to formation of amorphous spots. Although the direct relevance of such amorphous spots to dispersion of DPI formulations remains questionable [14,15], a small amorphous content can considerably affect physical and chemical stability of powder formulations. The influences of milling are functions of the milling time and intensity. The influences of mixing results mainly from the inertial, frictional, and press-on forces it generates. The influences of mixing are functions of mixing conditions, such as the technique, the time, and the speed of mixing, and formulation properties, such as the particle size and the surface roughness of carrier particles [15–22]. The roles of storage conditions are exemplified by the influences of relative humidity. The magnitude of capillary forces, which arise from moisture menisci at contact areas between particles, increases with relative humidity [23–25]. Depending on the solubility

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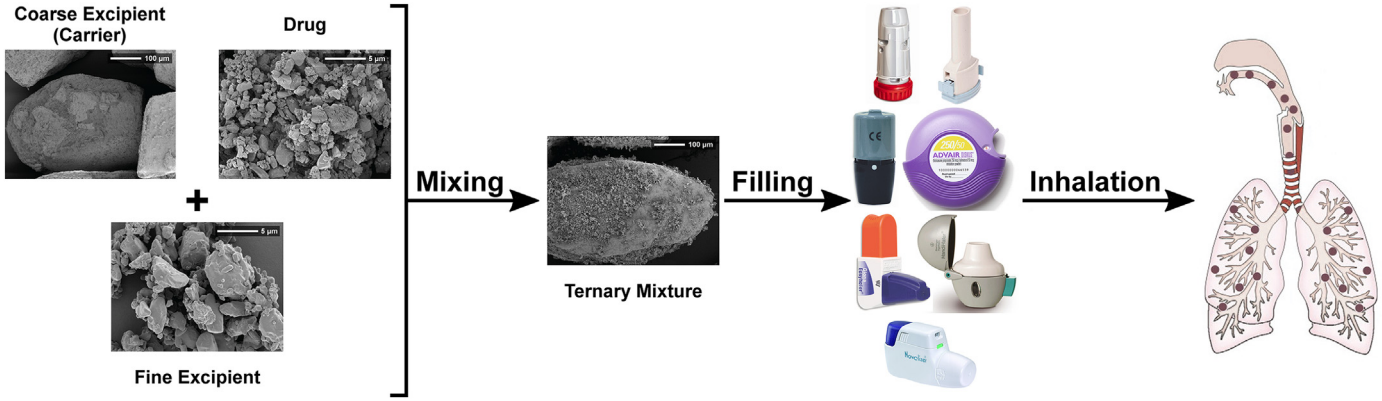

Fig. 1. The composition of carrier-based dry powder inhalation systems. The illustrative scanning electron micrographs are adopted from Ref. [32].

and the surface structure of particles, local dissolution and recrystallization may moreover lead to formation of irreversible solid bridges [25]. On the other hand, electrostatic forces are influential only at low relative humidity since moisture eases dissipation of charges [23,26].

Dispersion forces generated in a DPI device are drag and lift forces, shear and friction forces, and inertial forces [8–12]. Powder inhalation devices can be classified according to the dominant dispersion force generated during aerosolization mainly into turbulent-shear, e.g. Aerolizer®/Cyclohaler, Rotahaler®, and Diskus®, and inertial, e.g. Novolizer® and Twincer™, inhalation devices. The type of dispersion forces generated during aerosolization governs the dependence of the performance on physicochemical properties of formulations [15,27]. For example, dispersion of carrier-based DPI formulations by turbulent-shear and inertial forces depends differently on the macroroughness of carrier particles (c.f. Section 2.3). The structure and the geometry of inhalation devices control powder emission, dispersion, and deposition in the airways [15,28–31]. The resistance of inhalation devices to airflow controls powder dispersion and facilitates effective transformation of airflow into kinetic energy [28].

Because of complexity of interactions taking place in DPI systems and because of limited understanding of these interactions, development of DPI formulations depends till date on empirical rather than rational approaches. Mathematical modeling and computational simulations of drug delivery helps reveal hidden information, aids prediction of responses, advances rational development of formulations, and saves experimentation time and cost. This article critically reviews attempts made to model the dependence of the performance of carrier-based DPI systems on formulation properties. Modeling the dependence of the performance on inhalation device design is discussed elsewhere (c.f. references [15,29–31]).

2. Key performance determinants

The performance of carrier-based DPI systems is influenced by formulation properties, such as the size of carrier particles [20,31,33–44], the concentration of fine excipient materials [14,32,45–59], the surface roughness of carrier particles and the porosity of the powder formulation [31,33,39,60–68], the shape of carrier particles [33,36,39,62,65,69], the size of drug particles [70], and the concentration of drug particles [20,41–43,46,68,71–73]. These influences are not always straightforward and are often modulated by specific features of the formulation properties, thus requiring specific resolutions of measurements [61,74]. These influences moreover interact with each other and with other variables, such as processing, e.g. milling and mixing, conditions, the inhalation device design, and the inhalation flow rate [13,15,16,31,32,36,39,52,75]. The dependence of the performance of DPI systems on formulation properties demonstrates complexity of underlying interactions (c.f. Fig. 2).

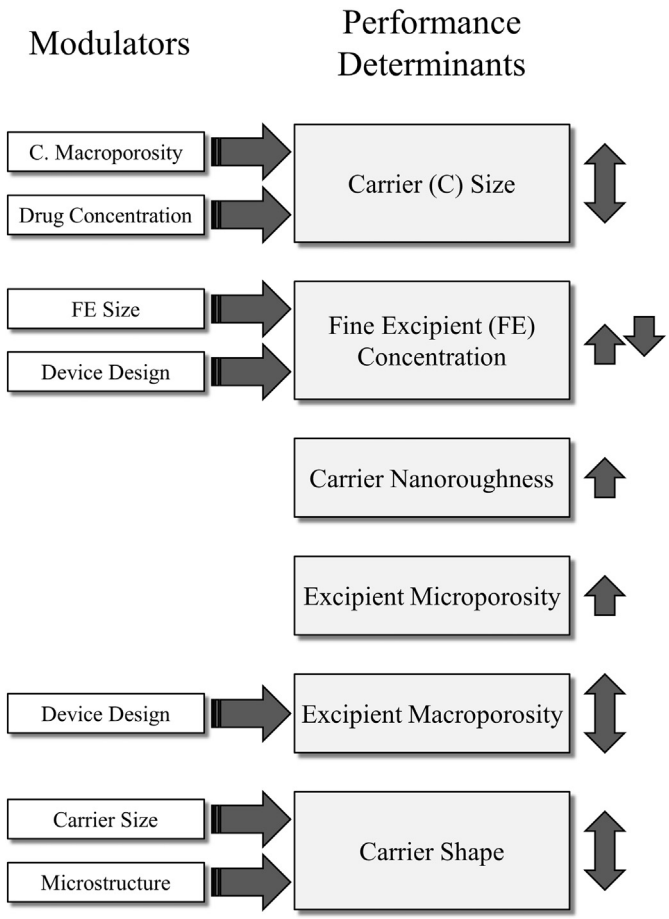

Fig. 2. Key determinants of the performance of DPI excipients/carriers. The chart illustrates the complex dependence of the preformance on excipient properties. For example, the influence of the size of carrier particles can be positive or negative and is modulated mainly by the carrier macroporosity and the drug concentration. Only major and not all modulators of the influence of each excipient property are given. The real picture is certainly more complex.

2.1. The size and size distribution of carrier particles

DPI excipients are usually blends of coarse and fine particles. The roles of the coarse and the fine components are different: coarse excipient particles act as carrier particles, whereas fine excipient particles are performance modulators. The influences of the size of each component on the performance of formulations should therefore be considered separately. This section discusses the influences of the size of