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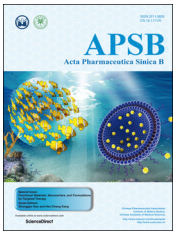

REVIEW

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.

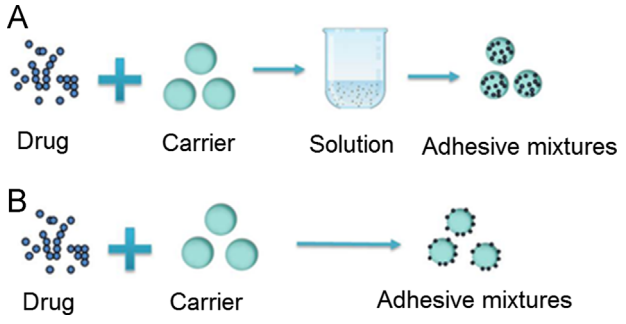

Figure 1 Two methods of combining drug and carrier for use in dry powder inhalers.

3. Interparticulate interactions

In the development of a DPI formulation, two types of interparticulate interaction should be taken into consideration *viz* the drug–drug cohesive force and the drug–carrier adhesive force[16]. The drug–carrier adhesive force fundamentally determines the performance of a DPI since excessive adhesion limits drug detachment from the carrier during aerosolization leading to poor drug dispersion[17]. Generally, the adhesion of a micron-sized particle to a solid surface is governed by physical forces (Fig. 2) including the van der Waals force[18], interlocking force[19], electrostatic force[20] and capillary force[21].

Under conditions where particles can dissipate excess electric charge and humidity is controlled, the van der Waals force is the dominant interaction and creates a so-called ''Velcro effect'' between particles[20,22]. The interlocking force is involved when drug particles fit into cavities upon intimate contact with the carrier surface[23]. The electrostatic force occurs when two materials with different surface charge come into contact and then separate[23,24]. The capillary force is developed due to the formation of a liquid bridge between particles which is influenced by the surrounding relative humidity and varies with the type of drug used in the formulation[21,25,26].

Overall, the contribution of these forces to particle adhesion is dependent on environmental conditions and several factors related to the particle such as its surface physical properties, mechanical properties[27], area, size and solid-state nature[26]. Because the performance of a DPI formulation depends on dissociation of drug from carrier particles and deaggregation of drug agglomerates during aerosolization, any factor that affects the drug–carrier interaction may also affect drug delivery and deposition[28]. To ensure an inhaled formulation is therapeutically effective, the interactions should be strong enough to ensure homogeneity and stability during powder handling but sufficiently weak to allow the formulation to be readily dispersed[18,29]. It is worth noting that the dispersion of a drug–carrier mixture is greatly influenced by the air velocity, the higher the airflow the greater the detachment of API particles from the carrier[30].

Several formulation approaches have been applied to improve the aerosolization performance of drug–carrier adhesive mixtures. They generally focus on minimizing the intrinsic cohesion of the powder and/or reducing the interaction between drug and carrier. Specifically, the approaches include particle size refinement[16], morphology design[31] and surface modification[32].

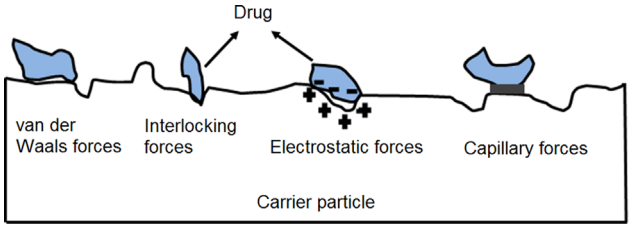

Figure 2 Physical interparticulate forces between the drug and carrier.

4. Mechanisms of aerosol generation and deposition

Unlike oral dosage forms, the efficiency of a DPI principally depends on the extent to which the drug particles in the formulation can be dispersed into an aerosol during inhalation[33]. Only free particles in the inhalatory airstream that have overcome the interparticulate forces within the bulk powder can be delivered deep into the lung. Therefore, one of the main challenges in the inhalation field is to reproducibly deliver the highest dose fraction of drug to the lung. Until now, most research into the development of DPIs has focused on improving the fine particle fraction (FPF) to generate an efficient aerosol by particle engineering of the carrier. FPF denotes the percentage relative to the total quantity of drug collected in the impactor or impinger that has a size ≤ 5 μm. The higher the FPF the better the aerosolization efficiency. FPF is influenced by the inhalation device[34], formulation[35,36] (characteristics and downstream processability of the carrier, drug to carrier ratio), and *in vitro* characteristics of the aerosol[37] (delivery time and rate of delivery).

However, the mechanism of aerosol generation by a DPI remains complex. The scheme of airway geometry shown in Fig. 3 indicates that the airway can be divided into two distinct zones *viz* the conducting zone and the respiratory zone[38]. The conducting zone consists of the first 16 generations beginning with

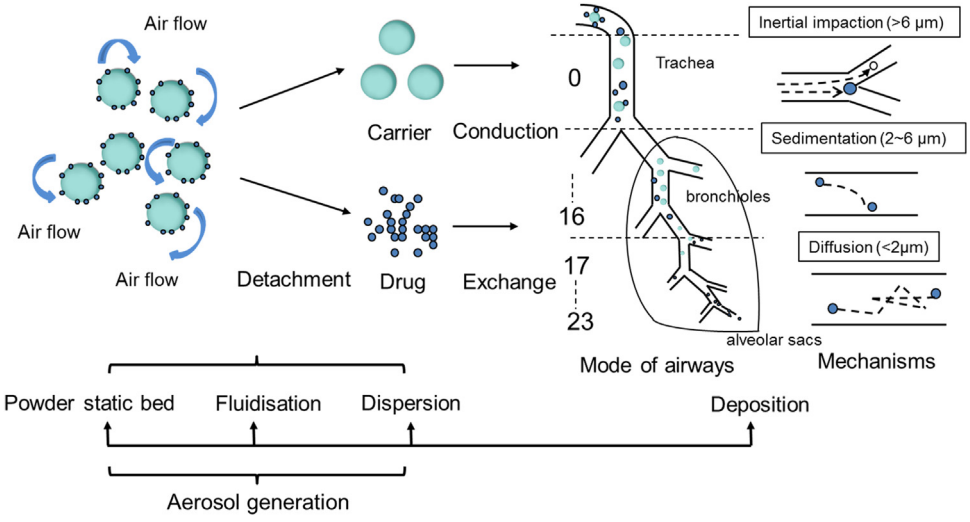

Figure 3 Mechanisms of aerosol generation and deposition of drug in the airways for a dry powder inhaler.

the trachea (generation 0) and ending with the terminal bronchioles (generation 16). Its main function is to allow the bulk flow of air to move into and out of the lung during each breath. The respiratory zone is where gas exchange occurs. It starts at the respiratory bronchioles (generation 17) and terminates at the alveolar sacs (generation 23). In moving from trachea to alveolar sacs, there are two pronounced physical changes along the airways; the airway caliber decreases and the cross-sectional area of the airways increases as the number of airways increases[12]. These changes lead to variations in air flow velocity and airway surface area which have significant effects on drug deposition in the lung.

According to Hickey et al.[39], the aerosolization process can be roughly divided into four consecutive phases: detachment from the static powder bed, fluidization, entrainment and drug resuspension (Fig. 3). The powder bed remains static until the airflow generated by the DPI device transfers kinetic energy into the bed causing powder deaggregation. Powder fluidization is the process in which the powder mass disturbed by the airstream exhibits "fluid-like" properties[40]. It is primarily governed by the packing properties of the powder which are closely related to the physical properties of the particles and their interfacial interactions[41]. Following fluidization, the powder is entrained into the airflow[42], and these two processes are critical in the ability of a DPI to generate a therapeutically effective aerosol. Drug resuspension is mainly performed by deagglomeration forces including turbulent, inertial and impacting stresses and is followed by deposition of drug in the respiratory tract[39].

Typically, there are three mechanisms (Fig. 3) governing particle deposition in lung airways. (1) Inertial impaction: this involves inertial deposition of particles onto the airway surfaces and mainly occurs close to bifurcations of the large conducting airways[43]. Most large particles (>6 μm) are deposited in the oropharyngeal and large airways because they are unable to follow the directional changes of the inspired airstream particularly in the oropharynx and at airway bifurcations. Thus loss of drug due to inertial impaction in the oropharynx is the major hurdle to achieve lung deposition using a passive dry powder device[44]. (2) Gravitational sedimentation: this usually involves small particles in the size range 2–6 μm and occurs in the small conducting airways where the airflow velocity is slow[12]. (3) Diffusion: this involves small particles (<2 μm) for which Brownian motion is important and occurs in the small airways and alveoli where the airflow is negligible[12]. Overall, aerosol generation results from a competition between interparticulate interactions within the adhesive mixture and separation forces resulting from the inspiratory airflow through the inhaler.

5. Influence of carrier characteristics on aerosol performance

5.1. *Particle size*

It is well recognized that particle size of the carrier plays a dominant role in the aerosolization performance of carrier-based DPI formulations. However, there is, as yet, no consensus on how carrier particle size affects DPI performance. One study reported that reducing particle size improves the amount of respirable drug delivered from a DPI[16] but has adverse effect on drug content uniformity and results in more drug deposited in the oropharyngeal region[16]. Interestingly, carrier particle size does not necessarily impact negatively on drug deposition after inhalation and in another study a higher FPF was observed[45]. These conflicting results could be due to the interdependence of physical properties. Whatever the case, particle size must be optimized to provide efficient aerosolization and overcome the disadvantages of small particles.

To establish the optimum particle size of aerosols, it is important to take into account the physical properties of carrier particles including their shape, surface roughness, density and geometric diameter[43]. The effect of these variables on aerosol performance has been studied by Ooi et al.[46] using three model polystyrene spheres with $d_{0.5}$ values of 82.8, 277.5 and 582.9 μm as carriers. The results showed that aerosol performance increased as particle size decreased, a finding ascribed to the decreasing particle size, including decreased number of drug particles per carrier and the increases in particle number, surface area, inter-carrier adhesion and number of collisions in the powder bed during

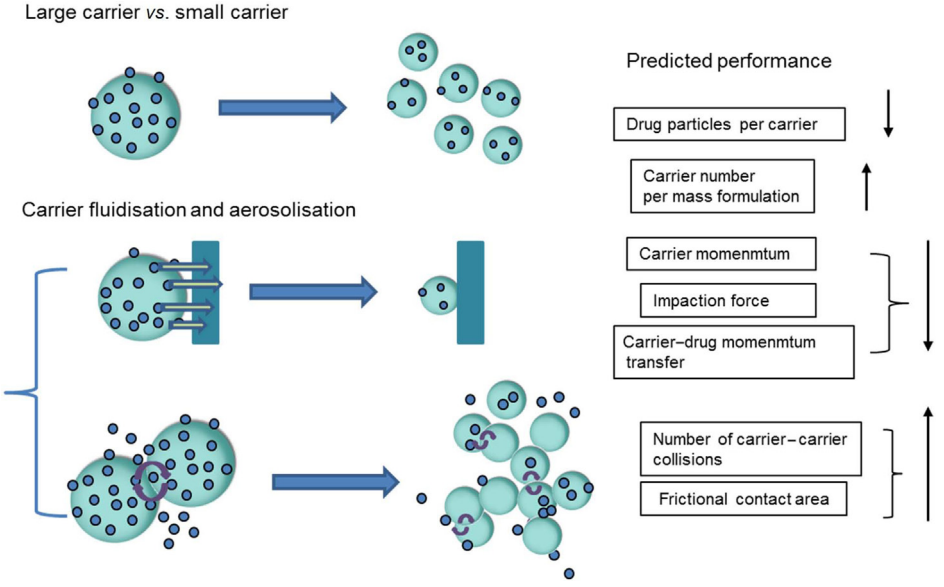

Figure 4 Concurrent changes of powder fluidization and aerosolization as a function of particle size (↑ increase, ↓ decrease).

aerosolization (Fig. 4). Drug release appears to be primarily driven by the number of frictional and rotational collisions rather than conventional momentum transfer.

5.1.1. *Particle size distribution*

Particle size distribution is important in terms of aerosol quality and efficiency[47]. It is commonly evaluated by determining polydispersibility (PDI) which is calculated according to Eq. (2). A larger value of PDI of the carrier indicates a wider particle size distribution, and produces a more heterogeneous mixture with drug. This may lead to higher variability in lung deposition of drug upon inhalation[16].

$$\mathrm{PDI} = \frac{d_{90} - d_{10}}{d_{50}} \tag{2}$$

Measurement of particle size and particle size distribution can be conducted using sieving, optical microscopy, and laser diffraction particle size analyzer. Sieving is considered to be a rough method in determining particle size because it does not give exact measurements of any dimension of the particles[48]. Microscope image analysis is used for umber-weighted size measurement, while laser diffraction volume is used for weighted size measurement. On the other hand, the accuracy of size measurement by laser diffraction is affected by the particle shape and surface properties. Particles with irregular shape and rough surface morphology may lead to "overestimated" size measurements, as observed by Kaialy et al.[49].

5.1.2. *Role of fine carrier particles*

The inclusion of a small amount of fine carrier particles (fines) in a DPI formulation is a well-researched technique to improve DPI performance. The actual definition of fines is unclear in the literature but there is agreement that fines have a small particle size compared to coarse particles[10,13,23]. It has also been suggested that fines with similar geometric size to that of the API should be used[50]. However, the optimum diameter of fines for use in a DPI formulation has not reached a consencus[51].

There have been numerous studies investigating how fines affect the performance of DPI formulations with contradictory results. Some studies showed that a small quantity of fines included in a powder formulation could increase the deaggregation efficiency and therefore the therapeutic efficacy of the DPI[52,53]. However, Hamishehkar et al.[54] demonstrated that the addition of fines with spray dried mannitol and leucine decreased both the deposition and dispersibility of microcapsules. Steckel et al.[55] also reported that the presence of fines caused a decrease in FPF. Several hypotheses to explain how the presence of fines affects the aerosolization performance of a DPI have been proposed based on studies of lactose fines. These include the active-sites[56], agglomeration[52] and fluidization theories[57], the buffer hypothesis[58] and case-dependent[59] theory. With the exception of case-dependent theory, these theories address the positive effects of fines on the dispersion performance of adhesive mixtures. However, the long-term safety of excipients for use as fines remains to be established and is a matter of concern to regulatory authorities[51]. For example, fines may cause irritation, coughing and even bronchoconstriction[60] and in the case of inhaled mannitol can increase bronchial hyperresponsiveness[61].

5.1.2.1. Active-sites theory. This was first introduced by Hersey[62] and subsequently widely applied to understand the behavior of adhesive mixtures. The so-called "active sites", defined as areas on the carrier surface that are more adhesive than others (Fig. 5A), are preferentially occupied by fines leaving the weaker binding sites to be occupied by drug particles[23,59]. However, Grasmeijer et al.[63] pointed out that a specific definition of "active sites" has never been established and that the theory is ambiguous in

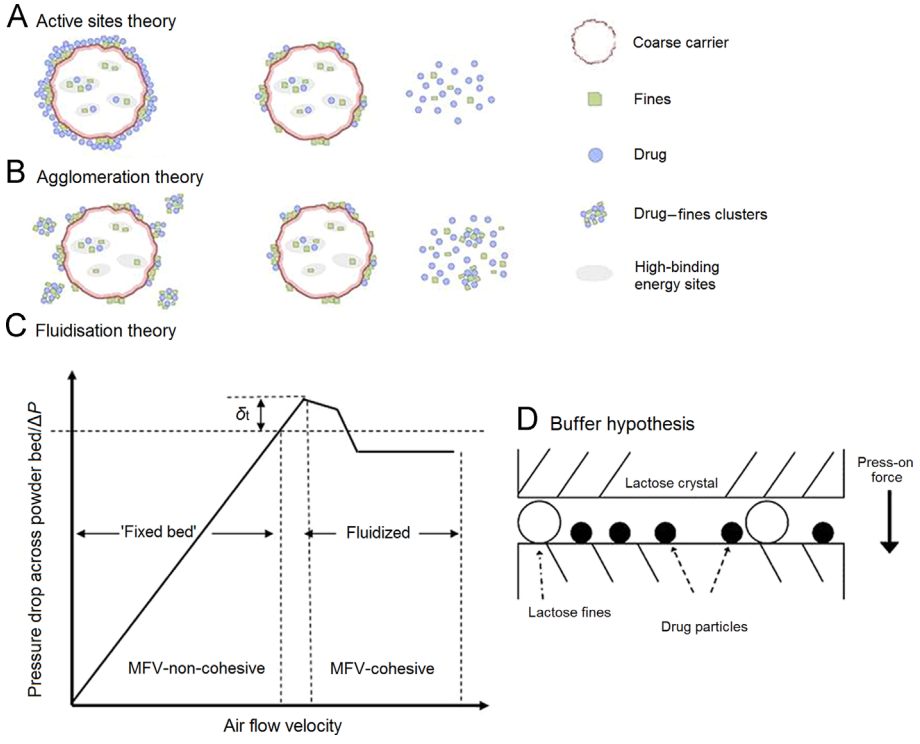

Figure 5 Theories and hypothesis describing the effect of fine carrier particles on the aerosolization performance of a dry powder inhaler: (A) "Active sites theory"; (B) "agglomeration theory"; (C) "fluidization theory" and (D) "buffer hypothesis" (modified from Refs. 47 and 48.

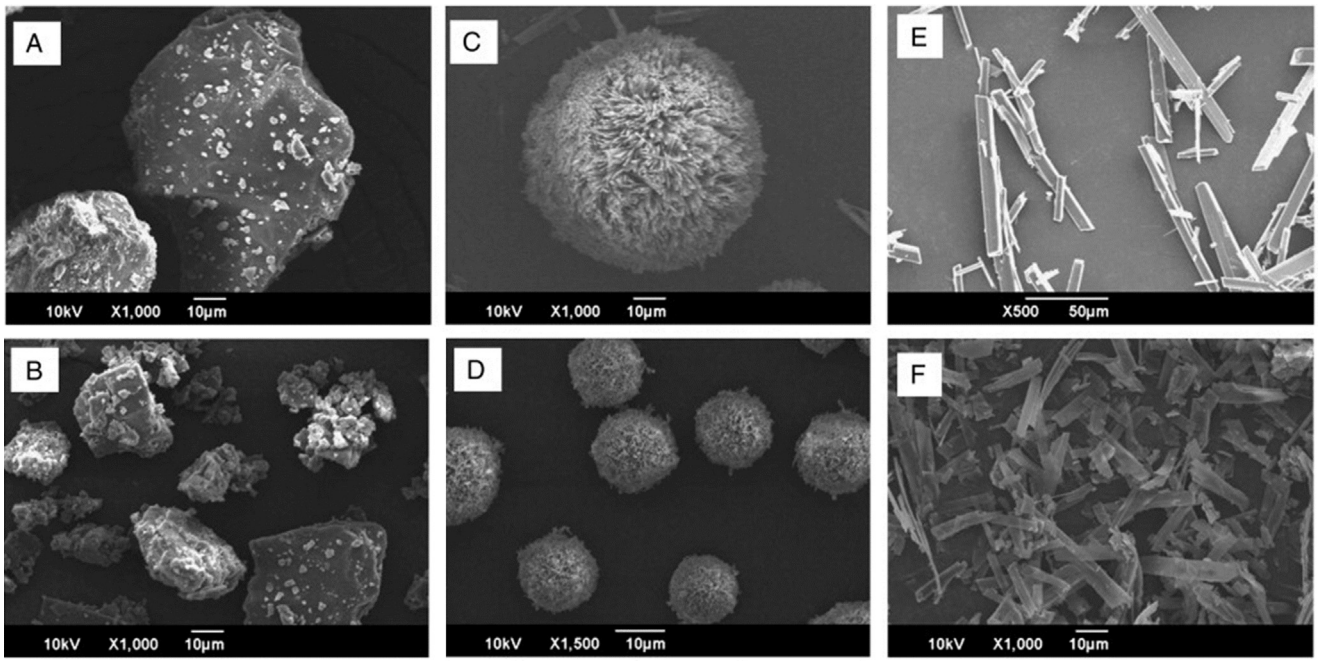

Figure 6 Scanning electron microscopy images of (A) large CL, (B) small CL, (C) large PL, (D) small PL, (E) large NL, and (F) small NL carrier particles (reproduced from Ref. 65 with permission).

predicting how active sites affect the performance of a powder for inhalation. As a result, "active sites" have been newly defined based on their ability to retain drug during dispersion which depends on the physical properties of the carrier surface, formulation and dispersion conditions. A rational choice of such conditions is of utmost importance in studies concerning carrier surface site activity.

5.1.2.2. Agglomeration theory. According to this theory and as shown in Fig. 5B, the improved DPI performance due to the presence of fines results from the formation of drug-fine agglomerates. These are more likely to be removed from the carrier particle surface than free API particles due to the greater aerodynamic drag force acting on agglomerates[64].

5.1.2.3. Fluidization theory. As illustrated in Fig. 5C, fluidization of a DPI formulation occurs when the pressure drop across the static powder bed is equivalent to the weight of the powder[40]. This pressure threshold is referred to as the point of incipient fluidization or minimum fluidization velocity (MFV)[42]. The addition of fines improves DPI performance by increasing the tensile strength of the formulation which is directly related to interparticulate forces and the free volume of the carrier. This significantly shifts the MFV and thereby increases the aerodynamic drag force exerted to fluidize the powder bed[57].

5.1.2.4. Buffer hypothesis. The commercially available brands of alpha-lactose monohydrate normally exhibit surface rugosity and carry natural fines and impurities on their surface which may influence their interaction with drug in adhesive mixtures for inhalation. In a study involving submerging lactose in ethanol–water mixtures, Dickhoff et al.[58] found that submersion removed the adhering lactose fines leading to a decrease in drug particle detachment without affecting the shape or size of carrier particles. This is the basis of the buffer hypothesis (Fig. 5D) which states that the adhering lactose fines act as a buffer between colliding carrier particles and protect smaller drug particles attached to the same crystal planes from the press-on forces that cause increased drug particle detachment during inhalation[58].

5.1.2.5. Case-dependent theory. Contrary to the mechanisms described above, Grasmeijer et al.[59] pointed out that fines do not always improve the aerosol performance of a DPI which is determined by the formulation and dispersion conditions. They studied the effects of "fine lactose fines" (FLF) with similar size and shape as micronised budesonide on drug detachment and compared the results with those obtained using "coarse lactose fines" (CLF) at varying inhalation flow rates, drug contents and mixing orders. It was found that the presence of CLF resulted in higher detachment of drug at all flow rates and drug contents and the effects of FLF were negligible at high drug content. These results implicate two new mechanisms. First, fines below a certain size reduce dispersion performance probably by increasing the effectiveness of press-on forces or the formation of coherent fine particle networks on the carrier surface. Secondly, the CLF may weaken or prevent the formation of fine particle networks possibly through lowering tensile strength.

5.2. *Morphology/shape*

The morphology/shape of carrier particles exerts a dominant effect on the aerosolization performance of a DPI[31]. Particles with different shapes may be subject to different drag forces and terminal velocities during aerosolization which, in turn, affect their deposition in the respiratory airways[47].

The effect of particle shape on aerosolization performance has been widely investigated. Kaialy et al.[31] examined carriers with different morphologies to investigate the effect of elongation ratio (ER). They concluded that the higher the ER the greater the delivery of salbutamol sulphate to the lower airway regions of the lung, indicating enhanced DPI performance. However, this

improvement was restricted to values below a certain "limit" since the higher the ER the more the drug remained in the inhaler device and deposited in the throat. Using lactose as a carrier, Kho et al.[65] also investigated the effect of carrier particle shape in two size ranges (*i.e.* 50–70 μm and 14–20 μm) (Fig. 6)[65] on aerosolization efficiency of drug–carrier particle blends containing amorphous nanoparticles of drug. The results revealed that lactose particles of tomahawk shape gave similar aerosolization efficiency to those with needle and pollen shape for both large and small carrier particles, a finding contrary to that of a previous study using drug microparticles[66–68]. Needle shaped carrier particles generally have a high ER which allows drug deposition in the small airways[44] resulting in more effective drug deposition in the lung[66]. Pollen shaped carrier particles with low density bind drug for longer periods and thereby give higher lung deposition[67,68]. According to Hassan et al.[67], pollen-shaped carrier particles give a higher FPF and reduce drug loss especially at low flow rates and high drug content. However, size and surface morphology of carrier particles can have opposing effects as indicated by the fact that an increase in particle size has a mild effect on emission dose (ED) but may significantly improve the FPF while a sparse surface has negligible effect on the ED at low flow rates but improves the FPF.

As shown in Table 1[7,16,28,31,69,70], shape analysis is commonly conducted using scanning electron microscopy (SEM), optical microscopy or some other imaging technique. The parameters used to quantify particle shape include ER, flatness ratio (FR), roundness (RO), shape factor (F_{shape}), angularity, and surface factor ($F_{surface}$).

ER and FR are considered to be first order shape descriptors[71]. ER is a measure of the irregularity of particles which reflects overall particle shape elongation[72]. A higher value of ER indicates a more elongated/irregular shape and/or a rougher surface[73] and follows a similar trend as RO. Carrier particles with high ER and RO values are likely to exhibit pronounced internal friction due to their angular shape and are expected to produce different aerosolization characteristics[74,75]. It has been reported that carrier particles with high ER can significantly increase the amount of drug delivered to lower airway regions of the lung but only up to a certain level. However, carrier particles with high ER are disadvantageous in DPI dose metering and processing at handling scale due to their poor flowability[31]. A high FR is indicative of a more flattened shape[7], while a high value of ER/FR is indicative of a more elongated/less flattened particle shape. Smooth spheres and perfect cubes have ER and FR of 1.

F_{shape} and angularity are second order descriptors of particle shape irregularity[7,71]. The value for F_{shape} ranges from -1 to 1 where a smooth sphere has F_{shape} of 1[70] and a smaller F_{shape} value indicates greater shape irregularity and/or rougher particle surface[7]. Particle angularity is independent of particle ER[76]. However, values of F_{shape} and ER alone may be insufficient to describe the effect of particle shape since these parameters are functions of particle orientation and contact area only which can influence the accuracy of shape assessment using microscopic image analysis[70,77]. SEM is also needed to characterize qualitatively the three dimensional shape and surface morphology of carrier particles.

$F_{surface}$ is a third order shape descriptor which refers to surface roughness only[7]. Cubic particles with smooth surface are expected to have $F_{surface}$ of 1, and a smaller $F_{surface}$ value indicates a rougher surface.

Of these various shape descriptors of particles, ER is solely determined by their macroscopic shape while rugosity and F_{shape} are dependent on both macroscopic shape and surface texture.

Table 1 Shape descriptors and characterization methods to evaluate particle shape or morphology.

Shape descriptor	Order rank	Equation	Determination method	Ref.
Elongation ratio (ER)	First	$ER = \frac{L}{w}$	Optical microscopy or scanning electron microscopy (SEM)	28,69
Flatness ratio (FR)	First	$FR = \frac{L}{w}$	Optical microscopy	7
Roundness (RO)	—	$RO = \frac{p^2}{4\times\pi\times A}$	Optical microscopy	31
Shape factor (F_{shape})	Second	$F_{shape} = \frac{4\times\pi\times A}{p}$	Optical microscopy	70
Angularity	Second	$Angularity = \frac{P_{convex}}{P_{ellipse}}$	Optical microscopy	16
Surface factor ($F_{surface}$)	Third	$F_{surface} = F_{shape} \times \frac{(1+ER)^2}{\pi\times ER}$	Optical microscopy	7

A, the estimated area of the particle;
Angularity, a parameter to quantify particle shape;
L, length, the maximum Feret diameter;
p, Perimeter, the estimated perimeter of particle with compensation for corners;
P_{convex}, perimeter of the minimum convex boundary circumscribing the particle;
P_{elipse}, perimeter of fictitious equivalent ellipse which has the same area and the aspect ratio of aggregate particle;
w, width, the minimum Feret diameter;
—, there has been no rank order designated for RO.

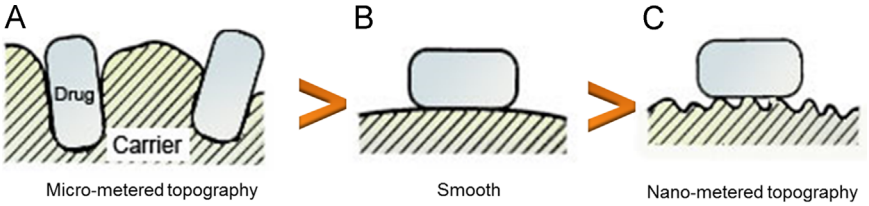

Figure 7 Carrier particles with three different sizes of surface roughness; (A) micrometer topography, (B) smooth, and (C) nanometer topography (modified from Ref. 78).

Table 2 Characterization methods to determine surface roughness of carrier particles.

Characterization method		Equation	Result	Ref.
Direct method	Atomic force microscopy (AFM)	$R_{RMS} = \sqrt{\frac{1}{n}\sum_{i=1}^{n} y_{i=1}^{2}}$	No significance between the surface roughness of composite carriers and regular carriers was observed due to the increased variability in sample morphology of the regular carrier.	8
	Scanning electron microscopy (SEM)	$R_a = \frac{1}{l}\int_0^l \lvert z(x) \times dx$	Particles produced at large scale exhibited changes not only in surface roughness but also in shape at varying outlet temperatures. A decrease in surface roughness led to a lower FPF.	29
	Confocal laser scanning microscope (CLSM)	—	The obtained roughness profiles were consistent with results of SEM image analysis and showed distinct trends. In general, rough particles obtained at low outlet temperatures were spherical, whereas higher drying temperatures resulted in particles with multiple surface indentations and smoother surface. Different roughness was a result of underlying crystallization processes.	15,82,83
	Particle image analysis	$\text{Roughness} = \frac{\text{Perimeter}}{\text{ConvexPerim}}$	All crystallized particles had rougher surfaces than the commercial lactose, leading to improved drug aerosolization performance due to lower drug–carrier adhesion forces.	70
Indirect method	Colloid probe microscopy	—	Median force ($F_{0.5}$) value was chosen as the best descriptor of drug–carrier adhesion force. The values for polymer coated/uncoated carriers followed a rank order of PVP coated > un-coated > EC coated lactose, which showed an opposite trend of FPF.	86,89,90
	Air depression sieving	—	It was considered as a simple method to evaluate drug–carrier adhesion force, based on the aspiration principle that the whole blend used in DPI was taken into account. The detailed procedure was presented by Le et al.[91]. Greater drug–carrier adhesion force was obtained under higher humidity, leading to decreased FPF. Kaialy et al.[7] also used this method to evaluate the adhesion force between salbutamol sulphate and different lactose grades in the same size range, demonstrating that lactose particles with more elongated/irregular shape, and rougher surface were preferred to improve FPF.	7,91

ConvexPerim, circumscribed particle perimeter;
l, length;
N, the number of data points in a topographical profile;
Perimeter, estimated particle perimeter;
R_a, the mean R_a values of several line profiles over the analyzed surface;
R_{RMS}, surface root mean square roughness;
y_i, the distance of asperities (i) from the center line;
Z, the deviation of all points from a plane fit to the test surface over sampling length l;
—, no equation was reported for the method.

Neither rugosity nor F_{shape} can distinguish the surface smoothness of two particles if they differ substantially in macroscopic shape. Therefore, in order to accurately compare the surface smoothness of particles with different ER values, a new shape descriptor, S_{rec}, was introduced by Zeng et al.[28]. S_{rec} is a factor that assumes a rectangular shape and takes both F_{shape} and ER into consideration.

5.3. *Surface roughness*

For efficient delivery of drug deep into the lung, drug particles need to be efficiently loaded onto and liberated from the carrier, processes which are largely dependent on characteristics of the contact area. Most pharmaceutical grade carriers for use in DPIs have particles with a certain amount of surface roughness[67] which can be categorized into three groups (Fig. 7)[78]. First, carrier particles of micrometer topography generally have a large contact area for micronized drugs to adhere to, resulting in strong interaction and poor aerosol efficiency. Additionally, entrapment of drug in the cavities or valleys of the carrier surface may further reduce drug–carrier detachment. Secondly, carrier particles of nanometer topography can provide binding sites for drugs which are favorable for drug detachment from the carrier surface after inhalation thus contributing to higher FPF values[7]. Thirdly, carrier particles with smooth surfaces also have a large contact area for drug attachment leading to poor drug–carrier detachment. Therefore, only carrier surface irregularity of a certain scale, namely nanometer topography, provides a sufficiently low total contact area for drug to bind with weak adhesive forces[78]. Particles with large surface irregularity (micrometer topography) or irregularity approaching zero (smooth) bind drug with strong adhesive force.

Reports about the influence of surface roughness on aerosolization performance of a DPI are contradictory. For example, Kaialy et al.[7,79] found that rougher lactose particles showed a smaller adhesion force with salbutamol sulphate and produced enhanced DPI performance. In contrast, Flament et al.[80] found a linear relationship between lactose roughness and FPF, the rougher the lactose surface the greater the adherence of terbutaline sulphate and the lower the FPF. This linear relationship can be explained as due to an increase in contact points between drug and carrier as surface roughness increases. This stabilizes the blend but leads to less drug deaggregation from carrier when the blend is carried by an airflow. Since particle size and shape also influence interparticulate forces, study of the influence of carrier surface properties on aerosol performance of a DPI becomes even more difficult. In one study, glass beads with different surface roughness but the same size and shape were used as model carriers to investigate the relationship[81]. The surface-modified glass beads were produced in a ball mill using different grinding materials and grinding times followed by plasma etching. The results indicate that the greater the surface roughness the higher the FPF.

These conflicting findings reveal that, in order to increase FPF, an optimum level of surface roughness is needed. They also suggest that modifying surface morphological properties is an effective way to alter particle interactions and improve aerosol performance. To date, various techniques have been employed to modify the surface roughness of carriers in order to achieve a high FPF value. These include mechanical milling[11], spray drying[82,83], freeze drying[47], anti-solvent precipitation from different media and under different crystallization conditions[31,84], polymer coating *via* spray drying[85], dry mechano-fusion[29], adding fine particles to fill in carrier "active sites"[23,59], and adding agents such as leucine[86], magnesium stearate[87], and polaxamer[88] to reduce surface passivation of high surface free energy sites.

Since surface roughness is closely related to surface energy and the adhesion force between drug and carrier, its assessment using direct and indirect methods is very important (Table 2[7,8,15,29,70,82,83,86,89–91]). Atomic force microscopy (AFM), SEM, confocal laser scanning microscopy (CLSM) and particle image analysis can directly provide data related to surface roughness. The drug–carrier adhesion force can also be measured by colloid probe microscopy and air jet sieving.

6. Conclusions

Carrier physical properties, such as particle size, morphology, and surface roughness, play significant roles in determining DPI performance since they directly influence the adhesion and detachment of drug and carrier. Studies of the effects of these properties on drug aerosolization efficiency have given controversial results for two main reasons. First, a complete understanding of the independent influence of each property remains challenging as the properties are interdependent. Secondly, most studies have focused on one property and given less attention to others. Despite these limitations, it is clear that higher drug deposition is achieved by reducing the adhesion force of drug and carrier in mixed DPI formulations.

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