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REVIEW

Surface modification strategies for high-dose dry powder inhalers

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Abstract

Background There is a growing interest in the use of dry powder inhalers (DPIs) for administering high-dose drugs with low potency to the lungs as carrier-free formulations to treat both local pulmonary and systemic diseases. The main purpose of particle engineering and formulation design in the development of high-dose DPIs without carrier is to reduce the cohesive property of the particles and overcome the large inter-particulate interaction while enhancing powder dispersion and lung delivery upon inhalation and maintaining stability without agglomeration during storage. In particular, the cohesive property of high-dose DPIs can induce several physiological and physicochemical problems that must be improved.

Area covered This review describes various particle surface modification methods, including sophisticated particle engineering (such as micronization) and formulation techniques, which are utilized to overcome the problems associated with high-dose DPIs.

Expert opinion Currently, changing the cohesive property of particles through various micronization processes and improving the surface properties of particles through co-processing with limited excipients have been mainly used as efficient methods for particle surface modification. Using these technological principles, novel approaches have been attempted to develop inhalable drug particles, such as high-dose antibiotics and high-value biopharmaceuticals. The research on high-dose DPIs has expanded widely, and consequently, the drugs that received recent regulatory approvals have been successful based on the research results. Thus, it is expected that the next generation of DPIs will be safer and have higher therapeutic efficacy beyond the limitations of traditional high-dose DPIs.

Keywords High-dose dry powder inhaler · Surface modification · Cohesive property · Stability · Particle engineering · Formulation

Introduction

Dry powder inhalers (DPIs) are promising for pulmonary drug delivery. They have various advantages including rapid delivery of therapeutic drugs without a propellant, low risk of microbial contamination, and improved physicochemical stability in the solid state, compared with pressurized metered dose inhalers and nebulizers (Brunaugh and Smyth 2018a, b). Pulmonary delivery of low-dose active pharmaceutical ingredients (APIs) as a DPI has been used widely to treat various diseases, primarily to locally treat asthma and chronic obstructive pulmonary disease (Sibum et al. 2018). These low-dose drugs include corticosteroids, β2 agonists, and muscarinic antagonists (Brunaugh and Smyth 2018a, b). However, as these agents are potent, they require doses at the microgram level to achieve the desired therapeutic effect with low systemic side effects (Smith and Parry-Billings 2003). Unfortunately, not all drugs have high potency; thus, high-dose DPIs with low potency are receiving increasing scientific interest (Farkas et al. 2015; Yazdi and Smyth 2016; Scherließ and Etschmann 2018). The interest in the pulmonary delivery of high-dose drugs has increased, and the significant advantages of high-dose DPI compared with oral or parenteral drugs have been shown. Targeted delivery of drugs to the lungs at high local concentrations with low systemic side effects is the main advantage, which will lead to improved therapeutic efficacy

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and rapid local and systemic responses (Sibum et al. 2018). Based on these specific advantages, DPIs can be a promising alternative to the conventional administration routes for the delivery of high-dose drugs (Scherließ and Etschmann 2018); for example, to deliver high-dose antibiotics for the treatment of tuberculosis (TB) and cystic fibrosis caused by *Mycobacterium tuberculosis* (Chan et al. 2014) and *Pseudomonas aeruginosa* (McKeage 2013), respectively. The local administration of antibiotics to the lung can maximize the concentration of API in the infected tissue. In addition, this route of administration leads to reduced systemic side effects compared with the oral route.

Moreover, the delivery of high-dose drugs to the lung has been studied for the systemic therapeutic efficacy of drugs such as insulin (Al-Tabakha 2015), which is a systemically acting API (Corcoran et al. 2013; Ali and Lamprecht 2014). Another advantage of pulmonary delivery of high-dose drugs is enhanced bioavailability, which is achieved through limitation of first-pass metabolism and the capacity of large molecules to be absorbed by the lower respiratory tract (Labiris and Dolovich 2003; Hoppentocht et al. 2014). Furthermore, lung macrophages that can limit infectious bacteria can also be targeted (Ahsan et al. 2002; Patel et al. 2015). The development of high-dose DPIs may also be needed for sustained-release formulations (Cook et al. 2005; Learoyd et al. 2009; Aragao-Santiago et al. 2016).

High-dose antibiotics, including colistin and tobramycin, have already been developed on the market as high-dose DPI products (Claus et al. 2014). In line with these developments, further expanded research is performed on other antibiotics and antiviral agents, such as amikacin, kanamycin, gentamycin, and isoniazid. TOBI® Podhaler™ (Novartis) is an inhalation product designed for the application of high-dose tobramycin powder to the lungs (VanDevanter and Geller 2011). Most of the reported side effects were mild to moderate in intensity. Therefore, the good tolerability and safety of high-dose drugs in the lungs following administration via a DPI can be estimated. Nevertheless, for the actual development of new high-dose DPIs, many challenges remain to be overcome (Healy et al. 2014; Brunaugh and Smyth 2018a, b; Scherließ and Etschmann 2018; Sibum et al. 2018).

Current issues of high-dose DPIs

Pulmonary drug delivery requires a respirable fraction of the high-dose DPI formulation to be delivered to the central and peripheral regions of the lung. This is achieved by the fine particle fraction (FPF) of an aerodynamic particle size below 5 µm or more preferably between 1 and 3 µm to obtain substantial central and deep lung deposition (Labiris and Dolovich 2003; Carvalho et al. 2011). The particle size reduction to the micron range for efficient pulmonary delivery of a drug powder leads to an increase in the surface area of the particles (Brunaugh and Smyth 2018a, b). When particle size is reduced, the forces of surface interactions, including Van der Waals (VdW) force, capillary force or liquid bridging, electrostatic force, and mechanical interlocking, can be larger than the gravitational force (Visser 1989; Dunber et al. 1998; Castellanos 2005; Weiler et al. 2010). Even though inhalable drug particles are small enough to be delivered via the pulmonary route, they can be subjected to adhesive and/or cohesive force. These inter-particulate forces are difficult to overcome for efficient aerosolization and reproducible delivery of drugs to the lung (Telko and Hickey 2005; Brunaugh and Smyth 2018a, b) (Fig. 1). In particular, the increased surface interactions induce both cohesion between micronized particles and adhesion between particle and inhaler devices, causing poor flow and/or aggregation of inhalable dry powders, rendering them unsuitable for powder handling and efficient device dispersion (Feeley et al. 1998a, b; Steckel et al. 2003; Hickey et al. 2007; Scherließ and Etschmann 2018). Furthermore, both in vitro aerosolization performance and in vivo drug deposition studies indicated that the amount of drug fractions delivered from DPIs in the required aerodynamic size fraction is quite low and that the dose delivered to the lungs from a DPI is considerably lower than the label claim (de Boer et al. 2017). This is due to drug losses in inhaler and substantial deposition in the mouth–throat region, called the oropharynx. The undesired loss of drug particles during pulmonary drug delivery via high-dose DPIs often represents more than 50% of the delivered dose. A probable cause for this poor performance and delivery efficiency of high-dose DPIs is the strong inter-particulate forces in the formulation. Particle agglomeration induced by these forces occur due to changes in the physical properties of the DPI over time during the distribution and storage periods. In addition, drug particles deposited in the oropharynx cannot exert their therapeutic effect but may cause unexpected side effects both locally and systemically (Rachelefsky et al. 2007). Owing to the severity of these issues, the reproducible dispersion property of inhalable dry powders has been regarded as a major challenge in the development of high-dose DPIs (Yang et al. 2014).

Nevertheless, for a DPI formulation to be dispersed and aerosolized from an inhaler device, it must undergo de-agglomeration following powder fluidization. In other words, the powder formulation should de-agglomerate during the inhalation process through the shear forces formed in the inhaler device even if it is unstable and agglomerated (Shetty et al. 2020). However, this is difficult to achieve in practice. The powder aerosolization properties for high-dose DPIs, are related to the powder dispersion, governed by the complex interaction between inspiration flow of patient, the powder aerosolization mechanisms of

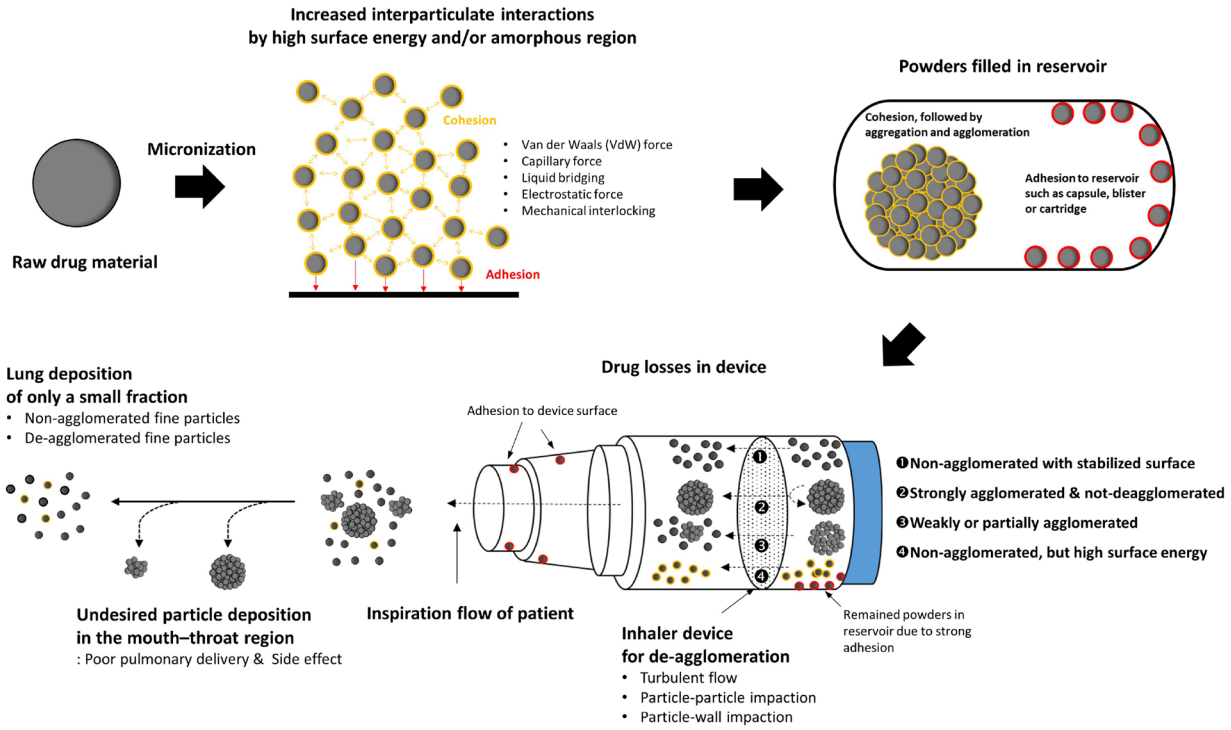

Fig. 1 Current issues and barriers to high-dose inhalable dry powder delivery

device such as turbulent, shear force and impaction stress, and the formulation. The inspired air interacts with the device to de-agglomerate the powder and then aerosolization of de-agglomerated fine particles suitable for lung deposition (Yang et al. 2014). In addition, for efficient de-agglomeration of powder, then fluidization, dispersion, and successful deposition of drug particles in the desired region of the lungs, the energy provided by the patient's own inhalation efforts is important. The amount of powder that can be administered via inhalation is determined by the inhalation volume based on the patient's inhalation capacity (Weers 2015; Weers and Miller 2015). Thus, variations in the inhalation volume and inspiratory profile of patients could be a particular concern for high-dose DPIs, as the desired dose may not be fully dispersed from the device. This could lead to suboptimal dosing caused by an increase in the amount of deagglomerated particles remaining in the capsule or blister within the device, inhaler losses, particularly in pediatric or elderly patients with reduced lung capacity (Ibrahim et al. 2015; Brunaugh and Smyth 2018a, b). This indicates that the poor aerodynamic and therapeutic performance of high-dose DPIs due to the agglomeration of the powder itself can become more serious when the poor device and the low patient inspiratory flow rate occur at the same time. Therefore, it is important to balance aggregation and de-aggregation of powders during the time of distribution and storage until use by patients.

Efforts for the development of a new inhaler device have been made to improve devices to eliminate this problem; however, current inhalation devices are not designed perfectly to disperse and deliver large amounts of agglomerated powder in one shot (Brunaugh and Smyth 2018a, b). Thus, the package labeling of several high-dose DPI products; TOBI® Podhaler™ containing tobramycin developed by Novartis (VanDevanter and Geller 2011), Colobreathe® containing colistimethate sodium developed by Forest Laboratories (Schuster et al. 2013), and Inavir® coantining laninamivir octanoate developed by Daiichi Sankyo Co., Ltd. (Brunaugh and Smyth 2018a, b) directs patients to inhale at least two times from the capsule. This instruction ensures that the capsule is completely emptied and most particles are fluidized and dispersed from the device. This complex administration procedures involving multiple steps not only increase patient errors but also decrease patient compliance and adherence.

For this reason, it was proposed that formulation strategies in combination with particle engineering technologies that promote the rapid fluidization and dispersion of powders from the device are more promising than the development of a new inhaler device. This means that it is of paramount importance that the resulting formulations should be stable

during both handling and storage to overcome efficiently the agglomeration of inhalable microparticles, despite such suggestion by some researchers, it is still generally accepted that it is desirable to use the combinations of device development with particle engineering and formulation techniques which enable inhalable dry powders that minimize the physiologic variability among patients that arises from differences in oropharyngeal and airway anatomies and in breathing profiles through maximizing bypass the mouth and throat (Weers and Miller 2015). The most common formulation approach to address main hurdle in the delivery of DPI formulations to the lungs is the use of interactive blends using a larger carrier excipient, which exploits the adhesion forces between micronized drug particles and carrier particles. However, this solution is only applicable for low-dose DPIs of high-potency drugs. For administering high-dose drugs with low potency, the traditional DPI formulation method utilizing large carrier particles to improve powder dispersion is not feasible because of the large powder volume (Hoppentocht et al. 2014; Weers and Miller 2015). Thus, for successful delivery of a high-dose inhalable dry powder, particle engineering approaches must be used to enhance the aerosolization of particles and appropriate micronization methods must be selected. Further, formulations with limited excipients must be rationally designed to optimally deliver the drug payload to the target site in the lungs (Telko and Hickey 2005; Hickey et al. 2007).

Both particle engineering and formulation strategies are closely related to the modification of particle properties, especially surface properties. Surface interactions controlled by various forces are affected by particle characteristics, such as intrinsic properties, particle size, crystallinity (or amorphous content), surface area, and roughness (Shetty et al. 2020). In particular, crystallinity, defined as the amorphous content in an inhalable dry powder, is important because moisture-induced crystallization may lead to physical instability of powders (Shetty et al. 2018a, b, c). Hence, various particle engineering and formulation methods to overcome cohesive surface forces have been explored by controlling the surface properties of these particles. This review will focus on these methods as strategies to deliver high doses of drugs with relatively low potency to the lungs.

Particle engineering technologies for DPIs and their impact on the particle surfaces

To improve powder flow and aerosolization performance, the physicochemical properties of the powders can be altered by applying an appropriate particle production method, modifying the operation parameters, and/or changing the formulation compositions (Begat et al. 2009). In particular, the conventional approach to improve the flowability and aerosolization of fine drug particles is reducing their intrinsic cohesiveness using particle engineering techniques without excipients (Adi et al. 2008a, b). In addition, to date, there are only a few pharmaceutical excipients approved for pulmonary delivery, including some sugars (lactose, mannitol, glucose), phospholipids or surfactants (1,2-Distearoyl-sn-glycero-phosphocholine, sodium lauryl sulfate), polymers (gelatin, carrageenan, hydroxypropyl methylcellulose), electrolytes or salts (sodium chloride, potassium chloride, trisodium citrate dehydrate, sulfuric acid), lubricants or glidants (magnesium stearate, silicon dioxide, titanium dioxide) and Fumaryldiketopiperazine (FDKP). Unfortunately, the degradation of sugars may have an effect on the stability of peptide drugs via interaction with amine groups (Maillard reaction) of API, it may cause many uncertainties. Many asthma therapeutic APIs such as budesonide and formoterol are also involved in decomposable drugs by sugars (Steckel and Bolzen 2004; Littringer et al. 2012; Lechanteur and Evrard 2020). In addition, sugars as a pharmaceutical excipient for pulmonary delivery is not suitable for patients with diabetes. Other substances such as phospholipids and bulking agents, and various biodegradable polymers not yet approved for pulmonary delivery (such as PLGA) can eventually trigger an adverse immune reaction in the lung, leading to cough, edema, and neutrophil infiltration (Xia et al. 2019). Considering the safety issues and the barriers to approval for clinical use of developed DPI formulation caused by using of new excipient, it could be more advantageous to tailor the desired particle surface properties with only the particle engineering technique without additives. These dry powder preparation methods are well-known to affect the surface properties of the drug particles of DPIs. Drug particles for DPIs can be produced using various particle engineering techniques for micronization, and these techniques can affect the aerosol performance of DPIs via changing in the morphology, size, and surface physicochemical properties of the drug particles, including the surface composition, energy, and roughness (Lin et al. 2015; Zijlstra et al. 2004; Shoyele and Cawthorne 2006; Kaialy and Nokhodchi 2015). This feature is applied more critically in high-dose DPIs.

For these reasons, the preparation of low-density inhalable dry particles with uniform size distribution has been researched for the development of high-dose DPI, based on above-mentioned particle engineering technologies without excipients (Begat et al. 2009). Thus, many reports have suggested that appropriate particle engineering techniques should be carefully selected for micronization, considering its importance in the development of an excipient-free high-dose DPI formulation (Hoppentocht et al. 2014; Lin et al. 2015). Various particle engineering approaches have emerged as alternative methods for the production of readily dispersed high-dose DPI formulations (Rasenack and Müller 2004; Tong and Chow 2006; Weers et al. 2007; Vehring

Table 1 Particle engineering technologies for the preparation of high-dose inhalable dry powder

Particle engineering technology	Key process condition	Typical particle characteristics	Representative application cases
Milling	Milling intensity, number of milling cycles, feed and grinding pressures (Brunaugh and Smyth 2018a, b)	Higher milling intensity resulted in higher FPF Too much stress-inducing conditions lead to decrease in FPF with large surface energy and cohesiveness	α-Lactose monohydrate (Steckel et al. 2006), Ciprofloxacin with L-leucine or MgSt (Mangal et al. 2019a, b, c)
Spray-drying	Atomizing air pressure	Non-porous corrugated particles showed enhanced aerosol performance over the smooth spherical particle	Bovine serum albumin (BSA) (Chew and Chan 2001)
	Drug solution consisted of a combination of solvent and antisolvent for drug material	Excipient-free nanoparticle aggregated nanoporous microparticles (NPMPs)	Bendroflumethiazide (Healy et al. 2008), Budesonide (Nolan et al. 2009), Sugar excipients (trehalose and raffinose) (Ógáin et al. 2011) (Amaro et al. 2011), Sodium cromoglicate (Nolan et al. 2011), Trypsin (NíÓgáin et al. 2012)
Spray freeze drying	Concentration of ingredient	Highly porous particle	Mannitol, Lysozyme, Bovine serum albumin (D'Addio et al. 2012), Budesonide (Parsian et al. 2014)
Supercritical technology	Temperature, pressure, use of organic solvents, and type and ratio of used organic solvent used	Particles with narrow size distribution suitable for inhalation, pure polymorph, or crystallinity	Terbutaline sulphate (Rehman et al. 2004)

2008; Kaialy and Nokhodchi 2015; Brunaugh and Smyth 2018a, b) (Table 1). Briefly, inhalable drug particles have been engineered using either "bottom-up" approaches, such as spray drying, spray-freeze-drying, and supercritical fluid (SCF) technology, or "top-down" approaches, such as milling (Shoyele and Cawthorne 2006; Verma et al. 2009; Sinha et al. 2013). The milling technique is a representative conventional method for size reduction of solid particles (Wu et al. 2010). Spray drying has been successfully applied to develop excipient-free inhalable drug powders. SCF technology is also a promising strategy owing to its capability to produce highly uniform particles (Fages et al. 2004; Tong and Chow 2006).

Milling

Bulk drug preparation through crystallization from solutions, filtration, and drying is the first step of DPI manufacture. Subsequently, reducing the drug particle size is necessary to generate particles in the inhalable size range of below 5 μm in diameter (Wu et al. 2010). Milling has been used extensively as a top-down approach to obtain inhalable drug particles in the desired particle size range for pulmonary drug delivery via inhalation (Shah et al. 2017). The mechanism of micronization using a milling technique involves fracturing particles with mechanical energy or shear (Lau et al. 2017; Shetty et al. 2020). The milling technology has the main advantages of being cheap, reproducible, and relatively easy to scale-up (Sibum et al. 2018). There are many different mills, three of which are used in the manufacture of APIs: fluid-energy mills, including jet mills, high-peripheral-speed mills, and ball mills. Milling can change the shape and surface properties of particle (Luner et al. 2012), thereby affecting the hydrophobicity and flowability of powder particles (Feeley et al. 1998a, b; Heng et al. 2006; Wu et al. 2010). In particular, different milling techniques exert different stresses on the solid particles, which may result in different surface energies (Zeng et al. 2000). Further, the regions of the solid particles with mechanical defects have high surface energy. Therefore, the type of milling method can affect the cohesiveness of the resulting particles. Nevertheless, milling is not particularly suited for the rational engineering of inhalable particles, considering the drawback of milling technology, i.e., its poor control over particle crystallinity, shape, size, and size distribution (Wu et al. 2010; Weers and Miller 2015). It can also produce strongly adherent agglomerates and poorly dispersed powders owing to the associated surface energy changes. In addition, milling can form unstable amorphous regions on the particle surface. Consequently, fine control of the amorphization and increase in surface energy is difficult to achieve by only adjusting the milling process parameters.

Among the various milling methods mentioned above, jet milling is the most commonly used particle engineering technique in the pharmaceutical industry to mill coarse particles into the inhalable size range for the preparation of inhalable dry powders. There are different types of jet mill designs, including fluid impact mills, opposed jet mills, spiral jet mills, oval chamber jet mills, and fluidized bed opposed jet mills (Shetty et al. 2020). Generally, pressurized gas is used for micronization via jet milling to create high particle velocity and high-energy interactions between particles and/or between particles and the chamber walls, which induces particle fracture and subsequent size reduction (Djokić et al. 2014). A jet mill machine typically comprises an inlet part for drug powder feeding and a milling chamber for particle grinding. The feeding pressures of the raw material, grinding pressure, and number of jet-milling cycles can be controlled as process parameters to alter the physical properties of the particle, thereby influencing the aerosolization performance (Brunaugh and Smyth 2018a, b; Mangal et al. 2019a, b, c). Several advantages of the jet-milling process include its relatively convenience and low cost. Jet milling can micronize particles relatively easily to a size suitable for inhalation, and has recently been reported to yield readily dispersed and aerosolized powder when it is used without excipients (Yazdi and Smyth 2016; Brunaugh et al. 2017). However, inhalable particles produced by jet milling have certain unfavorable characteristics. The jet-milled powder is often extremely cohesive and prone to strong agglomeration due to an increase in the surface energy and electrostatic charge (Shetty et al. 2020). Furthermore, the excess energy supplied during the milling process can lead to mechanical activation and local amorphous site development at the particle surface, which can result in instability due to recrystallization during storage in high-humidity environments. The recrystallization of the amorphous regions can lead to changes in the physicochemical properties of the micronized particles and formation of strong agglomerates, which have the potential to significantly affect the aerosol performance of the formulation.

Spray drying

Spray drying is a well-established bottom-up approach for particle engineering (Vehring 2008; Lin et al. 2015). It is an easy to scale-up, one-step process with an economical advantage for the commercial production of dry particles. It enables the control of particle properties over a wide range through fine-tuning of multiple process parameters. Thus, spray drying is a widely used approach to produce inhalable powders for pulmonary drug delivery. Briefly, the technique involves spraying a feed drug solution or suspension into fine droplets that are rapidly evaporated in a current of hot drying medium, such as air or nitrogen gas, to obtain dry particles. Finally, the dried particles were separated using a cyclone separation device and collected (Healy et al. 2014; Lin et al. 2015). The main advantages of the spray drying process are the ability to manipulate and control various process parameters, such as solvent composition, solute concentration, solution and gas feed rate, temperature, and droplet size. These parameters allow the optimization of particle characteristics, such as particle size distribution, shape, density, and surface morphology, including smooth or corrugated morphology, in addition to macroscopic powder properties, such as bulk density, flowability, and dispersibility (Maa et al. 1997; Islam and Gladki 2008; Healy et al. 2014). Careful control of the process parameters without the use of excipients can result in the formation of the desired particle characteristics with wrinkled, spherical, or porous morphology. Such morphological changes show that the density of the powder particles and, consequently, that of the powder bulk can be changed only by the spray drying process (Vidgren et al. 1987; French et al. 1996; Maa et al. 1997; Chew and Chan 2001; Lechuga-Ballesteros et al. 2008). Such ability for fine control of particle properties is useful for the development of high-dose DPIs because, with high-dose drugs, there is a limit to the powder volume that can be dispersed and inhaled, thus restricting the particle and powder density of APIs. Spray drying offers more flexibility and possibility of morphology control, in addition to size control, than conventional milling techniques. However, for thermally sensitive drugs or drugs that are prone to sublimation, the use of spray drying is limited owing to the narrow range of available process temperature (Sibum et al. 2018). Thus, a challenge in spray drying these drug molecules is to overcome the potential for degradation due to factors such as thermal stress during droplet drying and high-shear stress in the nozzle (Healy et al. 2014). Furthermore, spray-dried particles are often completely amorphous and generally tend to be highly hygroscopic and have high surface energy, making them more cohesive. Furthermore, many amorphous powders obtained through spray drying are physically unstable and tend to crystallize, especially when they are exposed to moisture and high temperatures. These can lead to stability issues because the physicochemical stability of amorphous powders is generally lower than that of their crystalline form. Thus, producing inhalable dry powders using spray drying techniques is a challenge to ensure long-term physical stability and minimize undesirable effect on aerosol performance (Zhang and Trissel 2006; Islam and Gladki 2008).

Despite these issues in spray drying, it is worth noting that this process has been increasingly used in the pharmaceutical industry to produce inhalable drug powders within the desired aerodynamic particle size range of 1–5 µm, as exemplified by the currently commercialized high-dose DPI products, namely Aridol®, Bronchitol® (Pharmaxis

Ltd., mannitol inhalable powders) (Warren et al. 2019), and TOBI® Podhaler (VanDevanter and Geller 2011), which are manufactured with spray drying as the micronization method (Brunaugh and Smyth 2018a, b). Another representative API approved as a DPI product and manufactured by spray drying is insulin (Exubera®, Pfizer) (Al-Tabakha 2015).

SCF technology

SCF technology has been investigated for the micronization of inhalable drug particles with desirable physicochemical properties, such as size, shape, crystallinity, polymorphism, and surface energy (Shetty et al. 2020). Supercritical carbon dioxide (SC-CO_2) is the most commonly used SCF because of its low critical temperature and pressure ($T_c = 31.04$ °C, $P_c = 7.38$ MPa). In particular, the low T_c of CO_2 makes it preferable to spray drying for processing heat-labile pharmaceuticals (Mawson et al. 1997; Sievers et al. 2003a, b; Fages et al. 2004; Sun 2016; Aguiar-Ricardo 2017). Other advantages of SC-CO_2 include its nontoxicity, nonflammability, and inexpensive cost (Knez and Škerget 2014).

SCF technology is an innovative powerful particle engineering platform technology for DPI formulations because it involves a single-step operation at near ambient temperature, which minimizes the potential damage of delicate active ingredients and ensures the consistency of the resulting DPI formulation (Sun 2015). SCF technology can control and tune the particle size, morphology, and surface properties of DPI formulations. These controllable physical properties of particles enable the prominent enhancement of the aerodynamic performance and pulmonary deposition of such inhalable dry powders. Various types of SCF technology have been developed in the pharmaceutical area depending on whether the SCF is used as a solvent, anti-solvent, solute (or plasticizer), atomizing agent, or extraction medium (Lin et al. 2015). Based on these various roles of SCF, SCF technology is typically divided into five types (Pasquali et al. 2008; Abuzar et al. 2018; Shetty et al. 2020).

The rapid expansion of supercritical solution (RESS) is one of the simplest SCF processes. In this process, a high-pressure vessel is used to solubilize drug particles and an SCF is used as a solvent. Subsequently, the drug-solubilized SCF is sprayed through a nozzle to allow precipitation of the drug through rapid expansion of the SCF in the expansion vessel (Phillips and Stella 1993; Meng et al. 2012; Gradon and Sosnowski 2014). RESS possesses several advantages, including no organic solvent requirement and narrow particle size distribution suitable for inhalation. Despite these advantages, RESS has a major limitation of poor solubility of most drugs in the SCF. Another most commonly used SCF process is the solution-enhanced dispersion by SCF (SEDS) process. It involves the precipitation of a solute from a conventional solvent by a supercritical anti-solvent (SAS) (Reverchon and Della Porta 1999; Abuzar et al. 2018; Prosapio et al. 2018). During precipitation, the solute is forced to crystallize because of its low solubility in the SCF, such as CO_2. However, the use of a co-axial nozzle in the SEDS process is its main difference from the general SAS process. Mixing with the SCF can occur in the co-axial nozzle, which enhances the dispersion of the drug solution in the SCF and, hence, induces fast mass transfer and uniform crystallization conditions, resulting in particles with narrow size distribution, pure polymorph, or crystallinity. Apart from RESS and SAS processes, SC-CO_2-assisted nebulization and dehydration of aqueous solutions to produce dry powders for inhalation was also developed (Sievers et al. 2003a, b; Reverchon et al. 2004). This method involves the formation of an emulsion between SC-CO_2 and an aqueous solution containing a water-soluble drug and an excipient.

These various types of SCF technology have been reported to finely adjust the properties of particles, especially the surface properties, through changes in various process conditions, such as temperature, pressure, use of organic solvents, and type and ratio of used organic solvent used (Martin and Cocero 2008; Sun 2015). In particular, by altering the pressure and temperature of the process, the density of the SCF and the solubility of the solute can be changed; hence, the supersaturation during drug precipitation can be controlled. SCF technology uses a different mechanism to form particles, which distinguishes it from commonly used conventional processes, such as milling, spray drying, and crystallization/precipitation. Furthermore, with SCF technology, supersaturation and the subsequent nucleation and crystal growth mechanisms can be controlled owing to the inherent characteristics of SCFs (Bristow et al. 2001; Shekunov et al. 2001; Knez and Weidner 2003; Martin and Cocero 2008).

Owing to these unique advantages, SCF is gaining popularity as a method for the production of DPIs, as it offers more flexibility than conventional crystallization with respect to the control of particle characteristics, which enables the generation of particles with more uniform shape, size distribution, morphology, and crystallinity. SCF technology has been successfully used to produce inhalable APIs, such as ipratropium (Kim and Shing 2008), budesonide (Velaga et al. 2002; Toropainen et al. 2006), salbutamol (Reverchon et al. 2001), salmeterol (Tong et al. 2001; Shekunov et al. 2003), and terbutaline (Rehman et al. 2004). These studies have shown that some dry powders produced via the SCF process had enhanced flow properties and dispersion from the inhaler device, which led to higher FPF, compared with micronized particles produced via other techniques (Rehman et al. 2004). This enhanced powder property is well-correlated with the reduced surface energy parameters of these powders compared with those of micronized dry powders. In contrast to the conventional spray drying

process, the SCF method has been shown to produce highly crystalline particles, which may exhibit decreased surface free energies and increased stability compared with those of conventionally micronized products (Shekunov et al. 2003; Begat et al. 2009). Thus, the SCF process provides an attractive alternative to achieve size reduction through micronization with lower energetic surfaces and potentially improved processing and pulmonary product performance characteristics (Feeley et al. 1998a, b). However, it should be noted that particles produced by SCF techniques can also exhibit smooth and planar crystal faces, which may result in a significant increase in the contact area between contiguous surfaces (Begat et al. 2009).

Surface modification strategies for enhanced pulmonary delivery of high-dose DPIs

As stated above, the micronization of inhalable drug powder can be achieved by the particle engineering technology in the micronization process for the preparation of inhalable dry powder. Despite various efforts using above mentioned particle engineering technologies, a decrease in particle size results in an increase in the particle surface area, which, in combination with the increased surface energy caused by micronization processes, can produce highly cohesive particles through an overall increase in the interfacial forces between the particles (Shah et al. 2015). The high energy required to de-aggregate the particles and reform respirable particles can, however, be difficult to achieve in practice (Begat et al. 2009; Xu et al. 2011). In particular, these problems are often difficult to overcome with particle technology alone because the aerosolization performance of inhalable drug powders without excipients is likely to be more dependent on the physicochemical properties of the drug itself (Hoppentocht et al. 2014). For this reason, these approaches are often not effective and difficult to achieve the goal of surface modification with particle manufacturing technology alone because the success or failure of improving the particle surface depends a lot on the nature of the drug itself. In addition, the effects of solid-state properties on aerosol performance are complex because particle engineering technologies can alter various properties, such as crystallinity, particle shape, electrostatic charge, and surface energy, simultaneously and in various degrees of complexity.

To overcome this limitation, understanding the effects of various particle production methods that provide mechanical and thermal treatments on the physicochemical properties of solid-state particles, especially on the surface properties, is important. In addition, how the physicochemical properties are correlated with the aerosolization performance and physical stability of the powders for high-dose DPIs must be well understood (Ward and Schultz 1995; Shetty et al. 2020). Based on this fundamental understanding, particle engineering techniques without excipients for high-dose DPIs have been tried to control the physicochemical properties of drug particles, obtaining the desired aerosolization performance via control of the process parameters in the micronization process.

In addition, formulation strategies using excipients could offer additional possibilities to obtain the desired powder properties. Excipients are critical components in the formulation of most inhaled drug products. Their important roles high-dose inhalable dry powder formulations are as follows: (1) modification of bulk powder properties through surface force control; (2) enhancement of physico-chemical stability; (3) control and improvement of pharmacokinetics and, accordingly clinical therapeutic outcome (Weers and Miller 2015). It has been reported that particle engineering in combination with formulation strategy using excipients can help obtain the desired powder properties by decreasing moisture uptake and reducing the cohesive property via surface stabilization, thus improving the dispersion and physicochemical stability of the powder (Sibum et al. 2018). As representative techniques of these formulation strategies, surface modification using force control agents (FCA) and manufacturing of microparticle with unique architectures have been introduced (Ungaro et al. 2012a, b; Koskela et al. 2018). As therapeutics through pulmonary drug delivery has rapidly developed based on these formulation strategies, more flexible formulation technologies to engineer respirable particles have been required as a platform technology with high probability of success in commercial scale-up production. Accordingly, it has been recently reported that formulation technologies for designing inhalable powders with stable and good aerodynamic properties can be applied to various APIs with diverse physicochemical properties. In addition to this, efforts to develop clinically available new excipients for inhalable dry powder formulation play a key role in enabling efficient drug delivery to the lungs (Weers and Miller 2015). Various surface modification methods using above described particle engineering technologies in combination with an additional particle surface stabilization process, control of process parameters, and formulation approach will be discussed below (Table 2).

Conditioning for stabilization of particle surfaces

Micronized particles are usually highly charged (Chow et al. 2007; Kaialy and Nokhodchi 2015) and are more surface-active (Feeley et al. 1998a, b). Unfortunately, this surface change makes the powder extremely cohesive and prone to aggregation and agglomeration (Malcolmson and Embleton 1998; Pasquali et al. 2006). These undesirable powder properties may lead to reduced aerosol performance (Taylor et al. 1999), as stated above. To overcome these potential

Table 2 Surface modification cases for high-dose dry powder inhaler through formulation strategies

Mechanism of surface modification	Drug	Force control agents (FCAs)	Preparation method	Summary of results
Surface coating	Salbutamol sulphate, Budesonide (Begat et al. 2009)	Leucine, Lecithin, MgSt	Mechanofusion	–Significant improvement of the FPF –Surface roughness decrease, hence generating smooth surface –Decrease in particle cohesion and improving the deagglomeration
	Salbutamol sulphate (Zhou et al. 2013)	MgSt	Mechanofusion	–Highly effective in producing ultra-thin coatings on micronized powders via high degrees of coating coverage –Significant increases in powder bulk densities, reduction in powder cohesion and substantially improve the powder aerosolization efficiency
	Levodopa (Luinstra et al. 2015)	L-leucine	Co-milling	–Increased the FPF
	Triamcinolone acetonide, Salmeterol xinafoate, Salbutamol sulphate (Zhou et al. 2010a, b)	MgSt	Mechanofusion	–Relatively low levels (5%, w/w) of MgSt to successfully improve the cohesion and aerosolization properties –No substantial granulation or size enlargement occurring –Reduction in agglomerate strength, decreasing powder intrinsic cohesion, and significantly improved aerosol performance
	Ciprofloxacin hydrochloride monohydrate (Mangal et al. 2019a, b, c)	MgSt, L-leucine	Co jet-milling	–Simultaneous size reduction and significant improvements in aerosolization –No retardation of dissolution –MgSt coating: reducing the surface energy and the friction between particles –L-leucine coating: less effect on the surface energy, but create more rough surfaces, thereby reducing inter-particulate contact area and hence total inter-particulate attractive force
	Ciprofloxacin hydrochloride monohydrate (Shetty et al. 2018a, b, c)	Lactose, D-Mannitol, Trehalose, L-leucine	Spray drying	–Reduced surface energy and formation of corrugated particles –Enhanced the aerosolization performance –Improved the physical and aerosolization stability

Table 2 (continued)

Mechanism of surface modification	Drug	Force control agents (FCAs)	Preparation method	Summary of results
	Ciprofloxacin hydrochloride monohydrate (Shetty et al. 2018a, b, c)	Magnesium nitrate, sodium chloride	Spray drying	–Increased particle roughness and reduced particulate contact area –Improved the physical and aerosolization stability
	Sodium heparin (Shur et al. 2008)	L-leucine	Spray drying	–Less cohesive than heparin alone, Improved aerosolisation performance –Rheological analysis: reduce the elasticity
	Salbutamol sulphate (Zhu et al. 2008)	Lactose monohydrate	Jet milling	–Adhesion force of the mixture decreased with RH initially, and then increased upon further increase in RH –Low moisture contents: increase in the FPF via reduction in electrostatic force due to charge dissipation associated with moisture sorption –High moisture contents: decrease in the FPF
	Gentamicin (Aquino et al. 2012)	L-leucine	Spray drying	–Improved maximum FPF of about 58.3% (FPF value of neat dried powders = 13.4%) –Improvement of the aerosol performance by the addition of leucine
	Disodium cromoglycate (DSCG) (Li et al. 2016)	L-leucine	Spray drying	–Enrichment of crystalline L-leucine on the surface of the composite particles –Significantly reduce the effect of moisture on aerosolization performances: minimize moisture-induced deterioration in the aerosol performance
	Sulbutamol sulphate (Balani et al. 2010a, b)	α-Lactose monohydrate, Adipic acid, MgSt	Co-milling	–Reducing the amorphization of salbutamol and prevention of recrystallization and change in morphology during the storage at high RH
	Salbutamol sulphate (Balani et al. 2010a, b)	Polyvinyl pyrrolidone (PVP)	Co-milling	–Improved stability by suppression of recrystallization of amorphous salbutamol with PVP –Formation of uniform amorphous dispersion at molecular level through homogeneous distribution of salbutamol and PVP

Table 2 (continued)

Mechanism of surface modification	Drug	Force control agents (FCAs)	Preparation method	Summary of results
	Salbutamol sulphate (Li et al. 2017)	L-leucine	Spray drying	–Salbutamol alone: moderately hygroscopic, amorphous, and exessive moisture absorption, hence decrreasing in the aerosolization performance –40% (w/w) L-leucine: eliminate the effect of moisture on the aerosolization performance at 60% RH and maximizing the aerosolization performance –Crystalline L-leucine on surface : increased the degree of particle surface corrugation : reduced particle fusion and cohesiveness to facilitate dispersion
	Colistin sulfate, Ciprofloxacin hydrochloride monohydrate (Shetty et al. 2018a, b, c)	L-leucine	Spray drying	–Result in amorphous particle –Increasing colistin concentration on the composite particles surfaces: improvement of aerosol performance of ciprofloxacin –Addition of leucine to ciprofloxacin and colisition composite particle: no particle fusion, enabling a stable aerosol performance
	DSCG (Yu et al. 2018)	Sodium stearate (NaST)	Spray drying	–The favorable effect of NaST –Increase the aerosolization performance of DSCG and effectively reducing the deleterious impact of moisture –Increased the crystallinity of the powders: high crystalline content presence on the particle surface reduced particle aggregations and cohesiveness –High concentration NaST reduce dissolution rate
	DSCG (Yu et al. 2017)	Isoleucine, Valine, Methionine	Spray drying	–Significantly reduced the deleterious effect of moisture on aerosol performance via moisture protection effect

Table 2 (continued)

Mechanism of surface modification	Drug	Force control agents (FCAs)	Preparation method	Summary of results
Corrugated particle	Budesonide (Boraey et al. 2013; Rattanupatam and Srichana 2014)	L-leucine	Spray drying	–Enriched leucine on the particle surface relative to the bulk composition –Low-density morphology and partial encapsulation of budesonide –Greatly improved dispersibility and manufacturability of the powder: FPF exceeded 80%
	Budesonide (Lu et al. 2019)	Arginine	Spray drying	–Predominantly co-amorphous particle –Emitted doses > 80%, and FPF > 50% –Physically stable co-amorphous dry powders for inhalation purposes
	Budesonide (Dufour et al. 2015)	Hydroxypropyl-β-cyclodextrin	Spray drying	–Microparticles with a specific "deflated-ball like shape" –Increased FPF and improved aerosolisation properties –Sustained budesonide release in a mouse model of asthma
	Budesonide (Vozone and Marques 2002)	Dimethyl-β-cyclodextrin	Spray drying	–Significant higher FPF of budesonide-cyclodextrin complex
	Netilmycin (Cui et al. 2018)	L-leucine	Spray drying	–Suitable micron size for inhalation and amorphous with a corrugated surface –Decreased water content and hygroscopicity with the addition of L-leucine (maintained antibacterial activity) –Improved the aerosolization performance and stability
	Netilmycin, Gentamicine (Lechuga-Ballesteros et al. 2008)	Trileucine	Spray drying	–Formation of trileucine coated corrugated particles with low-density by surface active trileucine's low aqueous solubility –Decrease in the measured surface energy, reduced cohesiveness and resulting in superior aerosol performance –Improved stability: decreased denaturation and aggregation in the solid state
	Aztreonam (Yang et al. 2015)	L-leucine, Histidine, Glycine	Spray drying	–Significantly decreased particle densities –Less cohesion between particles and increased the FPF

Table 2 (continued)

Mechanism of surface modification	Drug	Force control agents (FCAs)	Preparation method	Summary of results
	Rivastigmine (Simon et al. 2016)	L-leucine, Trehalose	Spray drying	–Wrinkled particle morphology with low densities –High glass transition temperature with a good stability –Lower residual solvent content, lower particle size, higher FPF, hence showing better aerodynamic properties as L-leucine content increased
	Albuterol (Lechuga-Ballesteros et al. 2008)	Trileucine, Raffinose	Spray drying	–Formation of trileucine coated corrugated particles with low-density –Decrease in the measured surface energy, reduced cohesiveness and resulting in improved aerosol performance
	Salbutamol (Seville et al. 2007)	L-leucine, Lactose	Spray drying	–Suitable micron particle size distribution for pulmonary administration –Low moisture content, improved in vitro particle deposition which means the better dispersibility and aerosolisation properties
Alteration of surface roughness	Ciprofloxacin hydrochloride monohydrate (Mangal et al. 2019a, b, c)	MgSt	Co jet-milling	–Reduced mechanical interlocking between particles through smooth surface –Improved flowability and aerosolization performance
		L-leucine	Co jet-milling	–More rough surfaces, thereby reducing inter-particulate contact area and hence total inter-particulate attractive force
Porous particle	Palmityl-acylated exendin-4 (Kim et al. 2011), human growth hormone (Kim et al. 2006a, b)	Pluronic F68/F127	Single O/W emulsification and solvent evaporation method	–The appropriate size range for inhalation and containing many surfaces and internal pores meaning low aerodynamic density –Sustained release and acceptable drug-loading –Longer in vivo efficacy

Table 2 (continued)

Mechanism of surface modification	Drug	Force control agents (FCAs)	Preparation method	Summary of results
	Poly(lactic-co-glycolic acid) (Yang et al. 2009) (Kim et al. 2006a, b; Kwon et al. 2007; Bae et al. 2009; Oh et al. 2011; Ungaro et al. 2012a, b)	Hydrogen peroxide, Ammonium bicarbonate, Pluronic F127, Sulfobutyl ether Beta cyclodextrin sodium salt	Spray drying or solvent evaporation or solvent extraction of W/O/W double emulsion	–Greatly enhanced the drug encapsulation efficiency –Efficient way of making polymeric microparticles for sustained local drug delivery by inhalation –Alteration of porosity by the controlling the concentration of pore forming agent –Created well inter-connected pores in the resultant microspheres
	Levodopa (Bartus et al. 2004), Salbutamol sulphate (Ben-Jebria et al. 1999), Insulin (Vanbever et al. 1999; Rosenstock et al. 2007)	Dipalmitoylphosphatidylcholine (DPPC), Albumin with ethanol/water co-solvent system	Spray drying (Air® technology)	–DPPC: the primary shell forming excipient –Albumin: change particle morphology and lower particle density –Large porous particle with reduced density and excellent performance for pulmonary drug delivery
	Tobramycin, Ciprofloxacin Amphotericin B, Indacaterol, Budesonide, Leuprolide	Perfluorooctyl bromide (PFOB) with phospholipid (Distearoylphosphatidylcholine, DSPC) as a disperision stabilizer and calcium chloride as a surface modifier	Emulsion-based spray-drying process (PulmoSphere™) (Geller et al. 2011; Weers and Tarara 2014)	–Improved intrapulmonary deposition efficiency, faster delivery, and more convenient administration over nebulized formulations –Significant improvements in lung targeting and dose consistency –Fine tuning of particle porosity by controlling of the ratio of PFOB/DSPC
	Hydroxyapatite (Sun et al. 2009), Bendroflumethiazide (Healy et al. 2008), Budesonide (Nolan et al. 2009), Budesonide with Ambroxol HCl (Tewes et al. 2013)	Ammonium carbonate	Spray drying (Combination of solvent and anti-solvent)	–Simple solution composition –Decomposition of pore forming agent with volatile during preparation –Formation of nanopores and increase in the specific surface area with low density –Improved in vitro deposition properties
	Mannitol (Peng et al. 2017)	Ammonium carbonate	Non-organic solvent spray drying	–Decomposition of pore forming agent with volatile during preparation –Enhanced particle deposition efficiency with the decreased particle density of prepared nanoporous particle

Table 2 (continued)

Mechanism of surface modification	Drug	Force control agents (FCAs)	Preparation method	Summary of results
	Hyaluronic acid (Iskandar et al. 2009)	Polystyene latex (PSL)	Spray drying of suspension	The size of the pore and the porosity could be easily altered by changing the concentration and size of the PSL particles
	Deslorelin (Koushik and Kompella 2004; Koushik et al. 2004)	SCF-CO_2 and Cyclodextrin	SCF-CO_2 pressure-quench treatment	–Increase in mean particle size and mean porosity after process –Reduced residual solvent content, sustained deslorelin release, and sustain drug delivery via the deep lungs
	Ciprofloxacin (Arnold et al. 2007)	Oils	Precision particle fabrication technology utilizing oils as extractable porogens	–Monodispersed large porous particles –Potential to control particle deposition and sustain release to the lung

limitations, alternative particle engineering techniques have been developed, but there is always the possibility that the particles produced by these alternative methods may also have low crystallinity or contain some partial amorphous content (Lin et al. 2015).

Many studies have attempted to eliminate the issue of instability in micronized particles. The amorphous regions in the particles undergo structural relaxation to a thermodynamically stable crystalline state during storage, but this can lead to an unexpected change in particle size (Feeley et al. 1998a, b). One of the approaches currently used in the pharmaceutical industry is to simply store the micronized particles for an extended period of time until the particles reach physical stability (Adi et al. 2008a, b). This is called 'conditioning' or 'relaxation' of the particles following micronization, especially for particles generated via milling (Lin et al. 2015; Shetty et al. 2020). In the conditioning process, the storage environment is controlled in terms of RH and temperature to enable the intentional phase transition of the amorphous to crystalline state. When the surrounding temperature is kept above the glass transition temperature (T_g) and the T_g of the powder sample is reduced via water adsorption of the solid powder at the stored RH, the molecular mobility can be increased, thereby leading to recrystallization (Chen et al. 2016; Miller et al. 2017; Chang et al. 2020). However, it should be noted that this recrystallization could be accompanied by undesirable particle growth and irreversible particle agglomeration, even though exposure to accelerated temperature and RH can improve the physical stability of the dry powder post-micronization by enhancing the structural relaxation rate and reducing the amorphous content and associated powder aggregation. Interestingly, particles stored at elevated RH conditions have shown better physical stability during storage than those stored at elevated temperatures, although the mechanism remains unclear (Lin et al. 2015). To date, several optimized conditioning or relaxation process parameters have been proposed for DPIs. Even so, it should also be noted that the relative magnitude of cohesive forces strongly depends on the conditioning parameters and duration, and the effect of surface stabilization through conditioning or relaxation depends on the type of API applied. Furthermore, such a conditioning or relaxation process is time-consuming and economically impractical, as storage time is largely dependent on the hydrophilic and hydrophobic properties of the API (Nakach et al. 2004; Ng et al. 2008; Wong et al. 2014).

Interestingly, several studies have reported that SCF can also be applied to conditioning. It was suggested that the semi-crystalline particles underwent surface conditioning in SC-CO_2 and ethanol mixtures, in which the particle surfaces relaxed into a more stable and less energetic state, thus improving the powder flow and aerosolization performance (Rehman et al. 2004).

Recently, to reduce the time required for the powder conditioning methods, in-process conditioning using gases such as nitrogen gas has been investigated (Brodka-Pfeiffer et al. 2003; Kazmi et al. 2018). The micronized particles move through the conditioning zone after mixing with the conditioning gas. To obtain the optimal outcome, conditioning process parameters, such as humidity, flow rate, temperature, nature of the condition gas, and contact time, can be finely controlled. Using this approach, the amorphous content of the micronized particles produced can be significantly reduced and high physical stability can be achieved. Furthermore, the combined use of solvent vapors and a conditioning gas is efficient to reduce the amorphous content on the particle surface. The type of solvent vapor should be chosen depending on the nature of the micronized particles. Generally, a water miscible organic solvent can be applied if the micronized particles have hydrophilic properties (Lin et al. 2015).

However, most of these conditioning methods have risk factors that can lead to unwanted changes in physical properties, such as an increase in particle size due to recrystallization, crystal growth, and irreversible agglomeration. Therefore, in recent years, particle surface stabilization methods have been attempted during the microparticle manufacturing process in terms of formulation strategy to avoid such a time-consuming additional conditioning process.

Surface coating with FCAs

Typically, particles are exposed to their environment primarily via their surfaces, thereby interact with various components of the external environment including solid, liquid and gas phases. These interactions are closely related with particle surface forces, thus, control of particle surface forces is critical to reduce cohesion between particles and adhesion between particles and other surfaces (e.g., device plastic or reservoir such as capsule and blister). An efficient way to control particle surface forces is a surface coating that allows to configure the particle surface composition as desired (Weers and Miller 2015). The surface coating method enables fine-tuning the particle surface properties by changing the composition of the surface, thereby reducing high surface energy and/or modifying surface morphology to improve cohesive properties, and hence suppress powder agglomeration to improve physical stability. In addition, it can suppress the formation of amorphous state on the surface, or stabilizing the amorphous region by forming a physical barrier, hence inhibiting recrystallization. The coated film barrier formed on the particle surfaces can also protect inhalable powders against external environmental stresses, such as moisture and temperature. It greatly improves the stability of the powders. In particular, it can prevent a sudden change in the physical properties of the powders due to recrystallization of the amorphous surface. Furthermore, water adsorption on the surface of the particles can lead to changes in the inter-particulate forces by altering the particle surface energy, thereby resulting in surface conductivity changes or increased interactions via capillary forces. Generally, as condensation of water molecules can occur between particles in close contact, the capillary forces may dominate over VdW forces at an RH of higher than 65% for hygroscopic materials. In particular, capillary forces are the main concern for optimized formulations of hygroscopic inhalable drug particles, which are more prone to reductions in aerosolization performance following moisture sorption and capillary bridging at a relatively high RH (Shetty et al. 2018a, b, c). Several new inhalable microparticle preparation techniques using surface coating have been conducted to achieve surface modification through a formulation strategy simultaneously with the micronization process.

FCAs

In particular, surface modification methods using surface coating with excipients with low surface-active forces which called as FCAs have been widely utilized for generating carrier-free DPI formulations with low potency and high dose (Brunaugh and Smyth 2018a, b). FCAs, low surface free energy materials, reduce particle cohesion by binding to host particles and modify the interfacial chemistry, resulting in improved fluidization and dispersion within the DPI. Generally, these FCAs have anti-adherent and anti-friction properties, and these properties are typically accomplished using hydrophobic force control agents (Begat et al. 2005). However, the effectiveness of FACs depends on whether the coating process can produce homogeneously mixed interactive mixtures through ordered mixing, it often has remained limited due to shortcomings of the applied coating process. In this respect, it should be noted that the formulation study using FCAs and development of effective coating process must be performed together to lead successful results.

Different types of FCAs are commonly used in various pharmaceutical processes including coating, i.e., (1) fatty acids, fatty alcohols, and hydrocarbons, (2) fatty acid esters, (3) metallic salts of fatty acids, (4) inorganic materials, (5) hydrophobic amino acids, and (6) surfactants or hydrophilic surface-active molecules. Most of these commonly used FCAs are lubricants or glidants. However, traditional glidants, such as colloidal silica, are unsuitable for inhalation because of safety concerns (Lin et al. 2015). Among FCAs, leucine and magnesium stearate (MgSt) have been explored widely as potential FCAs in DPI formulations to modify the surface of cohesive inhalable particles (Begat et al. 2009; Lin et al. 2015). It has been shown that MgSt act as a lubricant, FCA, surface control agents, physical barrier against humidity, or stabilizing agents in DPI formulations.

In particular, coating with MgSt results in a high degree of deagglomeration of pure drug powders compared with other FCAs. Principally, MgSt regulates the inter-particulate interactions including the force of adhesion and cohesion, and/or cohesive adhesive balance. In addition, the dissipation of electrostatic charge on micronized particles is another key mechanism for improvement of aerosolization performance (Mehta et al. 2020). By knowing these anti-adherents, anti-friction properties, and effective modification of the drug particle interfacial properties in DPI formulations, MgSt is recognized as safe for inhalation and currently approved as an inhalable drug product including commercial carrier-based DPIs (Breo® Ellipta® containing fluticasone furoate and vilanterol developed by GSK, Anoro® Ellipta® containing umeclidinium bromide and vilanterol developed by GSK) and Foradil® Certihaler® containin formoterol fumarate developed by Novartis), but it is likely to also be applicable for carrier-free high-dose formulations (Shur et al. 2016; Brunaugh and Smyth 2018a, b).

It has also been established that applying a surface layer of hydrophobic amino acids is a preferred way to modify the surface hydrophobicity of particles, hence leading the enhanced aerodynamic performance of particles. In addition, it has been suggested that amino acids are the endogenous materials which may have favorable safety for the pulmonary drug delivery. For this reason, the representative hydrophobic amino acid, leucine, has received much attention to use as a FCA in inhalable dry powder formulation. Moreover, amino acids and their derivatives can be used to physico-chemically stabilize various biomolecules in powder formulations (Weers and Miller 2015; Chen et al. 2016; Mehta et al. 2020). It has been show that leucine act as a lubricant for inhalable powders. Aerosolization performance of dry powder can be improved by the formation of leucine external layer due to a rather hydrophobic property of leucine with surface activity. Because of these properties, the addition of leucine can lead to less cohesive particles (Yang et al. 2011; Chen et al. 2016). It was also reported that leucine can also prevent capillary force followed by solid bridge formation between particles. Furthermore, the coated leucine external layer may protect the amorphous matrix against temperature and moisture, thereby enhance the physical and chemical stability of inhalable amorphous powder by preventing recrystallization of API and/or additives in powder formulation (Mehta 2018). In practice, leucine has been widely applied to incorporate onto the surface of hygroscopic drug particles to decrease water adsorption, thereby improving the powder dispersibility and physical stability of high-dose DPI formulations (Brunaugh and Smyth 2018a, b). The degree of moisture protection was reported to be related to the amount of leucine enriched on the particle surface (Li et al. 2016; Cui et al. 2018; Sibum et al. 2020). Consequently, the moisture protection effect of leucine at varying concentrations can affect the aerosol performance of spray-dried inhalable drug particles (Hickey et al. 1990; Brunaugh and Smyth 2018a, b). In spite of the various advantages of leucine, there are matters that need to be paid attention when applying it to the formulation. That is the solid-state property of leucine, whether it is present as an amorphous or either of two crystalline polymorphs and there is a polymorphic transition during storage. This concern should be considered because physical changes in leucine itself, not the drug, can affect the performance and quality of inhalable dry powders. To inhibit phase transition such as recrystallizatione, relatively low concentrations of other glass-forming excipients are often added to formulation in combination with leucine (Weers and Miller 2015).

By following the excellence of leucine, and systematic and comprehensive effort to improve its shortcomings, trileucine, which is a tri-peptide produced from three leucine residues, was discovered to have some prominent advantages beyond leucine as a shell-forming excipient (Lechuga-Ballesteros et al. 2008). Trileucine, as an oligopeptide, shows greater conformational flexibility and has better physical stability which is less crystallized during storage. In general, trileucine is also amorphous after a particle manufacturing process such as spray drying. However, the glass transition temperature (T_g) of trileucine is higher (104 °C) than that of leucine, which mean improved physicochemical robustness of trileucine. It was also shown that T_g of amorphous trileucine is dependent on the state of the solution before solidification, such as pH and concentration of anions, cations, and zwitterions of the system. The dispersibility of dried trileucine is mainly governed by the pH of a solution before solidification. In addition, trileucine is less water soluble than leucine (approximately threefold), so it can act as a shell-forming agent even at low concentrations. Its relatively low and pH-dependent aqueous solubility behavior can result in the formation of low density particles with reduced inter-particulate interaction and cohesiveness via a shell-forming mechanism. Such a surface modification using trileucine can inhibit the particle aggregation and agglomeration with improvement in the flowability of inhalable dry powder (Mehta et al. 2020). Furthermore, it was also known that trileucine is highly surface active, so that trileucine solutions having a markedly lower surface tension than those of leucine. Through the better surface activity in comparison to leucine, trileucine can more effectively prevent the process-induced degradation of biomolecules such as peptides and proteins when used in various pharmaceutical formulations. Typically, peptides and proteins e shear because of feeding and atomization of the e. This unfavorable shear and the creation of an air–liquid interface could result in protein unfolding and/or aggregation. This critical issue may also apply to air–solid and liquid–solid interfaces. However, trileucine e the protein from these interfaces, resulting in enhanced

stability via decreased aggregation in the solid state. Even considering the toxicity from inhalation, it is expected e to leucine becausee can be rapidly catabolized to leucine by peptidases in the lungs (Lechuga-Ballesteros et al. 2008; Weers and Miller 2015; Mehta 2018; Mehta et al. 2020) earginine (Lu et al. 2019), phenylalanine, cysteine (Faghihi et al. 2014) and methionine (Yu et al. 2017) for the preparation of both chemical and biomolecule drug powderse.

Other coating materials of polymers such as ethyl cellulose and polyvinylpyrrolidone (PVP) (Traini et al. 2012) and lipids (Pilcer et al. 2006; Maretti et al. 2014) such as cholesterol and phospholipid have also shown their capability to reduce agglomeration tendency and improve aerosolization. In particular, the lipid derivatives having phospholipid chemical structure similar to pulmonary surfactant or amphiphilic surface-active molecules can not only control particle surface force, but also easily disperse over the large surface of the pulmonary airways, hence facilitating drug diffusion across the mucus and lung epithelial cell and accordingly improve therapeutic efficacy (Mehta et al. 2020). In addition, hydrophobic fatty acids have been utilized to protect hygroscopic drugs from water adsorption (Hickey et al. 1990; Brunaugh and Smyth 2018a, b).

Various lipid-based delivery systems with these favorable characteristics have been widely used for pulmonary drug delivery to improve therapeutic efficacy but also safety with reduced side effects through enhance drug retention in the desired target of lungs (Cipolla et al. 2014). Representatively, microemulsions, nanoemulsions, solid lipid nanoparticles, liposomes and micelles are included in well-established lipid-based pulmonary drug delivery systems (Ngan and Asmawi 2018; Malamatari et al. 2020). Liposomes are spherical colloidal vesicles that consist of phospholipid bilayers surrounding an aqueous phase interior compartment (Storm and Crommelin 1998; Tsai and Rizvi 2016). Typically, both lipophilic and hydrophilic drugs can be incorporated into the bilayer membrane and in the aqueous interior of liposomes, respectively. Although liposomes have many pharmaceutical and biopharmaceutical advantages, they may have critical physical instability issues (e.g., hydrolysis, oxidation, sedimentation, and aggregation) during storage. Instead, proliposomes which are free-flowing dry powders that can form liposomes through immediate hydration following contact with water or biological fluids, overcome the instability issues of liposomes and can act as liposome precursors which upon hydration generate liposomes (Payne et al. 1986). These proliposomes can be used for a highly effective pulmonary drug delivery system by making surface-modified particles through the coating of a drug with phospholipids as FCA on the surface of another drug particles or matrix structure forming excipients (Ye et al. 2018). The hydrophobic nature of phospholipids available for the proliposome is critical in modifying the surface characteristics of particles. This decreases the surface energy, hence reducing VdW attractive forces. Generally, saturated phosphatidylcholines such as distearoylphosphatidylcholine (DSPC) and dipalmitoylphosphatidylcholine (DPPC) are applied preferably for the preparation of proliposome dry powders, because of their high gel to liquid–crystal phase transition temperatures. In contrast, the phase transition temperatures of unsaturated phospholipids are below 0 °C, so that it is very difficult to prepare dried free-flowing powders using general drying techniques at relatively high temperature (Weers and Miller 2015).

Particle surface coating technologies

The modification of surface properties through such formulation changes with FCAs can be achieved using various coating methods, which can be divided into two representative methods: a solvent-based coating method using a solvent and a dry coating method without using a solvent (Lin et al. 2015). Especially, the control of surface composition to enhance powder dispersibility is often a key objective of particle engineering using coating technology in combination of formulation with hydrophobic excipient including FCAs. Generally, enrichment of the hydrophobic excipient on the every particle surfaces can improve dispersibility of powder efficiently. Thus, it is first necessary to select a coating material suitable for particle surface coating, which is easily applicable to the coating process and has intrinsic properties that can be well coated on the drug surface through a unique coating mechanism of the used coating process. In order to achieve this first goal, a fundamental understanding of the coating technology principles must first be based (Weers and Miller 2015).

Solvent-based coating method Particle engineering techniques that can be used as a coating process can be applied to provide control of surface composition, and are particularly useful in development of DPI products. Co-spray drying is one of the most commonly used solvent-based surface coating methods for inhalable drug particles via a simple principle based on the dynamics of an evaporating liquid droplet (Lin et al. 2015). As mentioned above, the physical instability of spray-dried amorphous materials could be challenging to overcome via control of the formulation and process parameters. The co-spray drying with suitable excipient could solve the crystallization-induced physical instability of a spray-dried DPI formulation and help retain the optimal aerosol performance in the DPI with maintenance of physical stability during storage and handling (Hickey et al. 2007). The physical properties of spray-dried particles were significantly affected by the composition of the formulation and type of excipient added. Some excipients as a coating material may reduce the surface energy,

thereby reducing the particle density and/or decreasing the powder cohesiveness, thereby enabling enhanced aerosolization performance. Typically, above mentioned FCAs have been used as a coating material for co-spray drying. The particle surface coating using co-spraying is based on the core/shell particles formation, which is a unique principle of spray drying technology. The size of liquid droplet will be reduced and the concentration of all materials at the surface of liquid droplet will increase as solvent evaporates from sprayed droplets during co-spray drying process. This results in a concentration gradient that leads to the diffusion of each material molecule into the droplet. There will be a uniform distribution of the material molecules throughout the particle when material diffusion is relatively rapid compared to evaporation rate. In contrast, slowly diffusing materials will be positioned on the surface of a drying liquid droplet in a concentrated state (Weers and Miller 2015). Particularly, some of FCAs such as hydrophobic or amphiphilic surfactants are preferred to be distributed at the air–liquid interface of atomized liquid droplets of the drug solution during spray drying through their surface activity. Hence, the hydrophobic or amphiphilic nature of FCAs allows the coating material to dominate the surface of the spray-dried particles. Since the composition of the particle surface can be controlled by using the difference in molecular diffusion and surface activity between substances added in the formulation, including API and excipients, it can be usefully applied to surface coating. In addition, based on these surface coating mechanism, the type and number of molecules distributed on the particle surface can also be controlled by changing the solvent composition and temperature during the spray drying process. In particular for coating of leucine by co-spray drying, it was reported that it is critical to control formulation composition to ensure that leucine precipitates early during particle formation to enrich leucine on the surface of the particles during spray drying (Vehring 2008; Mehta et al. 2020). Recently, it has become possible to control the surface coating properties of FCA by using various types of spray nozzles, including specially designed multi-fluid nozzles with 3- and 4- fluid channel constructions, as well as a unique 2-solution mixing nozzle (Mizoe et al. 2008; Leng et al. 2018; Shetty et al. 2020) (Fig. 2a). Other solvent-based coating techniques focused on the modification of surface chemistry include the aerosol flow reactor method (Raula et al. 2009, 2010), fluid-bed coating (Iida et al. 2005), and spray-freeze-drying (Maa et al. 1999; Ali and Abdelrahim 2014). Co-spray drying has been used as a method for preparing proliposomes for lung delivery by coating phospholipids on drugs.

Co-spray drying has been used as a method for the preparation of proliposomes for lung delivery of drugs based on the coating of a drug with phospholipids as FCA on the surface of another drug particles or matrix structure forming excipients, as stated above. A proliposome formulation containing both hydrophilic tobramycin and hydrophobic clarithromycin was introduced for the treatment of respiratory infections (Ye et al. 2018). This proliposome was prepared by co-spray drying of a suspension consisting of

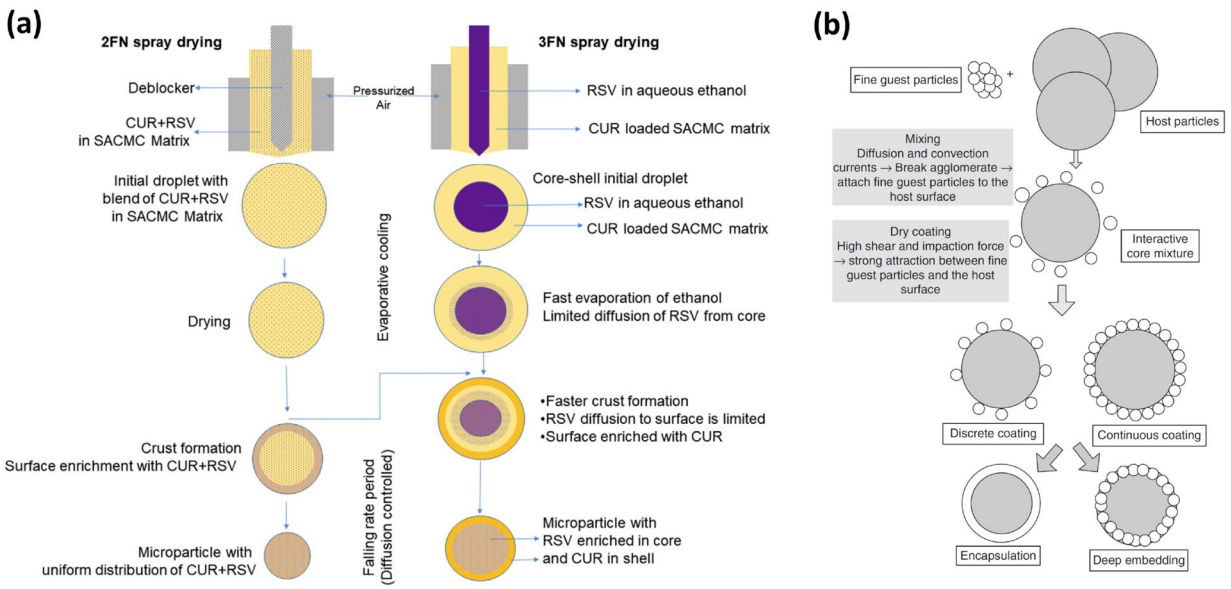

Fig. 2 Mechanisms of particle surface coating technologies; **a** spray drying process using two and three fluid nozzles [reprinted with permission from Elsevier (Leena et al. 2020)], **b** Schematic illustration showing interactive mixture and all types of dry coated particles. The inner part is the coarse carrier particle and the outer is particles of the cohesive fine guest particles [reprinted with permission from Elsevier (Dahmash and Mohammed 2015)]

mannitol and tobramycin particles dispersed in ethanol solution in which clarithromycin, soybean phosphatidylcholine and cholesterol are dissolved. This research paper shows that the lipid layer coated on the surface of the dry proliposome particles provided moisture protection and sustained drug release properties when compared to the pure drugs (Fig. 3). It was also reported that inhalable proliposome formulations containing isoniazid or rifapentine with phospholipids prepared by optimized co-spray drying method can result in improved the aerosolization characteristics, enhanced antimycobacterial activity, reduced cell toxicity, and sustained drug release (Rojanarat et al. 2011; Patil-Gadhe et al. 2014).

Dry coating method Over the past decade, dry coating has attracted interest as a method for modifying the surface properties of cohesive particles. Various methods have been employed as dry coating terminologies including mechanofusion (Gera et al. 2010; Beach 2011), hybridizer (Ishizaka et al. 1989; Pfeffer et al. 2001), theta composer (Elliptical rotor) (Endoh et al. 2004; Teng et al. 2009; Gera et al. 2010), magnetically assisted impaction coating (Gera et al. 2010; Beach 2011), rotating fludised bed coater (Pfeffer et al. 2001; Quevedo et al. 2006; Beach 2011), fluid energy mill (Teng et al. 2009; Han et al. 2011, 2013), cyclomix (Lefebvre et al. 2011), and turbo rapid variable (Monteith and Thomas 2006; Mehta et al. 2020). Detailed descriptions of each dry coating technique are provided well in other reviews (Pfeffer et al. 2001; Dahmash and Mohammed 2015; Mehta 2018; Mehta et al. 2020). Most dry coating technologies have been shown to be quicker, safer, cheaper, and more environmentally friendly than surface coating using a solvent (Zhou and Morton 2012).

In general, dry powder coating falls into several categories depending on the degree of particle surface coverage. The submicron-sized guest particles are coated onto larger micron-sized host particles to create the desired properties of the particle surface in dry coating procedure. In contrast to wet solvent-based coating, the fine guest particles come into close contact with the host particles via mechanical force. This dry coating starts begins with an interactive ordered consisting of a loose surface coating to a partial coating (discrete) followed by film formation and encapsulation (continuous coat), as shown in Fig. 2b. In general, the VdW interaction is strong enough to adhere firmly to the host particle because the guest particles are too small in size. Thus, since the attraction between the fine guest particle

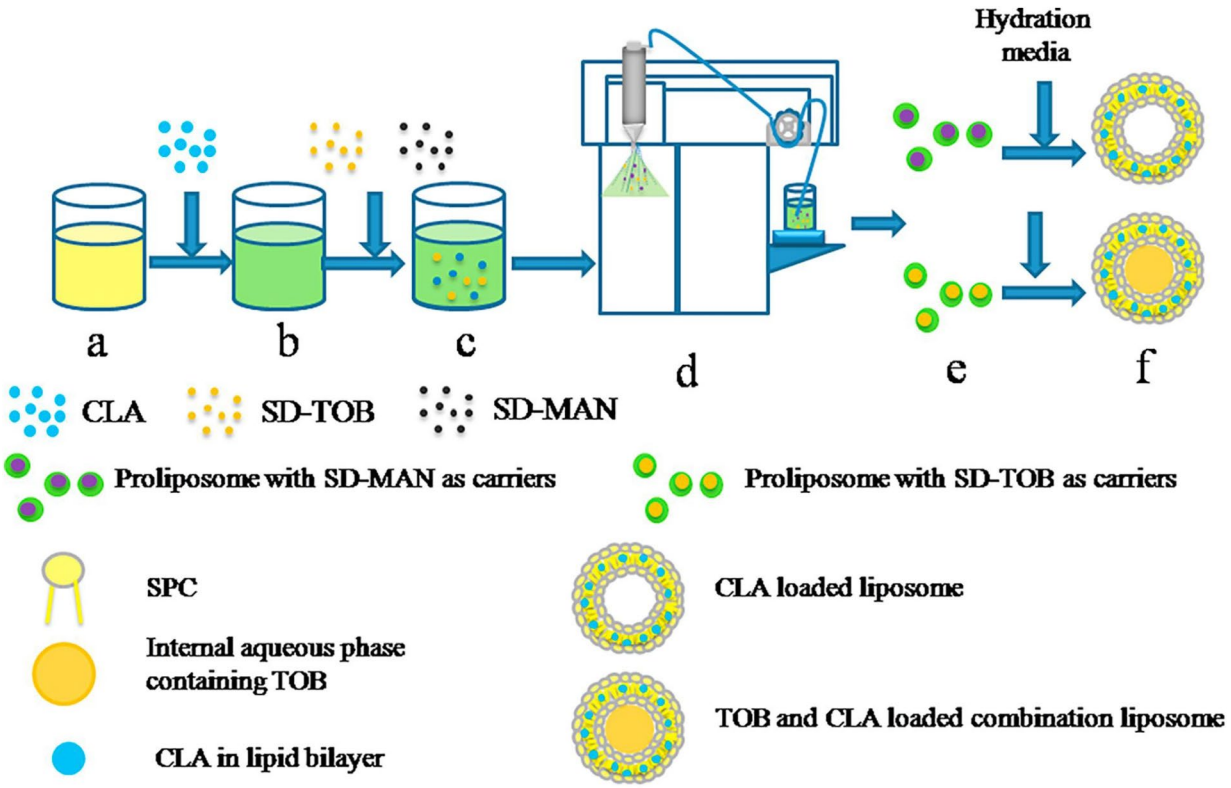

Fig. 3 The schemes of proliposome production and co-loaded mechanism: **a** ethanolic lipid solution; **b** CLA ethanoliclipid solution; **c** CLA ethanolic lipid suspension with combination core carrier; **d** one-step spray drying; **e** proliposome; **f** reconstituted liposome. *CLA* clarithromycin, *SD-TOB* spray-dried tobramycin, *SD-MAN* spray-dried mannitol, *SPC* soya phosphatidylcholine [reprinted with permission from Elsevier (Ye et al. 2018)]

and the host particle is usually stronger than the weight of the guest particle, dry powder coating can produce robust, functionalized particles that can withstand the removal of the coating material due to stresses that may occur during additional formulation processes or other powder handling (Chen et al. 2008). Either a discrete or continuous coating of guest particles can be achieved depending on a variety of process operating conditions including processing time, temperature and humodity, weight fraction of guest to host particles and various particle properties (Pfeffer et al. 2001; Dahmash and Mohammed 2015).

In the past, the principle of increasing fluidity of inhalable drug powder was implemented by attaching a pharmaceutical lubricant, which can be used as an FCA by simple mixing or conventional blending method, to the surface of drug particles. Tumble mixer, cube mixer, turbula mixer, and V-blender are the commonly used techniques for achieving ordered mixing through simple mixing with relatively low shear stress. These method was aimed to prevent cohesion via direct contact between drug particles. However, these dry powder coating by simple mixing or intensive mixing generally takes the form of discrete coating. Thus, the effect of improving powder properties compared to the amount of the applied coating material may be relatively poor. To enhance this effect, attempts have been made to coat an FCA more densely and uniformly on the particle surface. e studies on the improvement of powder aerosolization behavior have shown that high-shear dry coating techniques, such as the mechanofusion or co-milling of FCAs, significantly affect the interaction forces of inhalable particles by providing more effective coating than that with conventional blending methods (Begat et al. 2005, 2009). In contrast other conventional low energetic mixing methods, these recent dry powder coating techniques are designed to provide a relatively complete thin coating layer onto the host particle surface through the application of high shear forces (Begat et al. 2005). The improved flow and aerosolization of carrier-free drug powders for high-dose DPIs is attributed to efficient decreasing interparticulate interactions through uniformly formed dense layer of FCAs on the particle surface. In addition, FCA, which can also act as a lubricant, can prevent surface amorphization by reducing this shear stress during the micronization process. Thus, dry coating is an effective method for the preparation of powders in high-dose DPI with only a small amounts of excipient use (Zhou et al. 2013; Brunaugh and Smyth 2018a, b).

Several studies have suggested that the mechanofusion process (also known as mechanical dry coating) is an effective method for coating the surface of API particles using FCAs with little or no reduction in particle size. This technology was first developed by Staniforth and Morton for the preparation of inhalable drug powders (Pfeffer et al. 2001; Begat et al. 2009). High levels of energy are required to fragment and coat the FCA particles onto the host drug particle via solid sintering. This high-energy mechanofusion process can lead to a de-laminated and uniform coating of FCA on the drug particle surface, thus forming complete nanostructured layers around the surface of the host drug particles (Zhou et al. 2013). Unlike conventional simple blending methods, the mechanofusion method provides greater control of the shear and compressive forces. This unique process first separates the fine constituent powders through deagglomeration to expose their surface areas, followed by the introduction of guest coating materials on the surfaces of the host drug powders upon contact between the two materials. After that, the coating material is mechanically smeared over and fused to the drug particles (Zhou et al. 2010a, b; Qu and Av Morton 2015).

Another effective surface modification method based on high-shear dry coating is co-milling. Co-milling involves the co-processing of two or more components using a milling machine to produce a homogenous powder mixture with reduced particle size. It can be utilized to de-agglomerate strongly agglomerated particles and simultaneously coat the individual drug particles with an added FCA. The co-milling of an API with an FCA can improve the aerosolization performance and physicochemical stability of an inhalable drug powder. In particular, co-jet milling of drug particles with an FCA as a coating material may provide efficient surface coverage at a specific concentration to reduce cohesion by reducing inter-particulate interactions primarily through decreased surface energy and friction between particles (Shetty et al. 2020). Jet milling is a type of fluid energy mill. This shows that co-jet milling of drugs and lubricants as FCAs enabled simultaneous particle size reduction and surface coating to achieve satisfactory aerosolization performance. In addition, the dispersive surface energy of micronized drug particles was shown to decrease after co-jet milling with an FCA, and the energy distribution was more homogenous. Furthermore, particle surface coating with MgSt using co-jet milling showed also improved stability by controlling the moisture absorption (Tay et al. 2010; Mehta 2018). Quantitative correlations between the surface lubricant coverage and aerosolization behavior of co-jet-milled inhalable drug particles were established by Mangal et al. 2019a, b, c. During dry coating of inhalable drug particle, FCA forms thin layer with a nanometer range thickness on the surface of core drug particles which regulate the adhesive interactions between the micronized drug and used soft FCA. However, it should be noted that these favorable effects are highly FCA concentration-dependent (Tay et al. 2010; Mangal et al. 2019a, b, c). Thus, it is important to find an appropriate coating percentage for optimized dry coating. An optimum FCA content is a concentration that enhances powder flow the most and results in uniform thin film formation on every individual particle. At the same

time, the surface energy is also reduced within the proper dry coating ratio range. However, there could be a sharply reduced flowability by increased film thickness over the optimum FCA content. Moreover, the surface area and particle size distribution of FCA are also important key parameters that can determine coating efficiency (Mehta et al. 2020).

In dry coating such as co-jet milling, several studies have reported that leucine, a hydrophobic amino acid, has relatively lower effect in reducing surface energy than that of MgSt. This is presumed to be due to differences in the coating principle and surface modification mechanism of the two materials during dry coating. By these fundamental differences, surface coating efficiency using MgSt could be superior to that using leucine, showing higher surface coverage at a corresponding concentration (Stank and Steckel 2013; Lin et al. 2015). However, it was also reported that the aerosolization performance of dry powder coated using leucine could be better through the change of other surface properties such as roughness despite the poor coating efficiency.

These findings have shown that particle surface coating with FCAs can improve the flow, fluidization, and aerosolization of cohesive and adhesive particles by decreased cohesion and adhesion forces following reduced surface energy.

Corrugated particle

Corrugated particles mean particles with a corrugated surface (Fig. 4a). The advantages of corrugated particles in high-dose DPIs can be explained by the following theory. Generally, the dominant cohesive force in micronized particles is mainly determined by VdW forces. However, surface rugosity increases the separation distance by limiting the approach of two particles, thus reducing the VdW attraction (Visser 1989). This is the theoretical basis for the particle engineering approach for the preparation of corrugated particles, in which enhanced surface rugosity is estimated to decrease the cohesion of particles by reducing the contact area through a decrease in the radius of curvature in the contact zone (Weiler et al. 2010). Many researchers have found that non-porous particles with surface corrugation can lead to enhanced aerosolization performance with high FPF compared with particles with smooth surfaces (Brunaugh and Smyth 2018a, b). This difference also became more pronounced as the flow rate through the device was reduced, which means that the efficiency of drug delivery to the lung can be improved in patients with poor lung inhalation capacity. However, it should be noted that there is a limit to enhancing powder dispersion and aerosolization with increasing surface rugosity by corrugation (Chew and Chan 2001, 2002; Chew et al. 2005).

Interestingly, the corrugation of inhalable microparticles can be achieved by spray drying through alteration of the Peclet number, which describes surface accumulation based on the difference between the diffusional motion of the solute and the surface recession rate of the droplet during drying (Brunaugh and Smyth 2018a, b). For excipients with a low P_e value (< 1), the evaporation rate of solvent is similar to the molecule diffusion inside the drying droplet, thus, the distribution of the excipient molecule is uniform, hence forming spherical particles. In contrast, for excipients with a high P_e value (> 1), the material diffusion to the center of the droplet is slower than the solvent evaporation rate within atomized solution droplets, thereby resulting in the accumulation of the solute at the droplet surface during the shrinkage, followed by forming folded or corrugated particles (Focaroli et al. 2019; Lechanteur and Evrard 2020).

Based on this theory, the Peclet number can be altered by changing various process parameters, such as changes in the feed concentration or solvent composition, without the addition of excipients in the DPI formulation (Vehring 2008; Brunaugh and Smyth 2018a, b). These changes in the drying condition of the atomized droplet can interfere with water vapor diffusion, resulting in the formation of corrugated particles (Chew and Chan 2001). In particular, biopharmaceuticals can form corrugated particles preferentially by distributing on the surface of drying droplets when spray-dried without any additives due to their surface activity aroused from their amphiphilic structure. On the contrary, if the corrugated surface is not formed by the drug alone, the corrugated particles could be produced by co-spray drying through formulation with some excipients that induce wrinkled surface formation. Many studies on various additives inducing corrugated surface have been reported. It was shown that a critical factor to enrich leucine on particle surface during spray drying is the control of formulation composition to ensure that leucine precipitates early stage during particle formation. Based on the fundamental principles of spray-drying, it has been suggested that the corrugated surfaces formed by the addition of leucine is due to the shell-forming properties of leucine (Vehring 2008; Mehta et al. 2020; Mehta 2018).

Besides, trileucine can also be used to induce corrugated surface formation. It was reported that a change in the pH of the feeding formulation solutions can influence the morphology and crystallinity of the particles spray-dried with trileucine (Lechuga-Ballesteros et al. 2008). Interestingly, more highly corrugated particles were generated at a neutral pH solution than at a low or high pH solution. It was suggested that the relatively low and pH-dependent aqueous solubility behavior of trileucine could result in the formation of low density highly corrugated particles (Mehta et al. 2020).

It was reported that cyclodextrin has to form a shell layer around core particles (Dufour et al. 2015; Ramezani et al. 2017; Zhao et al. 2018; Lechanteur and Evrard 2020). Interestingly, the formulation of hydrophilic core material with HPβCD has improved powder flowability and low moisture

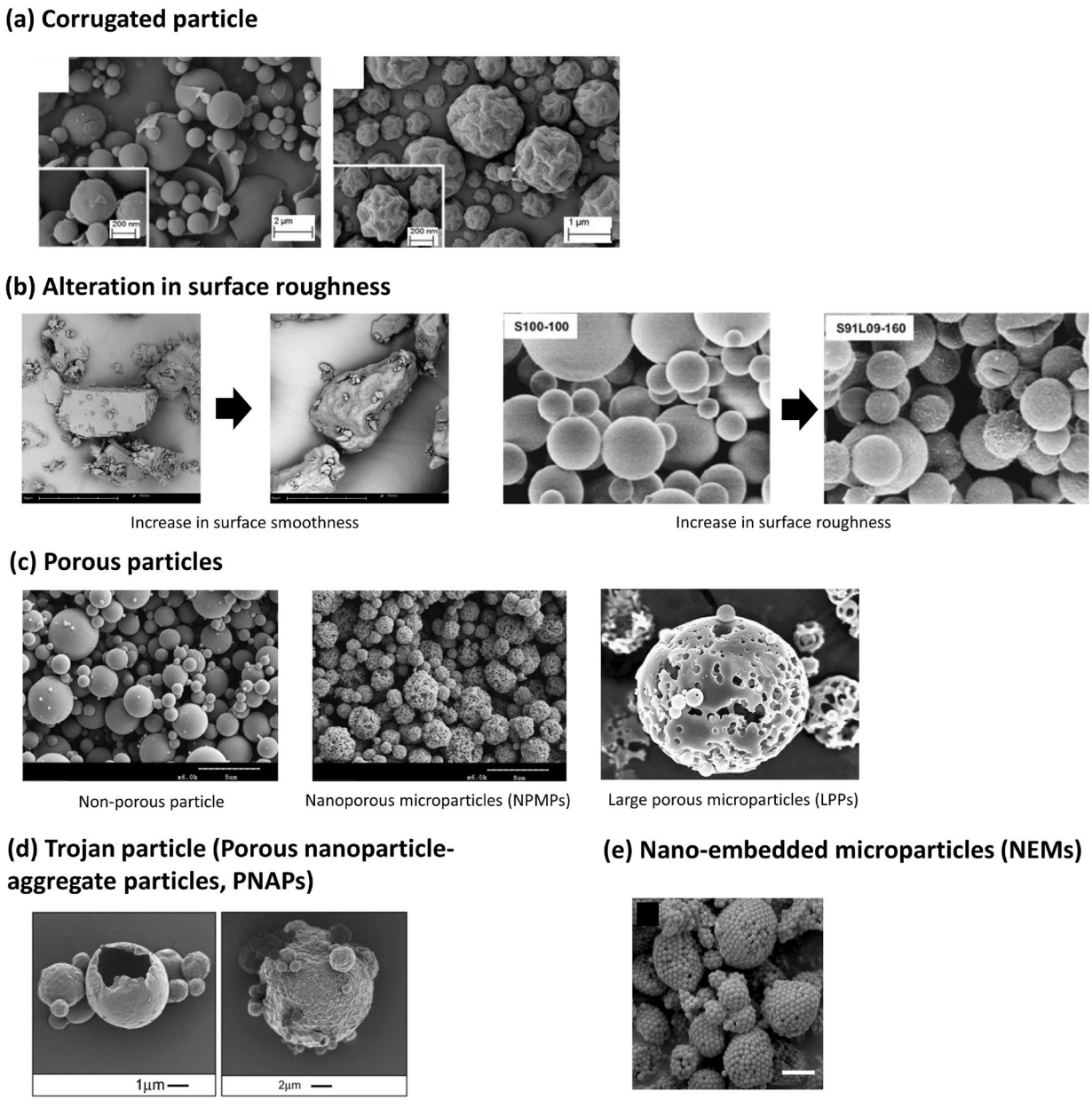

Fig. 4 Scanning electron micrographs of inhalable particles prepared using a combination of particle engineering techniques and formulation approaches as surface modification strategies: **a** lactose carrier-free spray dried particles containing rivastigmine hydrogen tartrate (left) without and (right) with 15% leucine [reproduced with permission from Elsevier (Simon et al. 2016)], **b** smooth surface formation of a cohesive lactose monohydrate powder by intensive mechanical dry coating (left) [reproduced with permission from Elsevier (Zhou et al. 2010a, b)] and rough surface formation of leucine coated salbutamol sulphate powders [reproduced with permission from Elsevier (Raula et al. 2010)], **c** spray-dried non-porous bendroflumethiazide particle (left), spray-dried nanoporous microparticles (NPMPs) bendroflumethiazide particle using ammonium carbonate (middle) [reproduced with permission from Elsevier (Healy et al. 2008)], and spray-dried Pulmosphere® tobramycin inhalation powder [reproduced with permission from Wiley Online Library (Konstan et al. 2011)], **d** spray-dried Trojan particles encapsulating dexamethasone acetate [reproduced with permission from Elsevier (Gómez-Gaete et al. 2008)], and **e** nano-embedded microparticles [reproduced with permission from Elsevier (Ruge et al. 2016)]

absorption. It was proposed that HPβCD forms a layer on the surface of a core particle. The relatively more hydrophobic component, HPβCD accumulate and wrinkled preferably at the outer layer of liquid droplet due to the high P_e number, whereas the relatively more hydrophilic component favorably diffuses to the center of liquid droplet. Thus, it was concluded that hydrophilic material forms a solid inner core, whereas the cyclodextrin forms a corrugated outer layer due to the different physicochemical properties of HPβCD and hydrophilic core material, during the drying. As such

hydrophilic core material may include water soluble drugs, it is supposed that cyclodextrins can be used to produce corrugated particles for various high-dose DPIs.

Alteration in surface roughness

The changes in the particle surface roughness, which in turn affect the total surface area of the particles, is a typical surface modification technologies of high-dose DPIs for improving pulmonary drug delivery (Table 2 and Fig. 4b). The roughness mentioned here excludes rugosity, such as corrugation, which is formed by wrinkles on the surface. Several studies on surface dry coating have observed a reduction in specific surface area (Dahmash and Mohammed 2016). This is because the surface modification method using dry coating was attributed to a reduction in the surface irregularities of dry powders, where the coating material filled the gap on the particle surface, thereby producing a smoother surface on the resultant composite particles. In this case, interlocking between particles is reduced, so that flowability and aerosolization performance can be improved. In addition, the optimal percentage of coating material to achieve complete coverage of the drug particle surface can be determined via the correlation between the percentage of the added coating material, the reduction in the specific surface area, and aerosolization performance. Soft lubricants based on fatty acids are often used as coating materials for this purpose. The strong adhesive force between the drug and soft lubricant particles will induce a thin film to be formed extensively on the surface of the core drug particle. Because of the continued shearing of the system, it will cause the soft lubricant to spread further until a monomolecular film is formed (Rowe 1988). In addition, the softness of the lubricant could fill even the finest gaps on the surface. This will decrease the number of strong cohesive interactions between the drug particles causing a decrease in agglomeration.

In contrast to soft lubricant such as MgSt, the surface modification mechanism of leucin has been reported to be different in co-jet milling. Numerous studies have shown that the proportion of the coating material distributed on the API surface and its pattern are different because the coating principle is different depending on the coating material. In contrast to MgSt, co jet milling of ciprofloxacin with L-leucine can create rougher surfaces, thereby reducing the inter-particulate contact area and, hence, the attractive force (Mangal et al. 2019a, b, c).

The hydrophobic amino acid leucine can also be used to alter the particle surface roughness of high-dose DPI formulations using various bottom-up particle engineering technologies (Yang et al. 2015; Brunaugh and Smyth 2018a, b). Several researchers have investigated the effects of L-leucine surface coating on carrier-free, high-dose inhalable drug particles (Lechuga-Ballesteros et al. 2008; Shur et al. 2008; Thai et al. 2010; Zhang et al. 2010; Boraey et al. 2013; Rattanupatam and Srichana 2014; Cui et al. 2018). A report showed that leucine was enriched on the droplet surface owing to its surface activity in aqueous solutions or its vapor deposition in saturated air (Raula et al. 2010). This study demonstrated that the leucine distribution in the inhalable particles and the particle surface smoothness can be varied by changes in the process conditions, such as the composition of solvent and leucine concentration. Due to the rough surface by coating of leucine, coated fine powders showed improved flowability and dispersibility. However, the aerosolization properties of the coated powders decreased as the surface roughness increased too at excess leucine coating ratio which is hypothesized as mechanical interlocking between the rough particles. In this way, when the surface roughness increases optimally, adhesion of the drug powder to the reservoir such as capsule or blister may decrease, thereby increasing the emission of the powder from the device. However, it should be noted that mechanical locking increases if the surface roughness is excessive, which in turn reduces the aerosolization property.

Porous particles

The preparation of porous particles is a widely applied approach to formulate desirable inhalable particles with large geometric diameters and low densities (Table 2 and Fig. 4c) (Lin et al. 2015). Edwards et al. introduced large porous particles (LPPs) for the pulmonary delivery of systemic agents, such as insulin (Edwards et al. 1997). Typically, LPPs were designed to have a low particle density of less than 0.4 g/cm^3, which enabled them to maintain a small aerodynamic diameter despite a large geometric diameter of greater than 5 µm (Brunaugh and Smyth 2018a, b). The porous nature of the microparticles can result in reduced cohesion via decreased inter-particulate interactions, consequently leading to a lower particle aggregation tendency. Thus, this improved physical property allows for the enhancement of flowability and aerosolization of inhalable drug particles (Healy et al. 2014). In addition, LPPs with large geometric sizes could escape the alveolar macrophage clearance in the lung more effectively than smaller non-porous particles (Edwards et al. 1997).

Spraying based particle engineering technologies have another very interesting advantage that porous particles can be manufactured by controlling of process parameters. It was reported that the nanoporous microparticles (NPMPs) of chemical drugs, sugars and protein molecules, consisting of roughly spherical formations with irregular surfaces of fused nanoparticulate spherical structures, were prepared from a solution consisting mixture of solvent and antisolvent for the applied materials (Healy et al. 2008; Nolan et al. 2009;

Amaro et al. 2011; Nolan et al. 2011; Ógáin et al. 2011; NíÓgáin et al. 2012). The selection of optimum solvent system considering the hydrophobic/hydrophilic nature of the investigated material is an important factor for NPMP production using spray drying.

In recent years, spray-freeze-drying has emerged as an alternative drying method to spray drying for heat-labile drugs (Cheow et al. 2011). It consists of a two-step process that involves atomizing the feeding solution into a freezing medium, which turns the fine spray into frozen droplets. The commonly used freezing medium is liquid nitrogen, and this cryogenic liquid can be agitated to prevent possible aggregation of the frozen droplets (Maa et al. 1999; Niwa et al. 2012; Wang et al. 2012). This was followed by lyophilization to remove the ice of the frozen droplets through sublimation, thereby obtaining dried powder. The advantages of spray-freeze-drying are preservation of the integrity of biopharmaceuticals and heat-labile drugs (Yu et al. 2004; Audouy et al. 2011), as well as high production yield. Interestingly, the removal of ice via lyophilization produces light and porous particles owing to the phase separation of solids from the ice crystals during freezing (Qian and Zhang 2011; D'Addio et al. 2012; Parsian et al. 2014).

These inhalable porous particles can appear to have enhanced aerosol performance by reducing the particle density and increasing surface areas compared to spray dried non-porous particle of same material (Ali and Lamprecht 2014). The advantages of such porous particles are currently receiving great attention, and applied research is being conducted widely. Therefore, spray draying and spray freeze drying will be more investigated to prepare various microparticles of biomaterials and chemical drugs suitable for inhalation (Amorij et al. 2007; Vehring 2008; Murugappan et al. 2013).

Air® is a well-known pulmonary drug delivery technology that produces LPPs via spray drying, which include phospholipids with albumin and saccharides with an ethanol/water co-solvent system (Vanbever et al. 1999; Chow et al. 2007; Vehring 2008; Ungaro et al. 2012a, b; Healy et al. 2014). PulmoSphere™ technology is the first to be commercialized as an inhalable LPP products. It acts by spray drying a unique emulsion containing a pore-forming agent such as perfluoroctyl bromide, surface modifiers such as calcium chloride ($CaCl_2$), and phospholipids as a dispersion stabilizing agent (Weers and Tarara 2014; Lin et al. 2015). The success of the PulmoSphere™ technology has focused a lot of attention on spray drying emulsions to produce porous particles. The LPPs produced by PulmoSphere™ are small with a geometric diameter between 1 and 5 µm with a foam-like morphology. The PulmoSphere™ technology has been applied to dry powder delivery for tobramycin (Newhouse et al. 2003), ciprofloxacin (Stass et al. 2013), budesonide (Duddu et al. 2002), indacaterol, leuprolide, and amphotericin B (Weers and Tarara 2014; Lin et al. 2015), which all showed improved aerosolization properties. The commercialized TOBI® Podhaler® using PulmoSphere™ technology indicates that such improved aerosolization properties leads to improved efficiency of drug delivery to the lung in vivo and significantly reduced dose compared with that with the conventional nebulization therapy of tobramycin (Banaschewski and Hofmann 2019).

Recently, several innovative novel technologies have been developed for the production of excipient-free porous inhalable particles (Healy et al. 2008; Nolan et al. 2009; Amaro et al. 2011). This method involves spray drying a solvent/anti-solvent solution with or without a pore-forming agent, such as ammonium bicarbonate. The ammonium bicarbonate decomposes into CO_2 during the preparation process, hence producing excipient-free porous particles. In addition, the double emulsion solvent evaporation or extraction method has been widely used for the preparation of LPPs (Healy et al. 2014). The original production process of LPPs was based on the double emulsion solvent evaporation technique (Edwards et al. 1997). The aqueous internal phase consists of an aqueous solution of API, which may contain other ingredients such as polymeric additives, cyclodextrin, solubilizing agents, or pH modifiers. The organic external phase may be composed of a polymeric carrier with or without a pore-forming agent dissolved in volatile organic solvents such as dichloromethane with the addition of an emulsifier such as phosphatidylcholine. To form a primary emulsion, the aqueous internal phase and organic external phase are homogenized and then injected into a secondary aqueous phase containing a stabilizing polymer such as polyvinyl acetate or polyvinyl alcohol (Patel et al. 2012). The organic solvent in the prepared double emulsion is eliminated by evaporation or extraction methods, thereby resulting in LPP formation via fabrication and hardening of the outer shell. Conventional vacuum drying, spray drying, and supercritical extraction are used as organic solvent removal methods for fabrication. Subsequently, LPPs are isolated by centrifugation, washing, and freeze drying to obtain a dry powder.

In addition, new technologies that modify these previous production processes for porous particle have been reported recently. An alternative approach to the production of porous particle implemented spray drying instead of isolation and final freeze drying to separate solids from aqueous and organic phases (Healy et al. 2014). In addition, expanding and combining the conventional approach to solution or suspension spray drying was introduced for the production of porous particle. As a representative example of this combination approach, porous particle was produced by spray drying of a "compressed emulsion," in contrast to the double emulsion solvent evaporation technique (Steckel and Brandes 2004). The aqueous external phase was basically composed of a water-soluble drug, surfactant,

and salt. Interestingly, this compressed emulsion consisted of an internal organic phase of a propellant. Furthermore, an alternative production method for porous particle was introduced by the preparation of porous particle using an emulsion solvent evaporation method and reprocessed using SC-CO_2. The prepared inhalable microparticles were subsequently stored under pressurized conditions using SC-CO_2. Here, SC-CO_2 acts as a solute distributed in microparticles, then permeated CO_2 expanded and escaped from the microparticles by depressurization and generated pores. SCF processing was able to produce porous particle by modifying the original non-porous microparticles using a relatively low process temperature (Koushik and Kompella 2004; Koushik et al. 2004).

Nanoparticle-aggregate particle

In addition to corrugated and porous particles, various strategies for design of unique architectures of inhalable microparticle to achieve micrometric nanoparticle-based inhalable dry powder have recently been investigated (Ungaro et al. 2012a, b). Especially, micrometre-sized composites formed by finely controlled nanoparticles aggregation can combines the several advantages of nanoparticles with the excellent aerodynamics property of microparticles (Fig. 4d). The nanoparticle aggregated micrometre-sized composites is designed to act as carrier particles that release nanoparticles once delivered to the desired target region of body (Ungaro et al. 2012a, b; Malamatari et al. 2020). Moreover, the increased surface rugosity due to the distribution of many nanoparticles on the surface will contribute to reducing adhesion force of the particles and improving the powder flowability and aerosolozation property. In general, inhalable nanoparticle aggregates of various drugs have been produced by spray drying, as the solidification step, following preparation of nanosuspensions using either top-down (e.g., wet milling, microfluidization, and high-pressure homogenization) or bottom-up methods (e.g., antisolvent precipitation) (Malamatari et al. 2016a, b, 2020). This innovative particle-engineering approach for the modification inhalable particle has been used for various drugs; budesonide (Šimková et al. 2020), cyclosporine A (Yamasaki et al. 2011), ibuprofen (Malamatari et al. 2017), indometacin (Malamatari et al. 2015), itraconazole (Duret et al. 2012), meloxicam (Pomázi et al. 2013), resveratrol (Liu et al. 2019), tadalafil (Rad et al. 2019), and theophylline (Malamatari et al. 2016a, b). In addition, porous nanoparticle-aggregate particles (PNAPs) through self-assembling, called Trojan particle, have been also developed (Tsapis et al. 2002; Sung et al. 2009; Muttil et al. 2010). However, care must be taken to maintain the original nanoparticle integrity during the process of inducing aggregation of nanoparticle. In addition, although the reason is not clear, improvement of aerosolization is well controlled in some cases of PNAPs. Recently, nano-embedded microparticles (NEMs) was introduced and considered as one of the most promising approach technology for the property modification of inhalable dry powder and have been extensively explored by several research groups (Yamamoto et al. 2007; Tomoda et al. 2008a, b; Ungaro et al. 2012a, b) (Fig. 4e). However, nanocomposite particles can be obtained by incorporation of drug-loaded polymer nanoparticles within inert carriers micoparticles. Because NEMs cannot be manufactured without a carrier material due to the principle of particle composition, currently there is a limitation to apply this technology to high-dose DPI formulations.

Co-formulation with APIs

As described above, hydrophobic excipient coatings are known to improve the aerosol performance and stability of hygroscopic inhalable drug particles by reducing the irreversible particle agglomeration and rate of particle growth (Hickey et al. 1990; Brunaugh and Smyth 2018a, b). However, achieving this goal without excipients is still challenging. A recent approach has been the elimination of excipients and the co-formulation of hydrophobic and hygroscopic drugs as an alternative to hydrophobic excipients or additives. In addition, co-formulated APIs can be micronized at the same time, resulting in particles containing multiple drugs (Adi et al. 2008a, b; Pilcer et al. 2013a, b; Zhou et al. 2014, 2016; Lee et al. 2016; Mangal et al. 2018; Chai et al. 2019; Mangal et al. 2019a, b, c). Generally, these approaches have been utilized in generating co-formulations of hydrophobic and hygroscopic drugs to improve the aerodynamic performance of a drug with unfavorable physicochemical properties or dispersion behavior. These co-formulations are based upon the known synergistic effect of the drugs, which can result in reductions in the required dose and the number of medications, thus improving patient compliance. Generally, it is possible to incorporate multiple components into a single particle in this one-step continuous manufacturing process using spray drying. Importantly, storage-induced crystallization, which is associated with high-dose spray-dried amorphous powders, can be prevented through co-spray drying of combination drugs, especially antibiotics. Co-spray drying of antibiotics with the polypeptide antibiotic colistin was shown to enhance the physical stability of the amorphous spray-dried antibiotic powder formulation stored at elevated RH conditions (Zhou et al. 2016; Shetty et al. 2018a, b, c; Mangal et al. 2019a, b, c). The stabilization mechanism of colistin in the co-spray-dried high-dose antibiotic DPI formulation is the formation of a polymer-like matrix by enrichment on the particle surface during co-spray drying, reducing the molecular mobility of amorphous drug particles, hence completely preventing its crystallization at elevated RH. Furthermore, the specific intermolecular

hydrogen bonding between two APIs can be an important factor for improving the physical stability of the composite DPI formulation. Recently, nanoparticle aggregates particles containing drug combinations have also been reported for tobramycin with clarithromycin (Pilcer et al. 2013a, b) and budesonide with theophylline (Leng et al. 2019).

Conclusion

Various particle surface modification methods, including sophisticated particle engineering and formulation techniques, have been utilized to overcome the problems associated with high-dose DPIs by changing the cohesive property through co-processing with excipients, such as FCA (Sibum et al. 2018; Shetty et al. 2020). Based on these technological principles, novel approaches have been explored to develop high-dose DPIs. It is worth mentioning that the research on high-dose DPIs has expanded widely; consequently, there has been successful development of drugs through attempts to overcome the remaining issues with high-dose DPIs (Brunaugh and Smyth 2018a, b). In particular, DPIs for high-dose combination therapy will be further developed, as well as high-dose DPIs containing one API. In particular, combination antibiotic therapy is a promising strategy to effectively address emerging human health concerns, as respiratory tract infections caused by multidrug-resistant gram-negative bacteria, particularly *P. aeruginosa*, are a serious public health threat worldwide (Mangal et al. 2019a, b, c). Thus, the development of high-dose DPIs in combinations with antibiotic therapies will be required to maximize the therapeutic efficacy and minimize the development of resistance in severe lung infections caused by gram-negative pathogens (Mangal et al. 2019a, b, c). Therefore, it is expected that the next generation of high-dose DPIs will be safer and have higher therapeutic efficacy beyond the limitation of traditional high-dose DPIs.

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Declarations

Conflict of interest All authors (H. Park, E.S. Ha, and M.S. Kim) declare that they have no conflict of interest.

Research involving human and animal rights This article does not contain any studies with human and animal subjects performed by any of the authors.

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