Progress in particle engineering science: Towards advanced dry powder inhalation systems

Insight into characteristics of HPMC capsules and development of engineered particles to achieve targeted product characteristics and performance criteria

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Abstract

Inhalation drug therapy has been used as a non-invasive delivery form to target drugs to the site of action or bypass the gastrointestinal tract to deliver biologic compounds to the systemic circulation. Capsule-based dry powder inhalation (cDPI) systems have gained significant interest as a drug delivery system, especially in emerging economies due to their cost effectiveness and ease of manufacture. DPI systems based on capsule technology comprise three important interacting components: the formulation, the capsule and the device. Carrier-based, formulation-filled, gelatin capsules have been successfully used over many decades for the treatment of asthma and chronic obstructive pulmonary disease (COPD). Recent progress in the treatment of other respiratory diseases and the increasing role of therapeutic biologic compounds have required advancements in capsule and formulation technologies to deliver higher doses as well as improve stability of sensitive biologic compounds. Beside other characteristics, capsules based on hydroxypropyl methylcellulose (HPMC) provide a broader design space for headspace humidity and mechanical resistance in inhalation devices. Particle engineering using spray drying technology can increase the drug load above 60%[1] and at the same time provide particles with an aerodynamic particle size in the desired range of about 2 µm. The performance of a DPI system with respect to product stability, powder release and powder dispersion is influenced by capsule material, inner capsule-surface properties, piercing or shearing behavior, engineered-particle interactive forces and aerodynamic particle size and shape. Capsules can be customized with respect to moisture level and inner lubrication, in conjunction with a specific formulation and device. This article will provide scientific insight into the characteristics of HPMC capsules and the development of engineered particles to achieve targeted product characteristics and performance criteria.

Introduction

Respiratory diseases remain a major global health burden, especially in emerging markets due to limited access and affordability of effective inhalation drug therapies.[2,3] In the late 1960s, capsule-based dry powder inhalation systems (cDPIs) were introduced into the market to provide sodium cromoglycate using the Spinhaler® (Fisons) as a delivery device.[4,5] The Spinhaler revolutionized inhalation therapy due to breath activation by patients, delivery of larger doses (20 mg) as a dry powder formulation and improved product stability.[6] Despite the development of sophisticated blister and reservoir-based inhalation systems, cDPI systems remain a "gold standard" technology, which has been confirmed by several recent product approvals, including Spiriva® Handihaler® (Boehringer Ingelheim) and Onbrez® Breezhaler®, Seebri® Neohaler and Tobi Podhaler® (all from Novartis). cDPI systems are increasingly considered for emerging markets due to their proven cost effectiveness and ease of manufacturing, enabling regional production using existing capsule filling lines and supplies.[7]

The performance of cDPIs is the result of the interaction of the powder formulation, the primary packaging (capsule), the delivery device and the airflow generated by the patient.[7] The majority of marketed DPI formulations are interactive powder mixtures of micronized drug particles with larger carrier particles to provide sufficient powder flow.[8] However, major limitations are the relatively low achievable drug load, with a typical drug:carrier ratio of 1:67.5,[9] as well as increasing interest in the delivery of proteins or other molecules into the systemic circulation where carrier-based systems may not be appropriate. To overcome this limitation, engineered particles or aggregates of micronized drug, with or without a carrier, as visible spheres or low density, porous particles have been considered as alternative formulation strategies.[10]

Upon activation, the device either pierces the capsules with needles at the hemispherical ends from the top as in the Aerolizer® (Novartis) or from the side as in the Handihaler or separates the capsule body from the cap by shear forces as with the Rotahaler (Cipla). The expulsion of the drug formulation takes place through the sheared or pierced capsule shell upon inhalation by the patient. The inhalation stream creates high energy airflow within the device that mechanically impacts the capsule to release and disperse the powder so the small drug particles are carried by the inhaled air into the deep lung.

Engineered particles are carrier-free formulation technologies that have been developed and investigated intensively to achieve suitable particle characteristics for pulmonary delivery, such as low density (e.g., porous particles) or special morphology (e.g., high rugosity particles). In January 2006, the United States Food and Drug Administration (FDA) approved the first carrier-free, engineered-particle system containing the protein insulin (Exubera™, Pfizer) for systemic treatment of diabetes. In June 2013, the FDA also approved a high-dose, carrier-free formulation of a 28 mg dose of tobramycin per capsule for the treatment of *Pseudomonas aeruginosa*-positive cystic fibrosis patients, using the Tobi Podhaler.

Since then, spray drying has been increasingly considered for the manufacture of particles for pulmonary drug delivery, including proteins and peptides,[11] vaccines,[12] DNA,[13] high-dose antibiotics[14] and small molecules.[15] Spray-dried particles include excipients suitable for inhalation purposes and are formed by the atomization of liquid containing the drug/excipients in the solution or suspension, followed by rapid solvent evaporation. The viscosity of the spray solution, type of solvent, atomization nozzle geometry and number of processing parameters such as feed rate, atomization pressure, drying temperature and inlet-air humidity determine the properties of the engineered particles achieved by spray drying. This article will focus on the development of cDPI systems by spray-dried particle engineering.

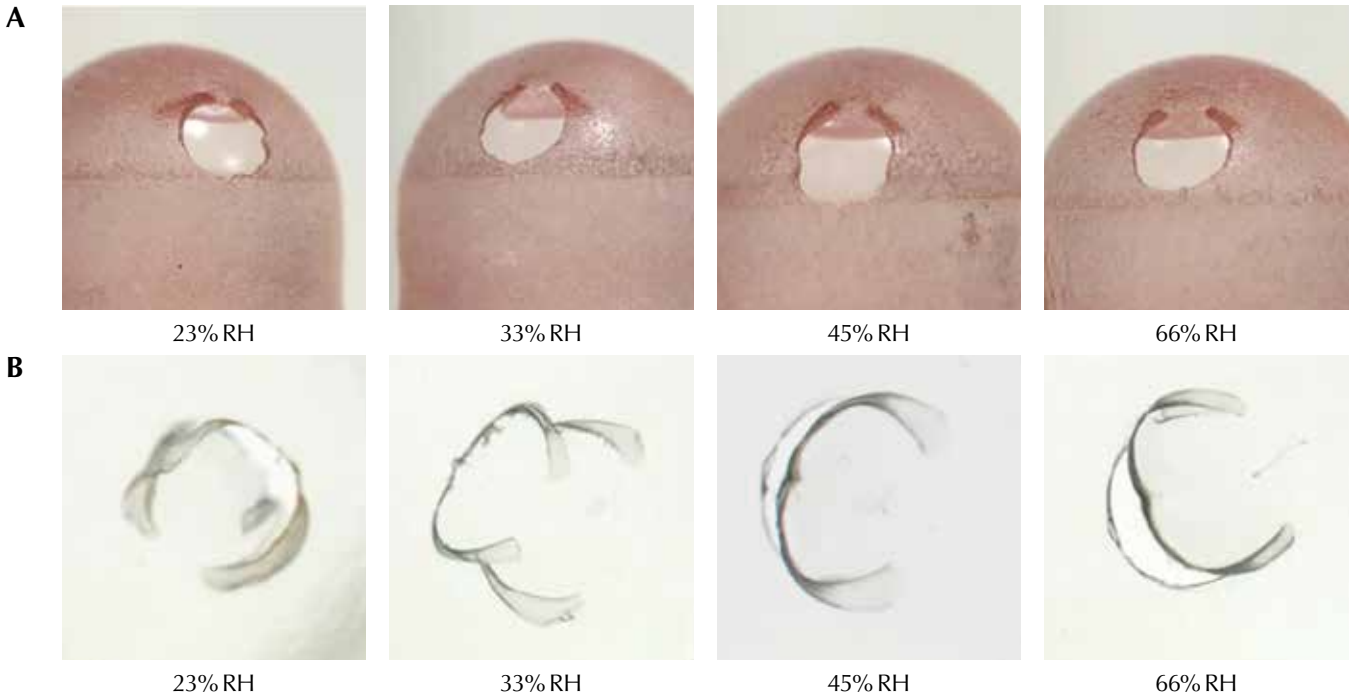
DPI capsules based on HPMC

With the introduction of hydroxypropyl methylcellulose (HPMC) capsules at the end of the 1990s, the design space for cDPI inhalation technology was substantially enlarged. Today, various HPMC capsules are available (such as those from Lonza), which are based on pure thermogelated HPMC (e.g., Vcaps® Plus DPI) or HPMC-containing a gelling system for technical reasons, which is either carrageenan-based (e.g., QualiV®, Vcaps® Gen C), gellan-gum-based (e.g., Vcaps® DPI) or pectin/glycerin-based (e.g., Embo Caps®-VG). The major characteristics of the capsules used for inhalation, which determine product stability and capsule emptying, include inner surface characteristics, lubrication, head-space humidity and mechanical resistance during device-specific opening performance.

The composition and process of the manufacturing of HPMC capsules has an influence on their physical attributes and microstructure. Thermogelated HPMC capsules have shown superior mechanical properties as determined by dynamic mechanical analysis (DMA),

Figure 1

Puncturing performance of HPMC capsules stored at different relative humidity conditions at room temperature (A: Gellan-gum-based HPMC capsule; B: Thermogelated HPMC capsule).



compared to carrageenan-gelling-system HPMC capsules, whereas pectin/glycerin-based HPMC capsules have shown insufficient mechanical resistance (damage).[16] Mechanical resistance is an important property for capsule opening (e.g., puncturing) under the lower relative humidity (RH) storage conditions often required for inhalation products.[17] Figure 1 shows the piercing performance of two types of HPMC capsules stored at room temperature under 23-66% RH. Piercing should neither lead to breakage of the capsules nor broken pieces nor should the holes re-close after release of the piercing needle. Visual inspection confirmed good mechanical properties and piercing performance for both types of HPMC capsules.

One of the most important advantages of HPMC capsules is their moisture content, which can be adjusted through equilibration at a certain relative humidities without impacting their mechanical properties (Figure 1). Moisture content of capsules is generally measured by loss on drying (LOD). Figure 2 shows the correlation between LOD values (measured in an oven or by microwave measurement sensors (TEWS Elektronik) and water activity (assessed using a Rotronic HygroPalm AW1) for HPMC capsules (Vcaps®), which is a critical parameter for dry powder inhalation formulation stability and performance.

Due to the large surface area created by the small particle size of the drug or engineered particles, head-space humidity is a critical factor for drug and formulation stability as well as release from the capsule. With increasing RH, interaction between particles is dominated by water adsorption on the particle surface and higher capillary forces, separation energies and a lower respirable fine particle fraction.[18, 19] With declining RH and therefore reduced moisture content of the formulation, electrostatic interactions between drug particles and the capsule shell increase.[20]

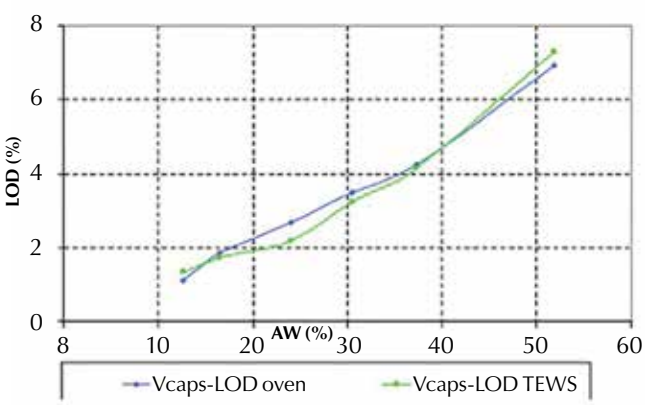
The impact of capsule moisture on powder retention and moisture transfer was investigated with HPMC capsules (Vcaps®) filled with 150 mesh lactose (Respitose® ML001, DFE Pharma) after exposure to different RH conditions for 48 hours. Results in Table 1 show that capsule moisture and powder retention were inversely correlated, with increasing powder retention at declining shell moisture. The elevated powder retention at low RH conditions can be explained by increased electrostatic interactions between the capsule shell surfaces, which interact with the electrostatically charged particles.

The inner lubricant levels in HPMC capsules are known to be an important parameter used to achieve desired, targeted product performance. Using an inhalation grade of lactose (Respitose ML001, DFE Pharma), the powder retention of HPMC capsules with different lubricant levels was studied by Lonza. The data summarized in Table 2 suggest that powder retention in HPMC capsules can be reduced to a negligible level of 0.1% by adjusting the lubricant level during manufacturing of the capsule.[21]

The impact of lubricant level differs among HPMC capsule types. HPMC capsules using carrageenan gelling systems have shown lower powder retention at higher lubricant levels, which correlated with declining internal surface roughness.[22] These findings suggest that powder retention of an inhalation formulation is a multifactorial interaction, requiring careful evaluation of critical material attributes and essential process parameters in order to select and adjust the capsule to achieve the desired product performance.

Figure 2

Correlation between Loss on Drying (LOD) and Water Activity (Rotronic HygroPalm AW1) in HPMC capsules (Vcaps®).



Engineering particles for inhalation by spray drying

Spray drying is an established technology used by the pharmaceutical industry to manufacture microparticles of solid dispersions or amorphous systems.[23, 24] Engineering particles for inhalation using spray drying has gained increasing interest over the past years.[25] Formation of the spray-dried particles is based on the composition of the drug/carrier solution, the atomization of the solution in the spray dryer and the solvent evaporation trajectory. These parameters also determine the particle size and shape, drug state (crystalline or amorphous) and physicochemical stability, as well as particle density.

To engineer particles for inhalation purposes, the spray solution is composed of functional excipients to enhance the physical and chemical stability of the drug as well as to form wrinkle-shaped particles of a 2 µm particle size. The excipient also determines the physical properties of the powder (flowability, electrostatic charging) and the interaction and dissolution in the lung fluid.[26, 27] Four different chemical classes of excipients may be used in the formulation of inhalation particles by spray drying: (1) amino acids, (2) sugars/polyols, (3) polymers and (4) lipids; each provides certain functionality to the spray-dried particles, as shown in Table 3.[28]

The selection and combination of the excipients is a critical step in the development process. To achieve sufficient stability of small and large molecules in amorphous form at room temperature, a high glass transition temperature of the particles is required. Different combinations of leucine and mannitol with trehalose, glycine and alanine were evaluated with respect to their solid state properties and aerolization of the formed particles. Leucine was found to provide the most desirable particle formation and surface properties, due to its saturation at the surface of the particle when combined with trehalose.[29] Recently, Dextran-10, a 10 kilodalton dextran sugar polymer, which is cleared from the lungs within 2-6 hours, has successfully been used to deliver insulin to the systemic circulation by pulmonary delivery.[30] The prepared particles were manufactured with a 70% drug load by spray drying then evaluated in a dog model. The prepared dextran formulation, which had a higher glass transition temperature at 50% RH, was found to be bioequivalent to the Exubera formulation in a beagle model.[31]

The process design (e.g., drying chamber geometry, atomizing nozzle design and principle) and process parameters (e.g., feed rate, inlet/outlet air temperature, air velocity/flow rate, drying gas and air humidity) are critical variables that influence the particle properties and quality. An intensive design of experiments (DoE) has been used to determine the critical variables and their impact on the particles for a spray-dried pulmonary formulation of insulin.[32] Using a Bayesian statistical model, the design space of a spray-drying process was successfully applied as a predictive risk-based approach for the critical quality attributes.[33] Alternatively, flowchart methodology can be used, which relies on mass and energy balance to calculate the critical process parameters by plotting them in a multivariate graph. When applying such methods in conjunction with computational fluid dynamics (CFD) and a very limited number of experiments, sufficient product and process understanding can be gained within a short timeframe.[34,35]

Due to the difference in equipment size and geometry, scaling up a spray-drying process can be challenging. In an internal research project, two formulations with 10% and 40% salbutamol sulphate load were scaled-up from a custom laboratory-scale dryer with 35 kg/h gas drying capacity (BLD-35) to a pilot-scale dryer with 100 kg/h gas drying capacity (PSD-1). The achieved particle morphology, visualized by scanning electron microscopy, showed particles with a rough and wrinkled surface structure (Figure 3).

With a mass medium aerodynamic diameter (MMAD) between 2.5-2.9 µm, an emitted fraction between 85.5-89.8% and a fine particle fraction (< 5 µm) between 76.6–81.5%, no significant difference was shown between the 10% and 40% salbutamol sulfate formulations on the laboratory-scale and pilot-scale. When the spray-dried particles were filled into thermogelated HPMC capsules (Vcaps® Plus) using Xcelodose® automatic filling equipment (Lonza) and released using a standard inhalation device (Plastiape RS01), the Next Generation Impactor (NGI) (Copley Scientific) (60 L/min, 4 sec) confirmed the equivalence between of the two formulations manufactured at different scales (Figure 4).

Conclusion

Over the past decades, important progress has been achieved through the introduction of new capsule types and advanced particle engineering. A range of HPMC capsules with distinct properties as well as customizable specifications have broadened the design space for cDPI systems. The use of spray-drying technology for advanced particle engineering allows the delivery of much higher drug doses and also enables the formulation and delivery of biological compounds via the pulmonary route. The increasing knowledge in material and process sciences, the use of simulation tools and new inhalation device technology will continue to promote pulmonary drug delivery for the treatment of respiratory disease and non-invasive alternatives for the systemic delivery of biological compounds.

Table 1

Powder retention and water content of HPMC capsules (Vcaps® filled with 25.0 ± 1 mg of 150 mesh lactose (inhalation grade) equilibrated at different relative humidity (RH) conditions (n=20).

Capsule Storage Condition % RH	Vcaps® Capsule Water Content (%)	Powder Retention (mg)	Powder Retention (%)
23	2.9 ± 0.2	0.48 ± 0.03	1.9
33	3.9 ± 0.1	0.33 ± 0.03	1.3
45	4.9 ± 0.1	0.17 ± 0.02	0.7
66	7.4 ± 0.2	Not measurable	Not measurable

Table 2

Powder retention of HPMC capsules (Vcaps® Plus) filled with lactose monohydrate 150 mesh for inhalation, based on the measurement of 20 capsule samples.[21]

Capsule Material	Lubricant Level (ppm)	Powder Retention (%)
HPMC	300	1.1
	100	0.1

Table 3

Excipients used in spray-dried dry powder inhalation (DPI) formulations and their potential functional contributions. (*Excipients approved for inhalation are listed in the Inactive Ingredients Database: https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm.)

Chemical Classes of Excipients Investigated for Particle Engineering with Potential Application for Dry Powder Inhalation*			
Amino Acids	**Sugars/Polyols**	**Polymers**	**Lipids**
Alanine Arginine Cysteine Glycine Leucine/Isoleucine Lysine Methionine Phenylalanine Serine Threonine Trileucine Tryptophan Tyrosine Valine	Lactose Mannitol Raffinose Sucrose Trehalose	Chitosan Dextran/Dextran-10 Hypromellose Polyethylene glycol Polyvenylalcohol Polyvenylpyrrolidone	Cholesterol Phospholipon Phospholipids Phosphatidylcholine
Possible Functionalities Provided			
Stabilization of API Surface properties Particle and surface morphology Flowability Dispersability	Stability of API Particle morphology Solubility Dispersability	Stability of API Morphology Particle density Drug release Dispersibility	Aerodynamic properties Dispersibility

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Figure 3

Morphology of 10% and 40% salbutamol sulfate particles manufactured on laboratory-scale (BLD-35) and pilot-scale (PSD-1) equipment.

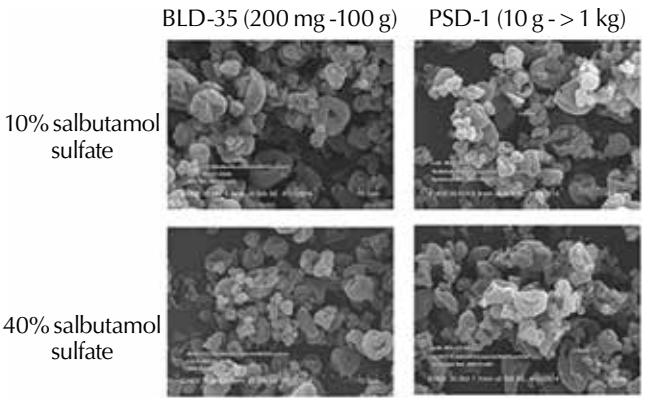
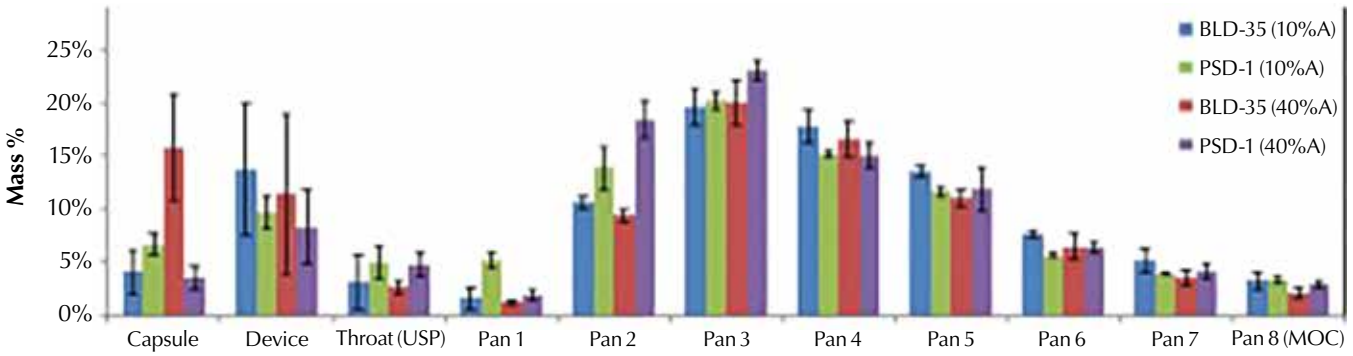


Figure 4

Performance of the 10% and 40% salbutamol sulfate laboratory scale (BLD-35) and pilot scale (PSD-1) spray-dried formulations filled in HPMC capsules (Vcaps® Plus) and delivered through a standard device (Plastiape RS-01).



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