

Advantages of capsule-based dry powder inhalers

HPMC capsules used in DPIs can provide key advantages in inhalation parameters

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Direct pulmonary drug delivery originated as a more relevant alternative for administering drugs directly to the lungs. Respiratory conditions such as asthma, chronic obstructive pulmonary disease (COPD) and emphysema are therapeutic areas of the pulmonary space. Thanks to recent advancements in pharmaceutical sciences, inhalation as an administration route is also beginning to expand its application into the treatment of non-respiratory conditions, as is in the case of Parkinson's disease, diabetes and migraines.

Pulmonary drug delivery technologies are focused on developing simple, easy-to-use, cost-effective devices (which provide patient-facing and adherence success factors), that in parallel must also be able to administer consistent amounts of drug with high levels of lung penetration and allow for multiple dosage (including performance and effectiveness indicators). Newer devices are being developed to minimize device size for easy handling and transport, to increase patient-friendliness without compromising drug delivery.

One attractive aspect of a capsule-based dry powder inhaler (DPI) is its simplicity. The powder formulation consists of either the API alone or as a mixture of the API with a carrier particle such as lactose or mannitol. A considerable amount of research into particle engineering has enabled the manufacture of particles with the correct aerodynamic and carrier properties to ensure effective pulmonary delivery of the API. The limited number of

ingredients in the formulation greatly reduces the amount of analytical work required in the early phases of product development.

Many types of validated DPIs have been developed. They are reasonably inexpensive to manufacture, while robust and effective in use. Such DPIs perform two main functions: firstly, to puncture or cut open the capsule shell wall so that the capsule contents can be released, and secondly, to provide the correct aerodynamic conditions that enable emptying the powder from the shell, detaching the active ingredient from the carrier, and incorporating it into the patient's inhaled airstream through the oral cavity and into the lungs.

DPIs: An Opportunity to Reduce Greenhouse Emissions

Another significant advantage of DPIs is their contribution to reduction of greenhouse gas emissions. It has been seven years since the 2008 passage of the Climate Change Act in the United Kingdom. Despite this, atmospheric carbon dioxide levels have increased recently, passing the 400 parts per million mark.¹ Although the potential impact of climate change on respiratory health is widely appreciated, it is less well known that respiratory drugs may be making a significant contribution to global warming due to propellant gases used in some metered dose inhalers (MDIs). DPIs for the delivery of respiratory drugs can reduce this source of greenhouse gas emissions. Current evidence suggests that DPIs, which have a carbon footprint 18 times lower than MDIs, are equally effective for the treatment of respiratory diseases.¹

HPMC capsules for DPIs

HPMC capsules used in inhalation are based on a hypromellose polymer, a gelling agent (normally carageenan) and a gelling promoter. The capsules are manufactured at room temperature by dipping two sets of stainless steel mold pins (one for the caps and the other for the capsule bodies) into a warm solution of

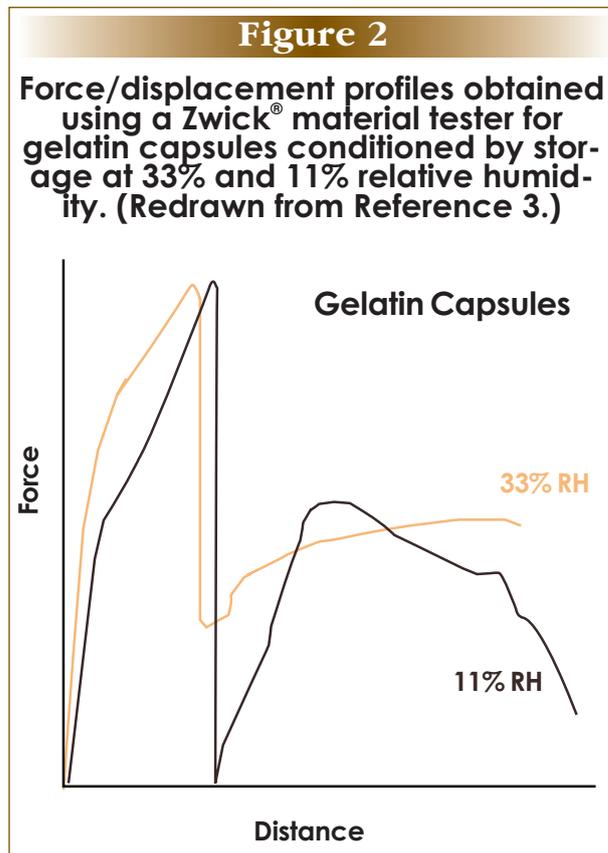
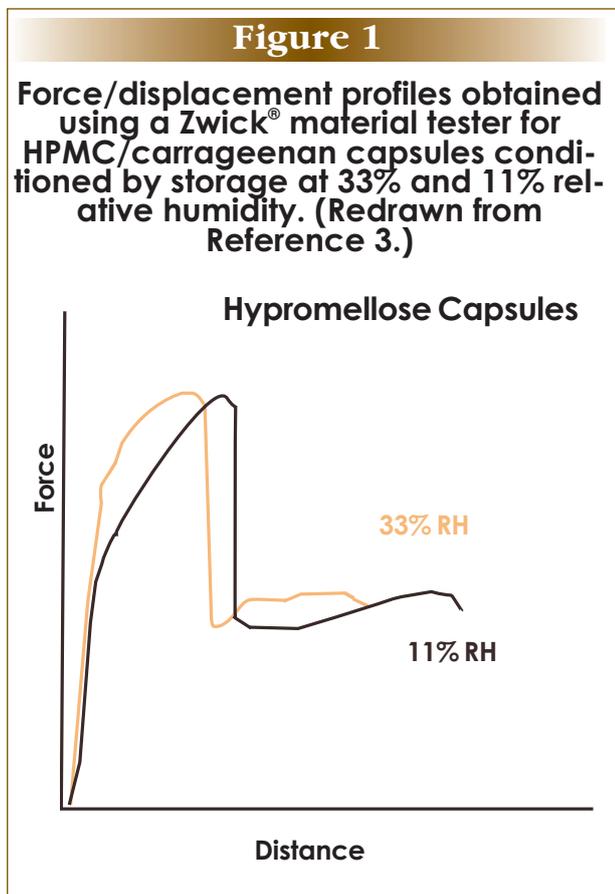
hypromellose, carrageenan and potassium chloride. The resulting change in temperature causes the HPMC solution to gel and form a film on the mold pins. These are then dried using large volumes of air at controlled temperature and humidity. The dried films are stripped from the molds, cut to the correct length, and joined together (caps and bodies) to form capsules.

The resulting HPMC capsules have shown excellent properties in terms of capsule puncturing, powder aerosolization and performance at low moisture content and relative humidities.²

Capsule puncturing

In order for hard shell capsules to function effectively as drug reservoirs in DPIs, the capsule must be capable of being punctured with sharpened pins or cut with blades to release the powdered medicament upon inspiration, without shedding pieces or creating hindrances in the outflow of the powder. For example, if a pin punctures the capsule, then the flap produced must stay attached, remain open and not reclose or obstruct the opening.

Qualicaps[®], in conjunction with the School of Pharmacy and Pharmaceutical Sciences of Cardiff University, Cardiff, UK, has developed a methodology that is able to characterize the forces involved in the penetration of a hard shell capsule by the pins that are employed in DPIs. The sensitivity of the methodology enables users to observe differences in capsule shell formulations using force displacement penetration profiles.



Figures 1 and 2 show the force/displacement profiles for Qualicaps pharmaceutical-grade HPMC and gelatin capsules developed specifically for inhalation at two different relative humidities (RH). The puncturing performance can be described by two values taken from these profiles: puncturing force (the maximum registered F_{max}) and the capsule displacement (displacement at maximal force dL at F_{max}). Values at 33% and 11% RH for HPMC/carrageenan capsules are given in Table 1. The results show the reproducibility of puncturing performance with these capsules at different relative humidities.

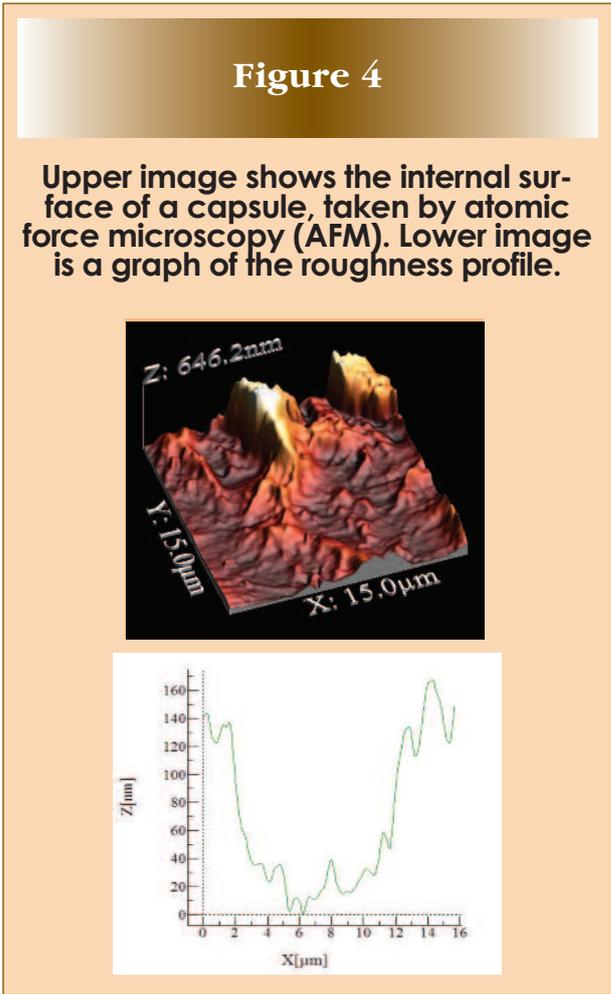
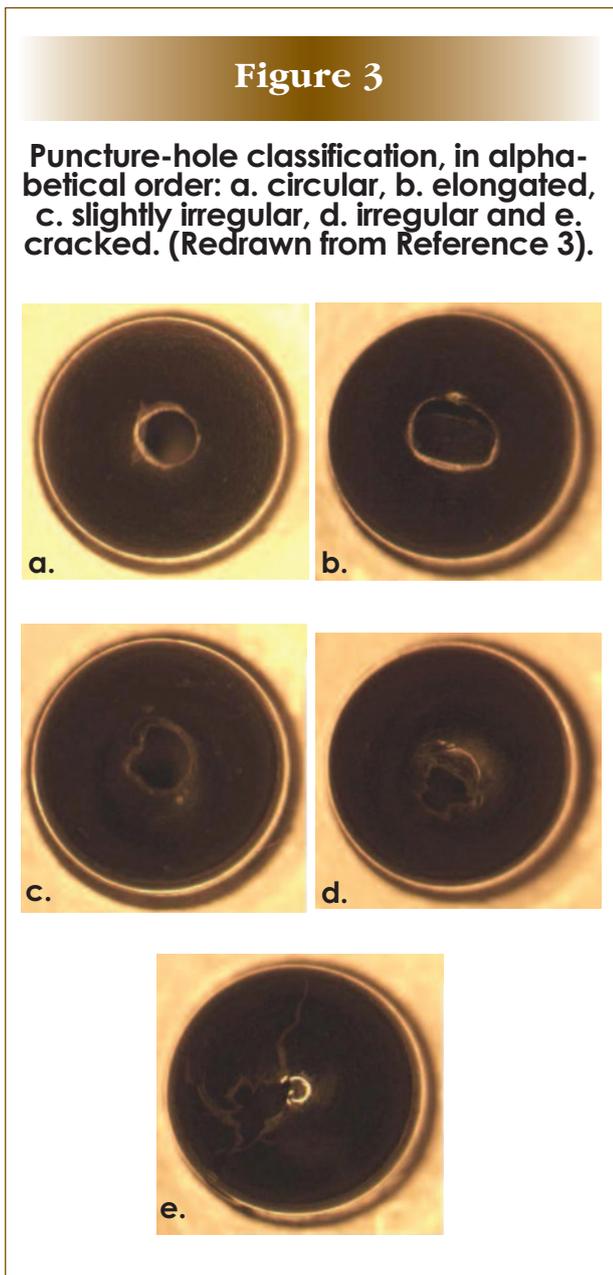
Relative Humidity %	Puncturing Force F_{max} (N)	Capsule Deformation dL at F_{max} (mm)
33	4.00 (± 0.38)	0.7 (± 0.1)
11	4.08 (± 0.58)	0.8 (± 0.2)

In addition to understanding the puncturing event, it is important to measure the puncturing area and shape, as

this defines the space through which the drug leaves the capsule. Small areas and irregular shapes can lead to non-reproducible emitted doses. Puncture-hole classification is illustrated in Figure 3.

Powder aerosolization

The emitted dose is not the only factor that measures the efficiency of powder aerosolization from a DPI. The other important driver is the powder particle size. Methods for determining particle size and distribution employ various geometric features of the particle's physicochemical properties. Aerodynamic diameter is defined as the diameter of an equivalent volume sphere of unit density with the same terminal settling velocity as the actual particle. This can be considered the most appropriate measure of aerosol particle size, as it relates to the particle's dynamic behavior by describing the main mechanisms of aerosol deposition (gravitational, settling or sedimentation, and inertial impaction).



HPMC/carrageenan capsules were first punctured in a DPI at different RH conditions, then the puncturing area and hole shape were measured. The results, shown in Table 2, demonstrate a high level of reproducibility.^{3,4}

To reach the peripheral airways where drugs are most efficiently absorbed, particles must be within the 1-5 µm

Table 2

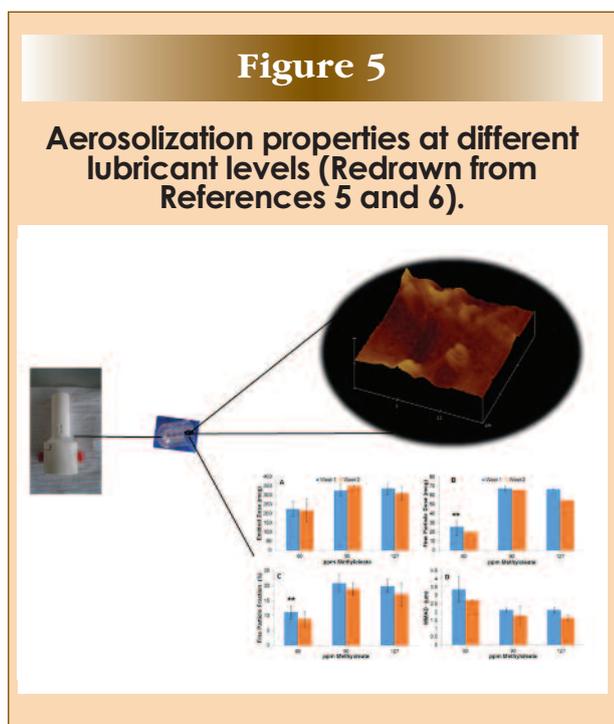
Effect of storage conditions on puncturing area and hole shape. Results for 30 Quali-V®-I capsules (HPMC/carrageenan capsules) at 33% and 11% relative humidities.

Relative Humidity (%)	Puncturing area (mm ²)	Circular (%)	Elongated (%)	Slightly irregular (%)	Irregular (%)	Cracked (%)
33	1.49 (0.242)	82	9	9	0	0
11	1.49 (0.179)	80	7	13	0	0

aerodynamic range. Particles larger than 5 μm usually deposit in the oral cavity or pharynx, from which they are easily cleared. In contrast, particles smaller than 0.5 μm may not deposit at all, since they move by Brownian motion and settle very slowly. The fine particle fraction (FPF) is the percentage of emitted dose particles within the 1-5 μm fine particle range.

Another variable to consider is the capsule's internal surface, which is not flat. Figure 4 shows an image of the capsule's internal surface taken by atomic force microscopy (AFM) and its corresponding roughness profile. From the image, it seems reasonable to assume that modifying the roughness of this surface would have an effect on aerosolization.

The capsule manufacturing process requires the use of a surface lubricant on the mold pins on which the capsules are formed. It enables the dried capsule parts (caps and bodies) to be removed from the molds without damage. The quantity of lubricant that remains in the capsule will modify the capsule surface properties and play a role in capsule aerosolization properties.



In Figure 5, the effect of the internal lubricant content on salbutamol aerosolization can be observed. The results show that a certain concentration exists at which capsule performance is optimal, though this value may vary for each drug.

It must be taken into account that internal lubricant levels are in the parts per million (ppm) range, therefore small quantities of this additive may cause large variations on aerosolization properties. A 30 ppm difference doubles the fine particle fraction in this case. Manufacturing technology can be used to minimize these variations.⁶

Performance at low relative humidities

The ideal container for the inhalation drug must have a low moisture content for several reasons. In general, inhalation drugs are moisture-sensitive. Moisture may promote agglomeration of drug particles, thereby decreasing the fine particle fraction, important to aerosolization.

Inhalation-grade HPMC/carrageenan capsules have a moisture content of 4.5 - 6.5%. However, the moisture content of these capsules can be further reduced without any influence on their mechanical properties, as these plant-based capsules do not become brittle in arid conditions, unlike gelatin capsules. A normal procedure for desiccation would be filling the capsules, storing them at a low relative humidity, i.e., 11%, which corresponds to a capsule moisture content of 1%, followed by blistering and packaging.

Conclusions

In order to market a successful drug product for inhalation, there are two facets of administration that are crucial: patient-friendliness to ensure adherence and correct delivery to the lungs to ensure effectiveness. With regard to the former, simplicity, ease-of-use, accessibility and affordability are key success factors. Although pressured metered dose inhalers (pMDIs) have been popular for these reasons, interest has emerged in using DPIs due to the latter facet, optimal pulmonary delivery.

DPIs offer ease of coordination with the respiratory cycle compared to pMDIs and a reduced amount of drug trapped in the oropharynx. In addition, devices that do not use chlorofluorocarbon propellants are better for the environment.⁷

Within the sphere of DPIs, HPMC-capsule-based DPIs are a compelling alternative due to capsule properties of puncturing, powder aerosolization, control of internal capsule surface and performance with low-moisture contents.

References

- 1) Hilman, T., Mortimer, F., Hopkinson, M., "Inhaled drugs and global warming. Time to shift to DPIs" *BMJ* 346: f3359 doi: 10.1136/bmj.f3359 (May 2013).
- 2) BCC Research. "Pulmonary Drug Delivery. Systems, Technologies and Global Markets" Chapter 3, (May 2014).
- 3) Torrisi, B.M., Birchall, J.C., Jones, B.E. et al. "The development of a sensitive methodology to characterize hard capsule puncture by dry powder inhaler pins" *Int. J. Pharm.*, 455, 545-552 (2013).

4) Dujovny, G., Morgan, C., Diez, F. et al. "Understanding intra- and inter-individual differences in capsule puncture following actuation of a DPI" Poster T3175, AAPS Annual Meeting, San Diego, CA, (2014).

5) Saleem, I., Diez, F., and Jones, B. "Influence of internal lubricant on powder aerosolization properties from inhalation grade hypromellose capsules (Quali-V[®]-I)" Poster R6177, AAPS Annual Meeting, San Antonio, TX, (2013).

6) Saleem, I.Y., Diez, F., Jones, B.E. et al. "Investigation on the aerosol performance of a dry powder inhalation hypromellose capsules with different lubricant levels" Int. J. Pharm., 492, 258-263 (2015).

7) Nakate, T., Yoshida, H., Ohike, A., et al. "Formulation development of inhalation powders for FK888 using the E-Haler[®] to improve the inhalation performance at a high dose, and its absorption in healthy volunteers" Eur. J. Pharm. Biopharm., 59, 25-33, (2005).

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