Advantages of capsule-based dry powder inhalers

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

Qualicaps Europe SAU

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 transporting 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 significant 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 significantly 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 available for the delivery of respiratory drugs can reduce this important source of greenhouse gas emissions. Current evidence suggests that DPI s, which have a carbon footprint 18 times lower that 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 carrageen) 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, then the two halves (caps and bodies), are joined together to form capsules.

These 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 stayed 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.

Figure 1

Force / displacement profiles obtained using a Zwick® material tester, using HPMC/ carrageenan capsules by storage at 33%RH

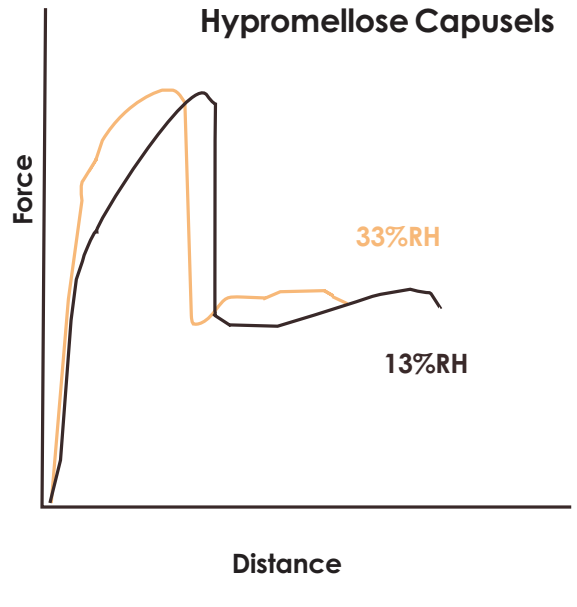
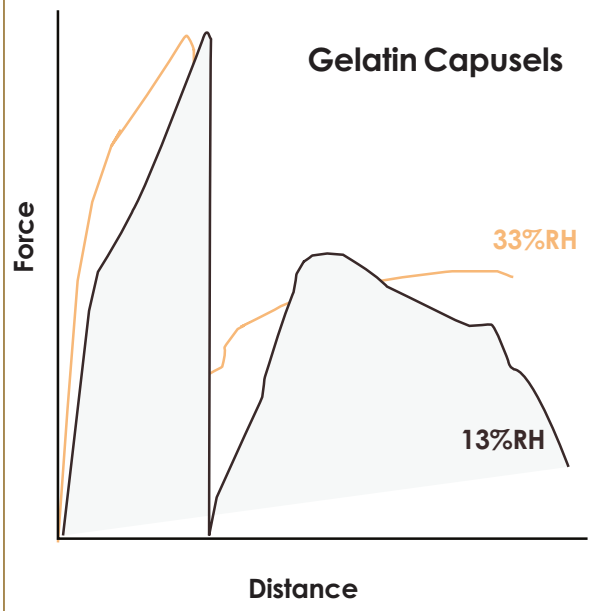


Figure 2

Force / displacement profiles obtained using a Zwick® material tester using HPMC/carrageenan capsules conditioned by storage at 11%RH



Figures 1 and 2 show the force/deformation profiles for Qualicaps pharmaceutical-grade 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 deformation (displacement at maximal force dL at F_{max}). Values at 33% and 11% RH are given in Table 1. The results show the reproducibility of these capsules at different relative humidities.

Table 1

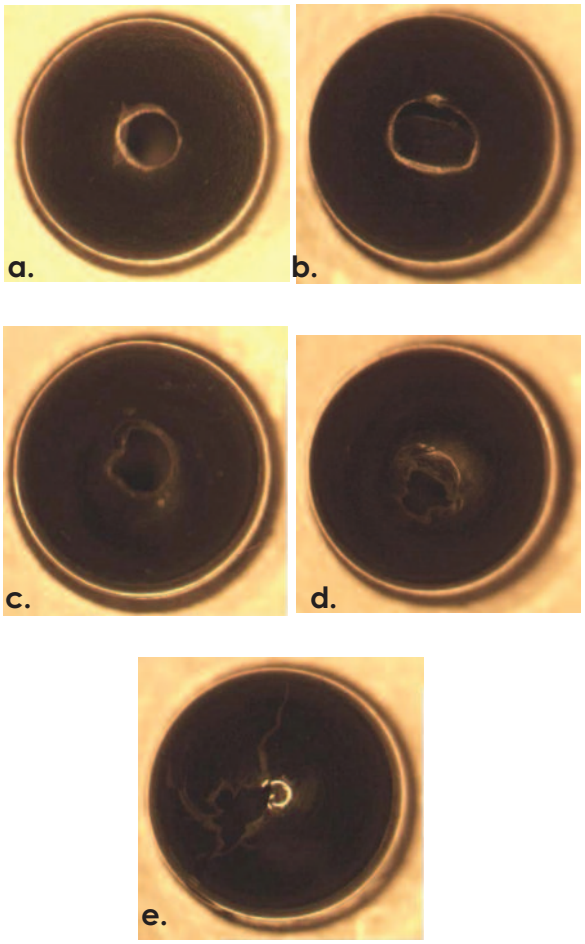
Mean and (standard deviation) for 30 capsules

Relative Humidity	(%)Fmax	(N)dL at Fmax (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 area of puncturing and the shape of the hole, as this defines the space through which the drug leaves the capsule. Low areas and irregular shapes can lead to non-reproducible emitted doses. Puncture hole classification is illustrated in Figure 3.

Figure 3

Puncture-hole classification. From left to right: circular, elongated, slightly irregular, irregular and cracked. Redrawn from Ref [3]



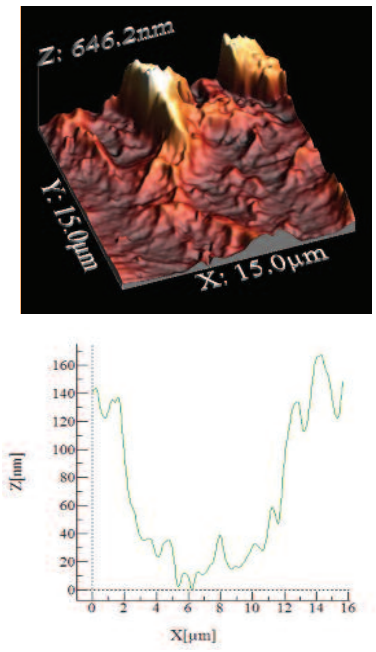
HPMC/carrageen capsules were punctured in a DPI at different RH conditions then the puncturing area and hole shape were measured. Results are shown in Table 2. The results demonstrate a high level of reproductibility.[3,4]

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 use various geometric features of their physicochemical properties. Aerodynamic diameter is the most appropriate measure of aerosol particle size because it relates to the particle's dynamic behavior. It describes the main mechanisms of aerosol deposition, which are gravitational settling (or sedimentation) and inertial impaction. 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.

Figure 4

Left-hand image shows the internal surface of a capsule. Image taken by AFM (atomic force microscopy). The right-hand image is a graph of the roughness profile.



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

Table 2

Results from puncturing Quail-V®-I with a DPI. The effect of storage conditions on puncturing area and hole shape.

RH (%)	Puncturing area (mm2)	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

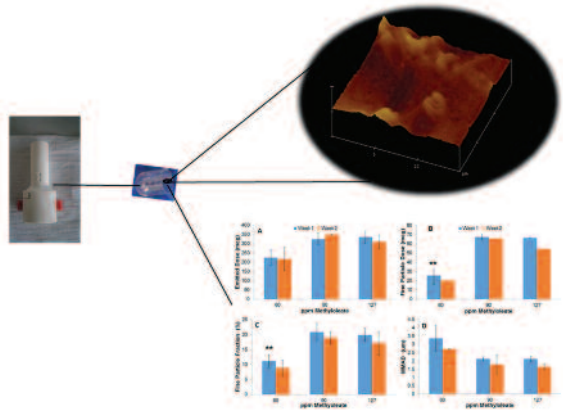
motion and settle very slowly. The fine particle fraction (FPF) is the percentage of emitted dose particles within the 1-5 µm fine particle range that reach the lung.

Another variable to consider is that the capsule's internal surface is not flat. Figure 4 shows an image of the capsule 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.

Figure 5

Aerosolization properties at different lubricant levels. Redrawn from [5, 6]



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. 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 aersolization 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 inhalers, pMDIs, have been popular for these reasons, interest has emerged in employing 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 chlorofluorocarbons propellants can be better for the environment.[7]

Within the sphere of DPIs, HPMC capsule-based DPIs are a compelling alternative due to capsule mechanical (puncturing) properties, powder aerosolization, control of the internal capsule surface and performance at low relative humidities.

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