AEROSOLISATION PROPERTIES OF QUALI-V®-I *VERSUS* GELATIN CAPSULES: AN IMPROVEMENT IN INHALATION DRUG DELIVERY

In this article, Imran Saalem, PhD, Senior Lecturer, Pharmaceutical Technology, Pharmacy & Biomolecular Sciences, Liverpool JMU, Liverpool, UK, Fernando Díez, Business Development Manager, Qualicaps Europe, and Brian Jones, Scientific Advisor to Qualicaps Europe, report the results of a study comparing aerosolisation properties of dry-powder formulations delivered from Quali-V®-I capsules with those of dry-powder formulations delivered from gelatin capsules.

INTRODUCTION

There has been an increase in respiratory disease in the last decade: chronic obstructive pulmonary disease (COPD) affects an estimated 210 million people worldwide and is predicted to be the third leading cause of death by 2020. Pulmonary delivery is being investigated as a route for delivering actives that cannot be given by the standard oral route and as an improved alternative to administration by the parenteral route.

The use of hard capsules in dry powder inhalers (DPI) to deliver formulations to the lung has been in use since 1970.[1] Pharmaceutical companies subsequently started to manufacture more complex delivery systems, such as powder depot devices or powder dispensed from blisters, but their complexity tended to make them less patient friendly. Lately there has been an interest in returning to capsule-based systems because they are simple to formulate, cheap to manufacture and patient friendly. They are easy to use and the patient can see when the dose has been taken.

The original inhalation-grade hard capsules were made from gelatin, which becomes brittle when exposed to low humidities. Inhalation-grade hypromellose capsules have been developed in the last few years to overcome this problem because water does not act as a plasticizer in their structure. Little has been published that compares the properties of the two types of capsules, except for studies that have measured their puncturing in DPI, which showed that hypromellose capsules had better performance.[2] In this investigation the effects of capsule properties on the aerosolisation of powders from DPIs were compared.[3]

"FPF % VALUES FOR QUALI-V®-I CAPSULES WERE ALWAYS HIGHER THAN GELATIN, WITH A SIGNIFICANT DIFFERENCE NOTED AS TEST TIME INCREASED (WEEKS 2-4)"

KEY PARAMETERS FOR INHALATION DELIVERY

Inhaled drug delivery systems can be divided into three principal categories: metered-dose inhalers (MDI), dry-powder inhalers (DPI) and nebulizers, each class with its unique strengths and weaknesses.

DPIs are typically formulated as one phase, solid particle blends, they have advantages from stability and processing standpoint, dry powders are at a lower energy state, which reduces the rate of chemical degradation and the likelihood

Mr Brian Jones
Scientific Advisor
E: bjcapsules@ntlworld.com

Dr Imran Saalem
Senior Lecturer, Pharmaceutical Technology
Pharmacy & Biomolecular Sciences
Liverpool JMU, Liverpool, UK

Mr Fernando Díez
Business Development Manager
T: +34 91 663 08 72
F: +34 91 663 08 29
E: fdiez@qualicaps.es

Qualicaps Europe, S.A.U.
Calle de la Granja, 49
Alcobendas 28108
Spain

www.qualicaps.com

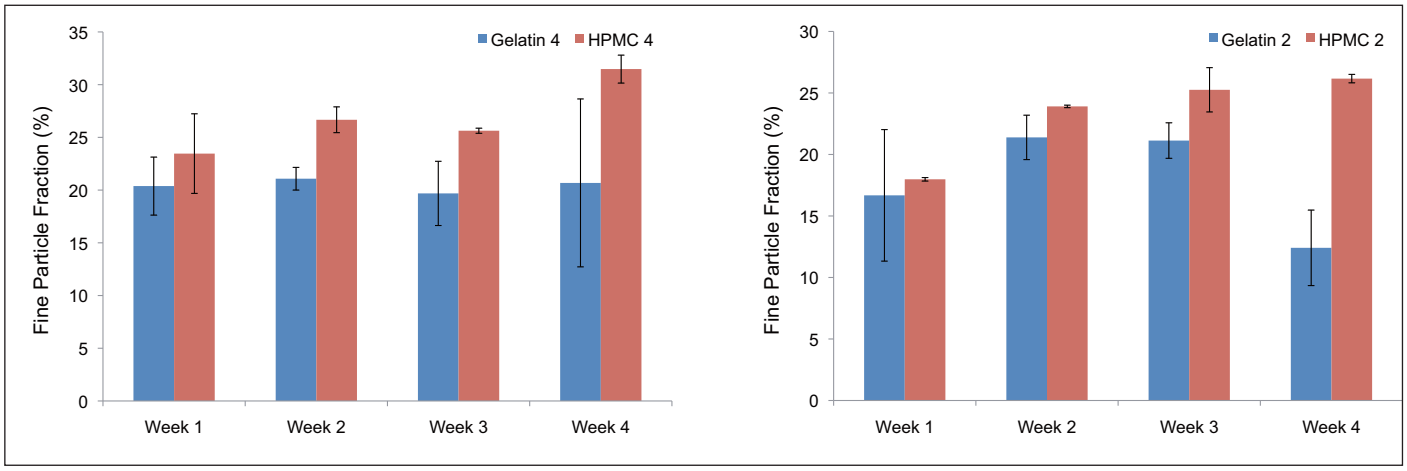

Figure 1: FPF% for gelatin and Quali-V®-I capsules. (The numbers "2" and "4" refer to the different inhalers used.)

of reaction with contact surfaces. In addition, DPIs are activated by the patient's inspiratory airflow and subsequently require little or no co-ordination of actuation and inhalation compared with MDIs.[4]

Particle size is the most important design variable of a DPI formulation. Methods for determining particle size and distribution use various geometric features or physicochemical properties. Aerodynamic diameter is the most appropriate measure of aerosol particle size, because it relates to the particles' dynamic behaviour and describes the main mechanism of aerosol deposition; gravitational, sedimentation settling and inertial impaction depending on the aerodynamic dynamic diameter. This is defined as the diameter of an equivalent volume sphere of unit density with the same terminal settling velocity as the actual particle

To reach the peripheral airways, where the drug is most efficiently absorbed, particles need to be in the 1-5 µm aerodynamic diameter 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 optimal size for delivery is always in the 1-5µm range. The fine particle fraction (FPF) is the percentage of emitted dose with particles in the fine particle range (<5µm)

EXPERIMENTAL STUDY: MEASUREMENT OF AEROSOLISATION PROPERTIES FOR GELATIN AND QUALI-V®-I (HPMC) CAPSULES

The aim of this study was to compare the aerosolisation properties, (FPF% and the mass median aerodynamic diameter (MMAD)) of a typical powder formulation (binary mixture of salbutamol sulphate and lactose) from two different types of inhalation capsules (gelatin and hypromellose) using two different DPI devices.

Inhalation-grade lactose (Respitose® (DFE Pharma, Goch, Germany, obtained from Laboratoires SMB, Belgium)) was fractionated to give particles of 90-125 μm and blended (Turbula® orbital mixer (Glen Mills, Clifton, NJ, US) for 30 min at 46 rpm with micronised salbutamol in a ratio of 50:1 (w/w). 20 ± 1 mg of this blend was filled in to inhalation-grade capsules, size three, gelatin and Quali-V®-I hypromellose previously stored in a humidity chamber (Sanyo Atmos Chamber) at 22°C 40% RH for 4 weeks. Samples were taken at weekly intervals and tested in two inhalers with either two or eight puncturing pins (Plastiape SpA, Italy) and then attached to a next generation cascade impactor (NGI) operated at a flow rate of 60 L.min^{-1} for four seconds. Salbutamol deposition on the various parts of the NGI, capsule and inhaler device was measured using HPLC. The FPF% and MMAD were calculated from the data: FPF% was the ratio of the drug mass depositing in the NGI (aerodynamic diameter <4.46 µm) over the emitted dose and the MMAD was calculated by subjecting the inertial impaction data to log-probability analysis.

RESULTS AND CONCLUSIONS

The fine particle fraction (FPF %) values for Quali-V®-I capsules (HPMC) are always higher than gelatin, with a significant difference noted as test time increased, during weeks 2-4 (see Figure 1).

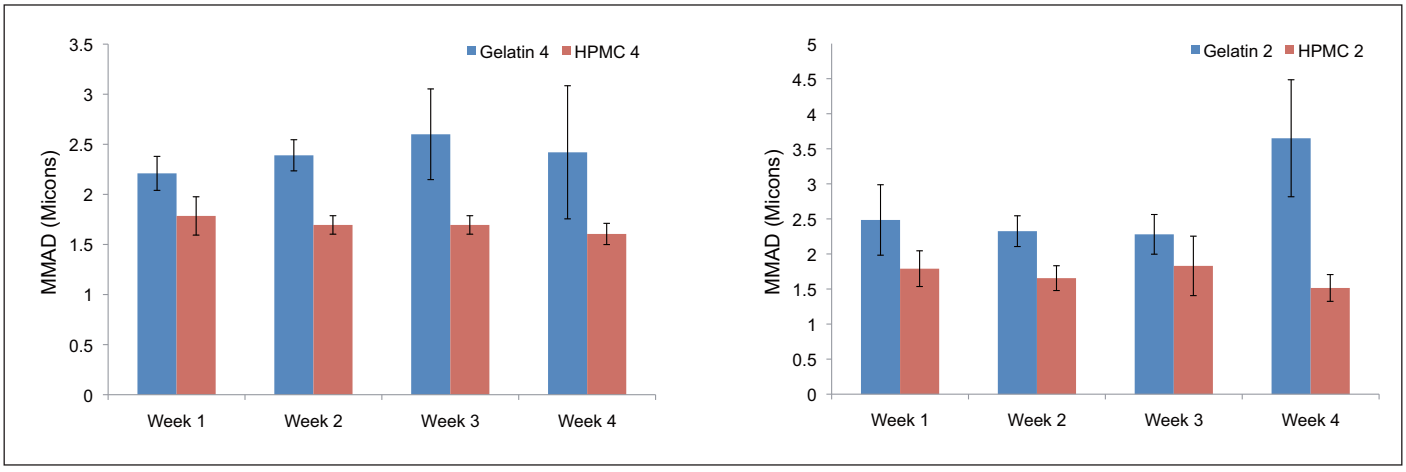

Figure 2: MMAD for gelatin and Quali-V®-I capsules. (The numbers "2" and "4" refer to the different inhalers used.)

The results for MMAD for both capsules, shown in Figure 2, confirm a lower MMAD value for Quali-V®-I compared with gelatin capsules, and agrees with the higher FPF% shown in Figure 1.

the capsules: for gelatin capsules it is between 13.0% and 16.0% and for Quali-V®-I it is 4.5-6.5%. This would lead to differences in relative humidity (RH) inside the capsules. The strength of the interaction between the drug and the

of particles surfaces resulting in fused particles and, therefore, larger particles size, leading to aggregation and particles that may not be of a respirable size.[5]

"QUALI-V® I HYPROMELLOSE CAPSULES HAVE BETTER PROPERTIES THAN GELATIN CAPSULES FOR USE IN PUNCTURING DPIS BECAUSE OF THEIR BETTER AEROSOLISATION PROPERTIES"

This demonstrates that Quali-V®-I hypromellose capsules have better properties than gelatin capsules for use in puncturing DPIs because of their better aerosolisation properties (FPF% and MMAD). The data also indicates the importance of device, capsule and storage conditions in obtaining an optimum therapeutic delivery, which could effect to patients over the course of their treatment.

One of the reasons for this behaviour may be the moisture content difference between

excipient carrier or the propensity for particles to detach is dependent on the forces between the particles (van der Waals, electrostatic and capillary forces) and can be influenced by relative humidity (RH). At lower RH, the adhesion force is mainly comprised of the van der Waals and electrostatic forces and as the RH increases capillary forces become prominent and a thin layer of water will appear on the surface of the drug and carrier particles creating a liquid bridge. These bridges may cause solidification

REFERENCES:

1. *Jones BE, "The evolution of DPI capsules". Inhalation, 2008, Vol 2(6), pp 20-23.*
2. *Jones BE, "Quali-V®-I: A new key for dry-powder inhalers". Drug Delivery Technology, 2003, Vol 3(6), pp52-57.*
3. *Saleem I, et al, "A comparison of two different types of inhalation capsules and inhaler device on powder aerosolisation". Poster M-1141, AAPS Annual Meeting, 2012, Chicago, USA.*
4. *Telko MJ and Hickey AJ, "Dry powder Inhaler formulation". Respiratory Care, 2005, Vol 50(9), pp 1209-1227.*
5. *Calaman KH, "The role of intelligent sorbents in respiratory drug delivery devices", Inhalation Magazine, February 2013, pp 9-13.*
6. *Magni, P, "Single-dose inhalers for capsules: a consolidated tradition with ample growth prospects". ONdrugDelivery, 2012, No 37, pp 26-27.*