A Comparison of Two Different Types of Inhalation Capsules & Inhaler Device on Powder Aerosolisation

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Formulation & Drug Delivery Research

BACKGROUND

❖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 3rd leading cause of death by 2020. Pulmonary delivery is also being investigated as a route for delivering other types of actives that cannot be given by the standard oral route.

❖The use of hard capsules in dry powder inhalers (DPI) to deliver formulations to the lung has been in use since 1970. However, pharmaceutical companies 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 capsules based systems because they are patient friendly; simple to formulate, cheap to manufacture 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[1-3]. In this investigation we compare the effects of capsule properties on the aerosolisation of powders from DPIs.

AIM

❖The aim of this study was to compare the aerosolisation properties [emitted dose (ED), fine particle fraction (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 (2 or 8 puncturing pins).

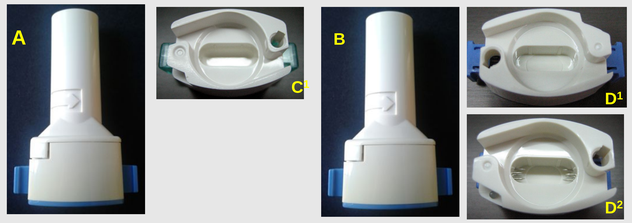

Figure 1. Dry powder inhalers from Plastiape, **(A)** 2-pin **(B)** 8-pin; **C1** & **D1** view of open base from above; **C2** & **D2** , buttons depressed showing puncture pins

MATERIALS AND METHODS

❖ Inhalation grade lactose (Repitose, SMB Technology) was fractionated to give particles of 90-125 µm and blended (Turbula® orbital mixer (Glen Mills, Clifton, New Jersey) for 30 min at 46 rpm with micronized Salbutamol sulphate in a ratio of 50:1 (w/w).

❖ 20±1 mg of this blend was filled in to size 3 inhalation grade gelatin and hypromellose (Quali-V®-I) capsules (Qualicaps Europe, S.A.U.) and stored in a humidity chamber (Sanyo Atmos Chamber) at 22ºC 40% RH for 4 weeks (n=3) to standardise the capsules before testing .

❖ The filled capsules were tested at weekly intervals , up to 4 weeks, by puncturing them in two DPI devices (2 or 8 puncturing pins) (Plastiape, Milano, Italy), see **Figure 1**, and aerosolised into a next generation cascade impactor (NGI) operated at a flow rate of 60 L min^{-1} for 4 s.

❖ Salbutamol was collected from the capsule, inhaler, mouthpiece, adaptor and NGI stages using distilled water and analysed by HPLC (Agilent Technologies) using a Kinetex C-18 column (50 x 4,7 mm i.d. packed with 2.6 µm Phenomenex,UK), mobile phase: methanol and 0.25% (w/v) 1-heptane sulphonic acid sodium salt (45:55 v/v), flow rate: 1 mL/min, injection volume: 10 µL, temperature: 25º C and wavelength of 200 nm. The retention time for Salbutamol was 1.5 min and the limits of detection and quantification were 0.19 and 0.57 µg/mL respectively.

❖ The ED (µg) was calculated as the total mass of drug depositing in the mouthpiece, induction port, pre-separator, and NGI stages. The FPD (µg) was determined as the mass of drug deposited in the NGI with aerodynamic diameters ≤ 4.46 µm and the FPF (%) (defined as the mass of drug deposited (d_{ae} < 4.6µm), was expressed as a percentage of the ED. MMAD was calculated by subjecting the inertial impaction data to log probability analysis.

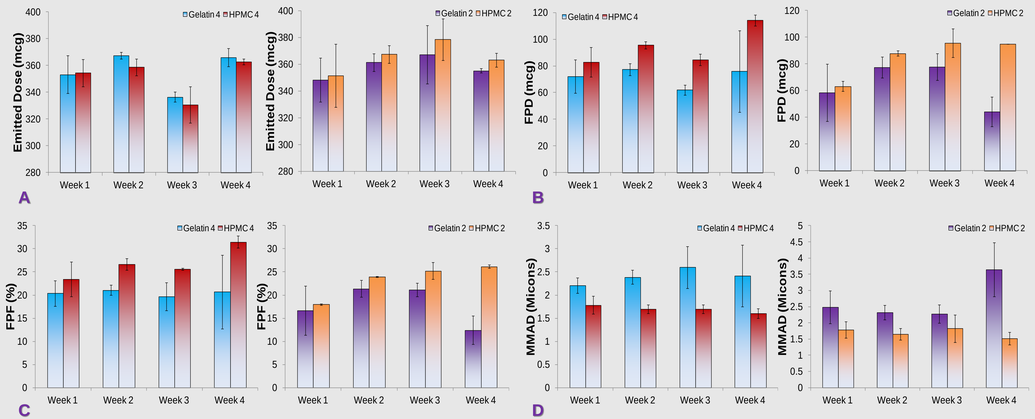

Figure 2. Effect of capsules, inhaler and storage on **(A)** Emitted dose **(B)** Fine Particle Dose **(C)** Fine Particle Fraction **(D)** MMAD

RESULTS

❖ The ED (µg) showed no significant difference (p>0.05 paired Student's t-test with two-tailed comparison) between gelatin and hypromellose capsules in the DPI device (2-pin and 8-pin), see **Figures 2A**.

❖ The FPD (µg) and FPF (%) showed a significantly greater value from the hypromellose capsules using the 8-pin DPI device at weeks 2, 3 & 4 compared to gelatin capsules (p<0.05 paired Student's t-test with two-tailed comparison), see **Figures 2 B & C**.

❖ However, significant difference was only noted at week 4 when using 2-pin DPI devices comparing gelatin and hypromellose capsules (p<0.05 paired Student's t-test with two-tailed comparison), see **Figures 2 B & C**.

❖ In addition, significant difference was noted between 8-pin and 2-pin DPI devices using hypromellose capsules at weeks 1, 2 & 4 (p<0.05 paired Student's t-test with two-tailed comparison), see **Figures 2 B & C**.

❖ The MMAD of Salbutamol emitted from hypromellose capsules was significantly lower than gelatin capsules using the 2-pin and 8-pin DPI devices at weeks 1 – 4 (p<0.05 per Student's t-test with two-tailed comparison), see **Figure 2 D**.

❖ In addition, the 2-pin DPI device produced significantly lower MMAD for hypromellose capsules compared with the 8-pin DPI device (p<0.05 per Student's t-test with two-tail comparison), see **Figure 2 D**.

CONCLUSIONS

❖The results show that the FPF are greater and the MMAD are lower for hypromellose capsules compared to gelatin capsules and the fine particle dose and FPF were greatest from the 8-pin inhaler with hypromellose capsules. This demonstrates that Quali-V®-I hypromellose capsules have better properties for use in puncturing DPI than gelatin capsules.

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