Performance of Hypromellose (V-Caps®) Capsules for Unit Dose Dry Powder Inhalation Devices

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INTRODUCTION

Hypromellose (hydroxypropyl methylcellulose) is a common polymeric pharmaceutical excipient, and hypromellose capsules recently have been introduced for use in unit dose dry powder inhalation (DPI) devices. The superior uniformity of capsule integrity (Stein 2007), lower baseline moisture content, and more stable hygroscopicity relative to gelatin capsules in varied relative humidity are a presumed advantage of hypromellose capsules (Nagata 2002, Birchall 2008). The stable moisture content should provide for more uniform puncture and consistent delivered dose in DPI devices.

To characterize the V-Caps brand of hypromellose capsules a puncture test method was devised using a 'standard' DPI device, the Aerolizer™. In addition, emitted dose uniformity was then tested using the Aerolizer device and V-Caps filled with inhalation grade lactose.

METHODS

V-Caps hypromellose capsules, batch #52029201, size #3 were used in all experiments. Capsules were placed into an Aerolizer and punctured according to the device's use instructions (Foradil Medication Guide). The halves of each capsule were separated and examined by using a Motic DM143 digital light microscope. A scoring system (Table 1) was devised to rank each puncture into one of six categories. One hundred capsules were punctured. Since the Aerolizer employs eight pins to puncture four holes at each end of the capsule, a total of 800 punctures were measured.

Table 1.

Capsule puncture ranking system. A – F indicate the various types of punctures that commonly appear in capsules used with unit dose DPI devices.

A	Clean puncture, typical size
B	Puncture, flap (chad)
C	Puncture w/atypically small hole
D	Fissure
E	Fracture, between holes
F	Shatter, hole larger than clean puncture, fragments produced within capsule

To measure emitted dose uniformity a USP dose uniformity sampling apparatus B (DUSA) was used. Capsules were filled with inhalation grade lactose excipient (either DMV Respitose ML003 or Friesland Domo Lactohale LH200). A nominal dose of 25 mg was targeted and the exact fill mass recorded. The Aerolizer device was operated according to its use instructions (Foradil Medication Guide) and actuated into a vacuum air flow of 60 LPM following the USP <601> compendial method, but using 2 liters of air volume. Capsules were again weighed after excipient dispersion.

RESULTS

Representative capsule puncture results are illustrated in Figure 1.

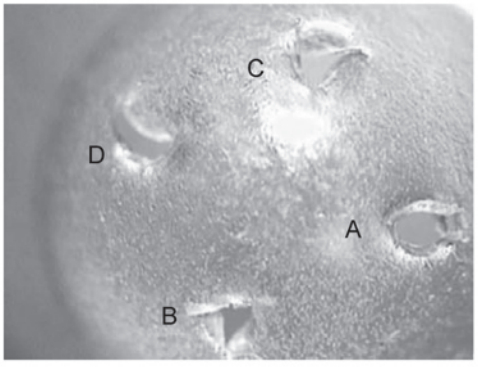

Figure 1. Exemplary photograph of puncture type (A – D) created by an Aerolizer in size #3 hypromellose V-Cap. There were essentially no instances of puncture types E and F.

Clean puncturing with or without flaps and fissures occurred in 30% of punctures. 'Chads' occurred in 11% of punctures, while atypically small holes accounted for 24% of punctures. Thirty-five percent of the punctures were characterized as fissures. Fractures and shattering were negligible.

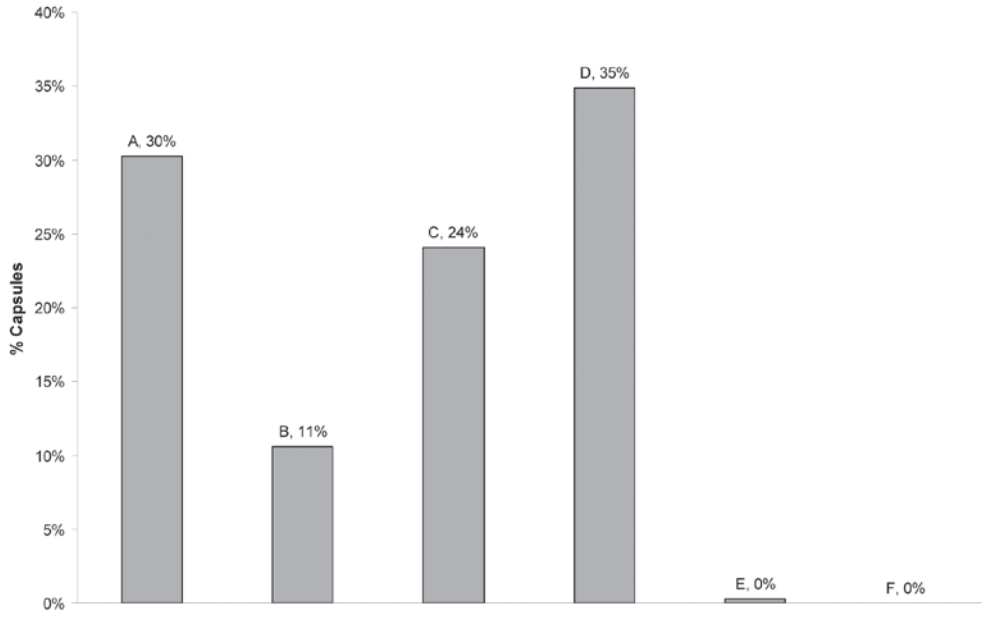

Figure 2. **Puncture uniformity of size #3 V-Caps hypromellose capsules. Percentage of capsule punctures of each type as defined in Table 1.**

The emitted dose uniformity of V-Caps is shown in Table 2, using the Aerolizer device and 2 different grades of lactose. The coefficient of variation for doses was well within the variability required for DPI applications, and there was no statistically significant difference in emitted dose between the two grades of lactose (p = 0.3).

Table 2.

Emitted dose uniformity of size #3 V-Caps hypromellose capsules. Capsules were filled with the indicated dose of DMV Respitose ML003 or Friesland Lactohale 200) and dispersed using an Aerolizer device. The amount of excipient remaining in each capsule was measured and the emitted dose calculated by difference.

Excipient ID #	**DMV Respitose ML003**			**Friesland Lactohale LH200**			
Test #	Fill Dose	Emitted Dose	% Emitted Dose	Test #	Fill Dose	Emitted Dose	% Emitted Dose
1	25.9	24.9	95.9	1	25.4	24.8	97.9
2	24.8	24.4	98.2	2	25.7	25.1	97.6
3	25.3	24.3	95.9	3	25.9	25.5	98.3
4	25.2	24.1	95.5	4	25.9	25.3	97.7
5	26.1	25.5	98.0	5	25.0	24.1	96.3
				6	25.6	24.8	97.0
Mean	**25.5**	**24.6**	**96.7**		**25.6**	**24.9**	**97.5**
SD	**0.5**	**0.6**	**1.3**		**0.3**	**0.5**	**0.7**
CV			**1.3%**				**0.7%**

CONCLUSION

When used with unit dose DPI formulations, gelatin capsules are known to fracture or even shatter, particularly if the capsule becomes brittle due to low ambient relative humidity (Chang 1998, Birchall 2008). Uniformity of hole puncture is an important parameter in the efficient performance of unit dose DPIs (Coates 2005), thus an alternative capsule composition to gelatin is desirable. The present study demonstrated consistent and high performance of V-Caps hypromellose capsules, measured both by puncture uniformity and emitted dose of excipient from an Aerolizer device. Thus, this type of capsule appears well suited for use in future DPI products.

ACKNOWLEDGEMENT

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