T3178

THE PUNCTURE PROPERTIES AND THE SHEDDING OF PARTICLES OF CAPSULES IN DRY POWDER INHALERS, EFFECT OF CAPSULE TYPE AND MOISTURE CONTENT

Brian E. Jones[1,2], Jeng Chong[1], Fernando Diez[2], James C. Birchall[1], Rosalind Chong[1], Sion A. Coulman[1]

1. The School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Cardiff, CF10 3NB,UK. 2 Qualicaps Europe S.A.U., 28108, Alcobendas, Spain

PURPOSE

- Reports in literature show that when gelatin and hypromellose capsules are punctured in dry powder inhalers (DPI) fragments of shell wall are produced[1,2].
- Large particles would not be expected to penetrate deep into the lung due to the inherent capture and clearance mechanisms[3] but smaller particles could be inhaled, a fact mentioned in patient information leaflets[4].
- The literature has reported that when gelatin capsules for DPI are stored incorrectly at low RHs there is a change in their physical properties and they become brittle[5].
- The aim of this study was to characterise and measure all particles shed, both visible and those smaller than the visible threshold, upon puncture of gelatin and hypromellose (HPMC) capsules and to examine the effect of capsule moisture on this.

METHODS

- Inhalation grade capsules size 3, gelatin and hypromellose (Quali-V®-I) supplied by Qualicaps, were manually closed and conditioned in desiccators over saturated solutions of either lithium chloride (c.11% RH) or calcium chloride (c.34% RH) for 10 days at room temperature. The selected RHs provide capsule moisture contents at the lower end of the specification limit and below this limit. Moisture content was determined by loss on drying (LOD) tests[4].
- Capsules were punctured, in dome of cap and body, by placing in chamber of Plastiape® Monodose 2-pin inhaler, see **Fig. 1A**, and depressing both buttons to push the steel needles into the shells, see **Fig. 1B & C**.
- Capsules were also punctured on a Zwick® materials testing machine (MTM) fitted with pin, supplied by Plastiape® from their Monodose inhaler, see **Fig. 2**. The capsules were held firmly in a metal bushing from a size 3 capsule filling machine (Qualicaps) and only the caps were punctured. A 500N load cell was used to determine forces generated during capsule puncture by the MTM² and the pin displacement at puncture. These are denoted in results as Fmax and dL at Fmax respectively.
- After puncturing the contents of all capsules were carefully transferred to the viewing platform of an AmScope stereo-microscope fitted with a digital camera. The number of visible particles was recorded and ImageJ® software was used to measure their area, circularity, flap attachment and circumference.
- A further samples of capsules were puncture by the MTM and the contents of each capsule were emptied onto an adhesive mount set on an aluminium stub, which was then sputter-coated with gold/palladium under partial vacuum. Four capsules were emptied onto each stub.

METHODS, continued

- The stubs were then examined by scanning electron microscopy (LEO S360, Oxford Instruments) and the size of the particles was measured using the instruments soft ware. A range of magnifications were used in order to detect particles in both the micron and sub-micron range.

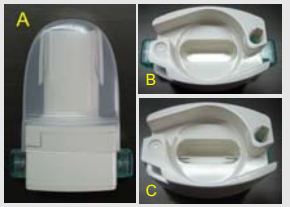

Figure 1. A, Plastiape 2-pin monodose inhaler; B, capsule chamber in base of inhaler; C, 2 buttons depressed showing pins in puncture position

Figure 2. The Zwick materials testing machine with a capsule held in a bushing for puncture

Capsule type & Moisture Content	Moisture Content*	F_{max} (Newton)**	dL at F_{max} (mm)**
Gelatin, Normal	13.0% (0.09)	5.81 (0.61)	0.7 (0.1)
Gelatin, Low	10.8% (0.54)	6.38 (0.65)	1.2 (0.2)
HPMC, Normal	4.7% (0.14)	4.00 (0.38)	0.7 (0.1)
HPMC, Low	3.4% (0.04)	4.08 (0.51)	0.8 (0.2)

Table 1. The moisture content of conditioned capsules, the force recorded during capsule puncture (F_{max}) using the materials testing machine the pin displacement at the point of capuple puncture. *Mean and (standard deviation) of 3 LOD tests;** Mean and (standard deviation) for sample of 20 for each test:

PUNCTURE DEVICE		PLASTIAPE® DPI		ZWICK® MTM	
Moisture Content		Normal	Low	Normal	Low
Particles	Total Mean/capsule	73 2.4(1.1)	172 5.7(1.7)	33 1.10(0.31)	84 2.80(1.10)
Area, mm²	Mean Max. Min.	0.49(0.25) 3.74 0.08	0.57(0.18) 2.23 0.07	0.35(0.06) 0.52 0.20	0.29(0.22) 1.33 0.06
Circumference, mm	Mean Max. Min.	2.82(0.57) 7.44 1.15	3.16(0.58) 7.08 1.09	2.44(0.19) 2.93 2.14	2.16(0.62) 4.57 1.03

Table 2. Results comparing the particles produced by puncture of gelatin capsules using either the Plastiape® inhaler or the Zwick® MTM. Particle number, area and circumference were recorded.

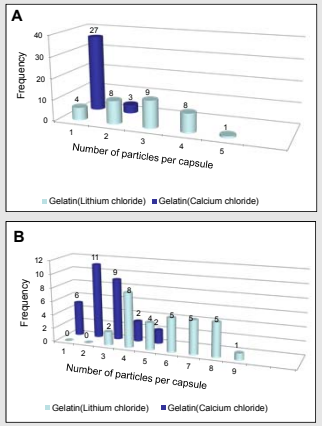

Figure 3. Number of capsule particles detected using a light microscope, when punctured by (A) a Zwick® MTM (cap only) or (B) a Plastiape DPI (cap and body). Thirty capsules were punctured at each of the conditions.

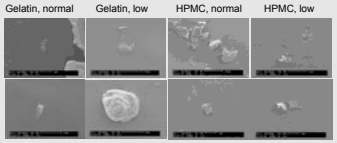

Figure 4. SEM images illustrating range of particle sizes. Length of all particles shown are < 50micron (visual limit).

RESULTS

- The moisture contents of both types of capsules met the desired levels, see **Table 1.**
- Visible particles were only observed in the gelatin capsules after puncture i.e. there were no visible particles upon puncture of HPMC capsules.
- Low moisture gelatin capsules produced more visible particles per capsule than at higher moisture content, see **Fig. 3,** when using both the DPI and MTM.
- Statistical analysis of Zwick® data (unpaired two-tailed t test) showed significant differences in F_{max} (p=0.0064) and dL at F_{max} (p< 0.0001) between gelatin capsules stored at different moisture contents but not HPMC capsules, see **Table 1.**
- The DPI punctured the capsule in cap and body but the MTM just punctured the cap and therefore there were approximately double the number of particles produced by DPI puncture of gelatin capsules compared to MTM puncture, see **Table 2.**
- The impact of moisture on the size of the particles created during puncture of the gelatin capsules was variable and therefore no conclusions can be drawn.
- Images taken by SEM are shown in **Fig.4**. Particles <50µm were observed in all 4 samples i.e. HPMC and gelatin. Some particles between 20 and 50µm had smaller particles adhering to their surface. It may be that particles <5µm became associated with larger particles during sample processing.

CONCLUSIONS

- Visible particles could not be detected by a light microscope after puncture of HPMC capsules, but are visible after puncture of gelatin capsules.
- More particles were detected per gelatin capsule in those with a lower moisture content.
- SEM enabled detection of smaller capsule fragments in both gelatin and HPMC capsules.
- To detect particles <5µm requires high magnification SEM. The number of sub 5µm particles and the area over which they are dispersed made quantitative assessment challenging within the time constraints of the project.
- Analysis of small particles,<2µm, resulted in beam damage to particles, resulting in poor quality images.

BIBLIOGRAPHY

1. Birchall, J.C., Jones, B.E., Morrissey, A. et al., **Drug Dev. Ind. Pharm.**, 2008, **34**, 870-876, "A comparison of the puncturing properties of gelatin and hypromellose capsules for use in dry powder inhalers"
2. Torrisi, B.M., Birchall, J.C., Jones, B.E., Díez, F., **Int. J. Pharm.**, 2013, **456,** 545-552, "The development of a sensitive methodology to characterise hard capsule shell puncture by dry powder inhaler pins"
3. Renswouw, D.C., van Laarhoven, A.C.M. et al., **J. Pharm. Pract.**, 2010, **23**, 548-552, "Storage conditions for inhalation capsules: consequences of incorrect storage and adherence in daily practice"
4. Wang, Y-B, Watts, A.B., et al., **Int. J. Pharm.**, 2014, **461**, 112-128, "The impact of pulmonary disease on the fate of inhaled medicines"
5. Onbrez Breezhaler (Novartis), EPAR Product information, Summary of product characteristics, p. 10, Diagram 10, additional information, gelatin particles