Hanne Kinnunen, Jag Shur, Rob Price, Pharmaceutical Surface science research group, Department of Pharmacy and Pharmacology, University of Bath, BA2 7AY, UK
Gerald Hebbink, DFE Pharma, Goch, Germany

Is the capsule filling process altering dry powder inhaler performance?

Inhalation

The memory of powders for past process history is of high relevance to dry powder inhaler (DPI) formulation. Here the impact of consolidation stresses on formulations with inhalation grade lactose on the DPI performance is tested. Lactohale powders with budesonide filled in capsules with the Omnidose TT and fired from the Cyclohaler were not affected by the filling process.

Introduction

Powders have a memory of past process history. Therefore, consolidation stresses encountered by the powders may be reflected in the fluidization properties of powders later on. This situation is relevant for a dry powder inhaler (DPI) formulation that has encountered consolidation stresses during capsule filling process. As a result of the consolidation stresses encountered, the powder fluidization properties, and consequentially the drug delivery from the formulation, may be influenced.

The current study aimed to investigate the impact of consolidation stresses encountered by the formulations during capsule filling process on the DPI performance of different formulations. In addition, the filling performance of formulations prepared with lactose fines with different process histories (milled vs. micronised) was investigated.

Materials and methods

The carriers used in the study were prepared by blending fine grades of Lactohale inhalation grade lactose to a coarse carrier. The following carriers were used: Lactohale 100 (LH100), and blends of Lacthale 100 with 10% Lactohale 300 (LH300), or 20% Lactohale 230 (LH230), or 20% Lactohale 210 (LH210).

LH100 was chosen because it does not contain fines and consolidation stress is anticipated to have little impact on DPI performance. Blends with fines were chosen because due to the presence of large amounts of fines, consolidation stress is anticipated to have larger effect on DPI performance. *(Figure 1)*

Budesonide (0.8 wt%) was blended with the lactose carriers in order to assess DPI performance.

Capsules (size 3 HPMC, Qualicaps, Spain) were automatically filled with the Omnidose TT automated capsule filling system (Harro Hoefliger, Germany). As reference a series of capsules was hand filled.

The *in vitro* performance was determined on an NGI (Copley Scientific, UK) equipped with a pre separator. Capsules were fired from a Cyclohaler (Teva Pharmaceuticals, Netherlands) at a flow rate of 90 L/min.

Cyclohaler

Results and discussion

The results of the filling processes are depicted in *Table 1.*

The filling with 20% LH210 at low vacuum gave fill weight closest to the target. *(Figure 2)* The filling of 20% LH230 at high vacuum gave the best reproducibility; however, the fill weight was relative far off from the target.

The data in *Figure 3* show that the formulations performed consistently independent of the consolidation stresses encountered during the capsule filling process both in terms of FPF_{ED} and MMAD. For LH100 and LH100 with 10% LH300 small but significant changes were observed, possibly caused by press-on forces or powder structure.

Conclusion

No or just a small effect on DPI performance by the capsule filling process was found in this study. However, the results of the study should not be generalized to other device types, such as blister or reservoir based devices, as different fluidization and deagglomeration mechanisms may be in place.

References
1. Kinnunen, H., Shur, J. Hebbink, G., Muresan, A.S. and Price, R. Lactose fluidisation properties and their relationship to dry powder inhaler performance. Journal of Pharmacy and Pharmacology 62:1342-1343 (2010)
2. Eskandar, F., Lejeune M. and Edge S. Low powder mass filling of dry powder inhalation formulations. Drug development and industrial pharmacy 37:24-32 (2011)
3. Castellanos A. The relationship between attractive interparticle forces and bulk behaviour in dry and uncharged fine powders. Advances in Physics 54:263-376 (2005)

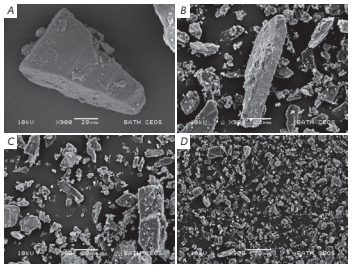


Figure 1: *SEM pictures of the lactose inhalation grade lactose use: Lactohale 100 (**A**); Lactohale 210 (**B**); Lactohale 230 (**C**); Lactohale 300 (**D**).*

	Low vacuum		High vacuum	
	Fill weight (mg ± S.D.)	RSD (%)	Fill weight (mg ± S.D.)	RSD (%)
LH100	11.71 ± 0.27	2.27	12.20 ± 0.13	1.05
+20% LH210	12.47 ± 0.13	1.01	12.79 ± 0.21	1.61
+20% LH230	12.44 ± 0.28	2.25	13.07 ± 0.09	0.69
+10% LH300	12.36 ± 0.16	1.33	12.44 ± 0.19	1.51

Table 1: *Summary of mean fill weight and the relative standard deviation for 20 capsules filled with the formulations at low and high vacuum using the Omnidose TT, target fill weight was 12.5 mg.*

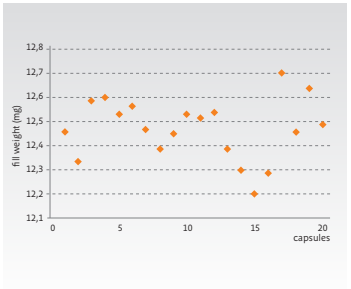
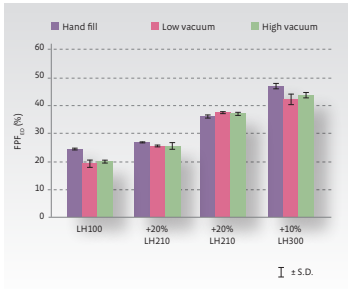


Figure 2: *The reproducibility of fill weight for 20 capsules illustrated with 20% LH210 at low vacuum.*



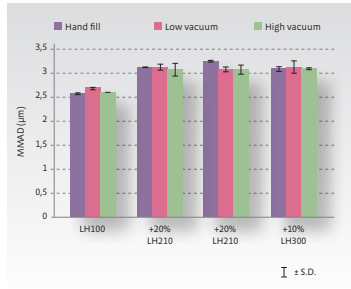


Figure 3: *The fine particle fraction of emitted dose (FPF_{ED}, left) and mean mass aerodynamic diameter (MMAD, right) of the formulations investigated after hand fill and automated filling on the Omnidose TT at vacuum level of -0.3 and -0.8.*