

Understanding impact of fines on flow behavior of lactose blends with and without magnesium stearate and its impact on filling using membrane filling technology

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Summary

Filling low amount of powders for inhalation into blisters is a challenging process. Limited knowledge is available on the use of magnesium stearate as ternary agent in inhaled formulations and its effect on the filling of powders into the blisters. A study was initiated to understand the interaction of lactose fines and magnesium stearate on the flow and the filling of powders into blisters. The particle size fraction below 30µm showed a strong correlation with the compressibility and permeability of the lactose and lactose magnesium stearate blends. An increase in this fraction increases the compressibility, permeability and the fill weight of the powders. Blends having permeability values higher than 6, consistently showed lower relative standard deviation values (below 3.0%) in fill weight. This insight will help to develop robust dry powders for inhalation.

Key Message

Strong correlations have been found between lactose particles below 30µm and compressibility as well as permeability for blends with and without magnesium stearate. For the membrane filling systems, permeability and compressibility are important parameters to tune the relative standard deviations and mean fill weight.

Introduction

Dry powder inhaler (DPI) formulations traditionally contain lactose as single excipient. Newer formulations entering the market contain besides lactose also magnesium stearate [1]. The role of magnesium stearate in DPI formulations have been described as a lubricant [2], performance enhancer [3], water barrier [4], force control agent [5] and stabilizer [6]. While there are differences in literature in the interpretation of the role of magnesium stearate, there is a general consensus on its overall benefits in improving DPI formulations.

Number of studies have been conducted looking at the interplay of various lactose-based formulations and machine operating variables on specific types of automatic capsule filling machines [7]. However, for membrane filling technology there is limited understanding about the correlations between blend flow properties and filling consistency. Furthermore, addition of magnesium stearate into the formulation would lead to further complexities. The current research focuses on the influence of lactose with different coarse and fines ratios and a fixed fraction of magnesium stearate on the flow and filling properties of the blends using membrane filling technology.

Material and methods

Lactose: Four different standard Lactohale (LH) products, all from DFE Pharma (Borculo, The Netherlands), were used in the study with LH206 as the coarse carrier and LH300 (D50 of 4 micron), LH230 (D50 of 9 micron) and LH210 (D50 of 16 micron) as the fine lactose fractions. Magnesium stearate LIGAMED MF-2-V PREMIUM sourced from Peter Greven, (Germany) was used.

Blending: The lactose preblends were prepared using a Nauta conical screw blender (Hosokawa Micron B.V.). The Nauta is a low intensity (0.5-2 m/s), convective blender. Axial mixing in the Nauta is achieved by a rotating screw which gently lifts the powder up. An orbiting arm ensures mixing in the tangential direction (see Figure 1). The ratio of coarse and fines is as shown in Table 1. Thereafter, 1% magnesium stearate was blended with the pre-blended lactose using a 1-liter Cyclomix (Hosokawa Micron B.V.). The Cyclomix is a high shear blender and its working principle has been described in literature [8]. Blending speed and time were 498 rpm and 15 minutes respectively.

Characterization of blends: The particle size distributions (PSD) of the pre-blends were measured using Sympatec Helos laser diffraction instrument in conjunction with Rodos dry powder dispersing system and Vibri powder feeder (Sympatec GmbH, Germany) at a disperser pressure of 1.5 bar. In addition to considering the traditional percentiles D10, D50 and D90 in the analysis of the PSD, the Q30 (particle fraction below 30 µm) was also considered. It has been shown in earlier work that the properties of the blend can be influenced by tuning the fraction of fines [9]. The powder flow and fluidization properties

were characterized using the FT4 powder rheometer (Freeman Technology, Welland, UK). In particular, the focus was on measuring the compressibility (change in a powder's density as a result of a directly applied consolidating load) and permeability (resistance to air flow between particles and through the powder bed) of the different blends. For all these tests, a stress of compressive stress of 15kPa was applied.

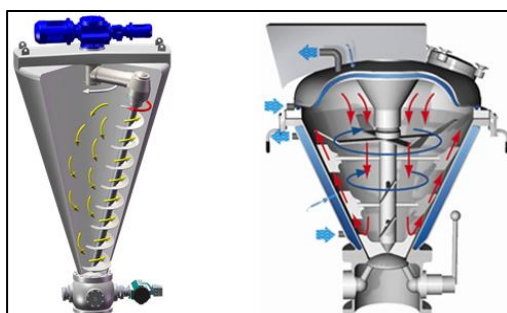


Figure 1. Schematic representation of The Nauta blender used to prepare the lactose pre-blends (left) and the Cyclomix high shear blender for blending the different lactose grades with magnesium stearate (right)

Filling: To investigate the powder filling properties, the blends were filled into blisters using a membrane filler (SSP2, Harro-Höfliger Verpackungsmaschinen GmbH, Germany), as illustrated in Figure 2. The membrane filling consists of a filling head with powder hopper and small powder transfer nozzles, which are incorporated into the membrane surface. The filling head moves downwards onto the aluminum foil web and each blister is hermetically sealed onto the membrane surface. By means of vacuum, the air in a blister evacuates through the membrane which makes powder flow through the nozzle into the blister cavity until it was 100% filled to the rim. From the tests, the mean fill weight was calculated and recorded.

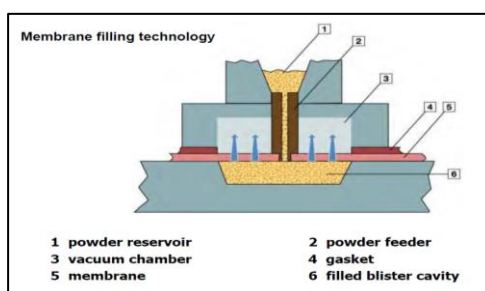


Figure 2. Schematic representation of the working principle of the membrane filler

Results and discussions

Lactose preblends as well as lactose blended with magnesium stearate were characterized for particle size distribution and results are shown in Table 1.

Table 1 : Particle size data of the various lactose and magnesium stearate blends.

Type of fines	Ratio coarse/fines (%w/w)	Particle size without magnesium stearate				Particle size with magnesium stearate			
		D10 (μm)	D50 (μm)	D90 (μm)	Q30 (%)	D10 (μm)	D50 (μm)	D90 (μm)	Q30 (%)
LH210	(90:10)	9.2	70.2	131.0	21.1	18.1	76.1	133.0	15.5
	(80:20)	5.1	55.4	124.5	32.3	5.2	61.0	128.1	29.2
	(70:30)	3.9	41.1	119.0	41.2	3.3	46.6	120.5	40.2
LH230	(90:10)	4.7	67.3	130.7	27.3	8.5	76.9	133.8	17.9
	(80:20)	2.9	46.7	122.8	42.1	2.4	51.5	123.6	39.7
	(70:30)	2.3	20.3	114.9	55.4	1.9	25.9	117.8	51.9
LH300	(97,5:2,5)	6.9	77.3	120.6	15.7	30.5	81.9	134.3	9.8
	(92,5:7,5)	2.5	67.5	116.8	26.9	2.8	73.1	133.6	21.8
	(87,5:12,5)	1.8	54.6	110.8	38.1	1.7	61.3	129.4	33.6

In all cases, it was observed that as the lactose fines increases, particle size of the blends decreases. This was evidenced by the decrease in D10, D50 and D90 and increase in Q30 values. Addition of magnesium stearate (D50, 9 μ m) into the lactose blends resulted in increase in the particle size. This could be due to coating effect and also due to agglomerations. However, this feature was not observed for the blends with high lactose fines (LH210 80:20 and 70:30) and LH230 (80:20 and 70:30), where a decrease in D10 values was observed. This observation was not clearly understood and requires further investigations.

Flow properties for all the blends were measured using FT4 Rheometer. In case of plain lactose pre-blends, with the increase in lactose fines concentration (Q30 μ m), an increase in permeability and compressibility was observed. Similar trends were observed after addition of magnesium stearate. However, when lactose blends blended with magnesium stearate were compared to plain pre-blended lactose, compressibility values decreased while permeability values were observed to be increased (Fig 3 and 5). In case of permeability, lactose blended with magnesium stearate blends LH206:LH210 and LH206:LH230 with 70:30 ratio could not be measured due to high cohesiveness of these blends.

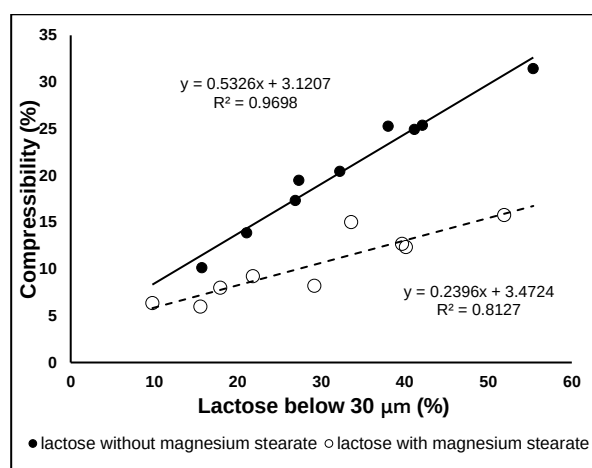


Figure 3– Relation between particle size below 30 micron and the compressibility of the blend. (•) Lactose without magnesium stearate, (o) Lactose with magnesium stearate.

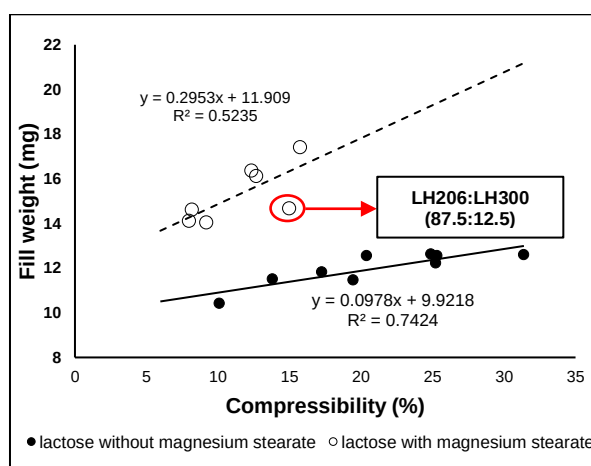


Figure 4 – Relation between compressibility and the fill weight of the blends. (•) Lactose without magnesium stearate (o) Lactose with magnesium stearate.

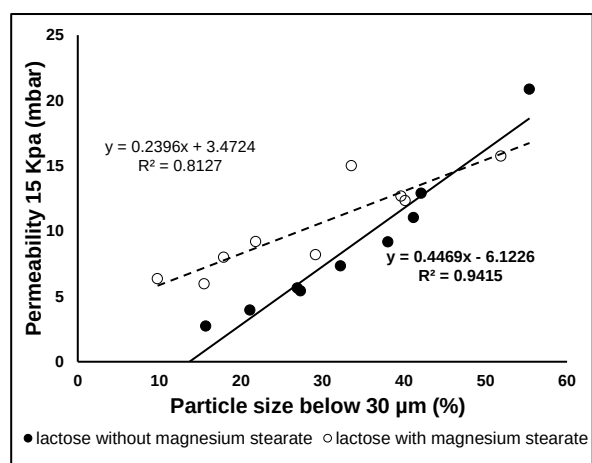


Figure 5 – Relation between particle size below 30 micron and the permeability of the blends. (•) Lactose without magnesium stearate, (o) Lactose with magnesium stearate.

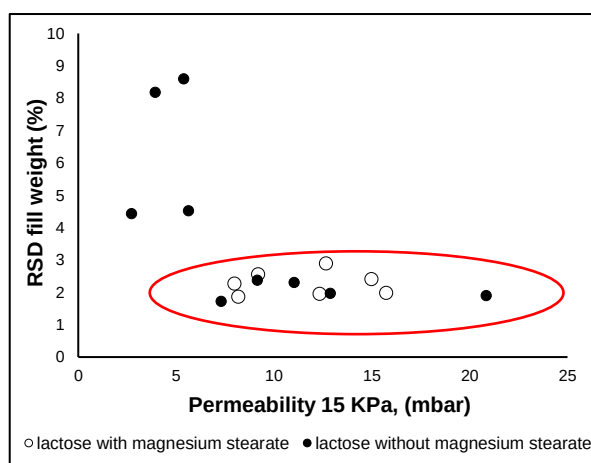


Figure 6 – Relation between permeability and the RSD of the fill weight of the blends. (•) Lactose without magnesium stearate, (o) Lactose with magnesium stearate.

All the blends were filled into the blisters using membrane filling technology. It was observed that powders with low fines concentration have higher relative standard deviations. With low fines concentration, powders have more flowability. This prevents powder compaction inside the nozzle of the membrane filler leading to poor control on filling, leading to high relative standard deviations. In case

of lactose powder blends blended with magnesium stearate, pre-blends with low fines concentration specifically, LH206:LH210 (90:10) and LH206: LH300 (97.5:2.5) were not possible to fill, due to good flowability of these powders. However, remaining blends showed good filling consistency with relative standard deviation (1.87 - 2.89%).

Correlation were developed linking lactose PSD specifically Q30 to flow properties (compressibility and permeability). Further, the graphs were also plotted correlating the flow properties (compressibility and permeability) to mean fill weight data and relative standard deviations of the filled powders. Good correlations were observed between the Q30 and compressibility and permeability in both plain pre-blended lactose as well as lactose pre-blends blended with magnesium stearate (Fig 3 and 5). In case of dry powder inhalers, it is well known that the fine lactose particles such as particle below 4.5 μm have strong correlation with the fine particle fractions [9]. However, based on the correlation data, focusing on Q30 can also assist in modulating the flow properties of the powder which can have direct impact of filling as well as powder aerosolization from the device. Good correlation was observed between compressibility and mean fill weight for plain preblended lactose (Fig 4). However, poor correlation was seen in case of pre-blended lactose further blended with magnesium stearate. This lower correlation was due to batch with high concentration of micronized lactose LH206: LH300 (87.5:12.5), wherein observed mean fill weight was lower than expected (Fig 4). This lower fill weight could be due to agglomeration of the over amount of lactose fines with magnesium stearate, resulting in more void space and lower fill weight. Excluding this batch, the observed correlation between mean fill weight and compressibility was around ($R^2 = 0.9314$). With regards to correlation between permeability and relative standard deviations, good trends were observed in both plain preblended lactose as well as preblended lactose further blended with magnesium stearate. Blends having permeability values higher than 6, consistently showed lower relative standard deviation values (Fig 6). However, blends with poor permeability either were not possible to fill or showed higher relative standard deviations. This could be due to good flowability of the powder, which leads to poor compaction of the powder in the nozzle of the membrane filler.

Conclusions

The study demonstrated good correlations between PSD of the blends, flow properties and filling performance. In case of membrane filling systems, it was observed that the powder characteristics has strong influence on the filling results. Particle size distribution and flow properties changed significantly after addition of magnesium stearate and the impact was clearly seen on mean fill weights and RSD during filling. However, filling behaviour can be further optimized by modulating particles below 30 μm . More mechanistic understanding is required to explore interactions between lactose and magnesium stearate. Further studies are planned to understand the effect of blending speed and time and its impact on extent of magnesium stearate coating and its interactions on lactose surfaces.

References

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