On the performance of coarse and fine lactose blends for DPIs: Part A – rheology behaviour

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Summary

Typical dry powder inhalation (DPI) formulations are composed of an Active Pharmaceutical Ingredient (API) and a carrier excipient, most usually lactose. It is also common to add a second grade of lactose, known as fine lactose, in order to improve the fine particle fraction (FPF) of the formulation. However, increasing the percentage of fine excipient can also have a negative effect on the rheology of the formulation, leading to loss of efficiency on the downstream process, like high rejection rates during automatic capsule filling steps. Additionally, an impact on the overall flowability may also lead to aerosolization challenges upon device actuation, with a potential negative impact on the Emitted Mass (EM). For these reasons the rheological characterization of these powders becomes important.

In this work, different grades of coarse and fine lactose were used to prepare excipient blends with different percentages of fine lactose. Rheology testing was conducted using an FT4 powder rheometer. A partial least squares (PLS) regression was applied to the gathered data and a high degree of correlation was found between formulation composition and rheology parameters. It was observed that the basic flowability energy (BFE), the conditioned bulk density (CBD) and the pressure drop (PD) across the powder bed are mainly governed by the percentage of fines and the particle size of the coarse lactose. On the other hand, the aeration energy (AE) depends mostly on the percentage of fines and the particle size of the fine lactose. This model allows the prediction of rheology parameters of DPI formulation blends which are then correlated with capsule filling and device performance in Part B of this article.

Introduction

During development of formulations for dry powder inhalers (DPI) it is common to use lactose coarse particles as a carrier excipient. In this type of approach, the objective is to maximize the fine particle fraction (FPF) of the formulation, that is, the fraction of API that reaches the deep lung. In order to improve the FPF, it is usual to add a certain percentage of a different grade of lactose, with a finer particle size (fine lactose), which prevents the API particles from adhering as strongly to the coarse carrier, and therefore improves the detachment of API during delivery [1-3]. However, a composition that favours FPF can have a deleterious effect on the overall process, as the flow properties of these formulations may have a significant impact on the capsule filling performance of the final dosage form, as well on the emitted dose performance of the inhaler. Therefore, it becomes important to evaluate trade-offs and, in this way, identify compositions that are able to benefit the process as a whole. The objective of this work was to study the influence of the particle size of coarse and fine lactose and the percentage of fine lactose on the flowability of the powders, through rheological parameters. The ultimate goal was to derive a statistical model based on the experimental data, capable of predicting these parameters from the composition of the blend and evaluate, in Part B of this work, if such model can also translate the observed capsule filling and device performance, when selected blends with different rheology properties are considered.

Materials and Methods

Coarse lactose grades used were Respitose SV003 and SV010 from DFE Pharma; fine lactose grades were Lactohale 300 and Respitose ML006 from DFE Pharma and Sorbolac 400 from Meggle Pharma (Table 1). Blends with different coarse and fine lactose grades and with different percentages of fines (0, 4, 10 and 16%) were prepared. A total amount of 500 g of lactose grades (one coarse and one fine) were sieved through a 450 μm sieve and placed in a 2 L container. The mixture was then blended in a Turbula® T2F for 30 minutes at 46 rpm. The blends were left resting for at least 24 hours to allow relaxation of the powder. After that, all blends were analysed in an FT4 powder rheometer. Stability and variable flow rate, aeration and permeability standard tests were performed in triplicate. The obtained data were analysed using SIMCA software (from UMETRICS).

Table 1 – Lactose grades used to prepare different carrier based blends.

Grade	Supplier	Coarse/Fine	Dv50 (μm)
SV010	DFE Pharma	Coarse	105
SV003	DFE Pharma	Coarse	60
LH300	DFE Pharma	Fine	5
Sorbolac 400	Meggle Pharma	Fine	10
ML006	DFE Pharma	Fine	17

Results and Discussion

FT4 powder rheometer results for basic flowability energy (BFE), conditioned bulk density (CBD), aeration energy (AE) and pressure drop at a normal stress of 15 kPa (PD) are presented in Table 2. BFE and CBD parameters are outputs of the stability and variable flow rate standard FT4 test, with results demonstrating a good reproducibility given the low Relative Standard Deviations (RSD) observed. The same is verified for the permeability test, which provides low RSDs for the PD parameter. On the other hand, the aeration test showed a decreased reproducibility for these powders, with RSDs ranging from 12.15 to 91.48% for the AE parameter.

SIMCA software was used to perform a partial least squares (PLS) regression, considering the blends composition as input variables and the FT4 data as output variables. The model results are presented in Figure 1 for the global model and for the different rheology parameters. A logarithmic transformation was applied to the PD parameter. The results for the global model demonstrate that the experimental data is well fitted, with an R^2 of 0.83 and a χ^2 of 0.75. The model also shows a good fitting of the individual variables BFE, CDB and PD, with R^2 between 0.90 and 0.91 for all of these variables, and χ^2 between 0.84 and 0.87. However, the model presents lower R^2 and χ^2 values (0.61 and 0.44, respectively) for the AE parameter when compared with the other outputs. This can be explained by the larger RSDs observed during the aeration test, which lead to results that are affected by variability that cannot be linked nor captured by a mathematical model.

Table 2 – FT4 powder rheometer results for the different blends.

Blend	Coarse lactose	Fine lactose	Fine percentage	BFE (mJ) (RSD%)	CBD (g/mL) (RSD%)	AE (mJ) (RSD%)	PD (mbar) (RSD%)
1	SV010	LH300	4	346.7 (2.68)	0.712 (0.29)	23.97 (53.22)	1.470 (1.80)
2	SV010	LH300	10	341.7 (1.95)	0.695 (0.30)	54.40 (18.50)	3.733 (3.20)
3	SV010	LH300	16	263.3 (4.18)	0.623 (0.49)	45.13 (13.53)	4.900 (22.22)
4	SV010	Sorbolac 400	4	351.3 (2.88)	0.718 (0.29)	5.07 (32.13)	1.240 (6.60)
5	SV010	Sorbolac 400	16	246.3 (6.20)	0.673 (0.86)	40.60 (18.13)	3.707 (17.24)
6	SV010	ML006	4	431.3 (8.28)	0.741 (1.75)	4.06 (27.98)	1.110 (10.62)
7	SV010	ML006	10	390.0 (0.44)	0.738 (0.75)	4.82 (91.48)	1.690 (8.76)
8	SV010	ML006	16	334.3 (2.54)	0.692 (0.74)	36.17 (13.26)	2.353 (9.36)
9	SV003	LH300	4	284.3 (2.06)	0.683 (0.34)	6.14 (37.81)	3.120 (0.85)
10	SV003	LH300	10	187.7 (2.15)	0.640 (1.81)	35.07 (13.55)	7.207 (9.47)
11	SV003	LH300	16	119.0 (4.20)	0.589 (1.91)	18.93 (12.15)	11.423 (15.04)
12	SV003	Sorbolac 400	4	267.3 (4.65)	0.662 (0.52)	17.90 (35.96)	2.463 (5.92)
13	SV003	Sorbolac 400	16	166.7 (7.83)	0.601 (0.80)	26.87 (24.87)	5.073 (17.47)
14	SV003	ML006	4	244.0 (15.36)	0.664 (0.54)	7.34 (22.14)	2.330 (3.24)
15	SV003	ML006	10	218.0 (12.37)	0.637 (0.68)	28.67 (17.39)	2.617 (6.09)
16	SV003	ML006	16	202.3 (4.20)	0.609 (0.66)	28.67 (16.73)	3.010 (8.81)
17	SV010	-	-	461.3 (5.54)	0.740 (1.24)	2.90 (36.54)	0.922 (10.33)
18	SV003	-	-	249.0 (9.75)	0.673 (1.35)	3.67 (36.29)	1.867 (7.27)

In Figure 2, the biplot with all X variables (inputs = formulation composition parameters), Y variables (outputs = FT4 rheology parameters) and observations is presented (left side), as well as the model coefficients for each of the outputs (right side). The axes of the biplot represent the principal components. The points of the biplot represent the scores of the observations and variables on the principal components. Output variables perpendicular to input variables when considering the origin as a reference point show no correlation. Output and input variables close to each other or in opposite locations of the plot are highly correlated. From these two graphs it is possible to infer which parameters of the formulation govern each of the rheology parameters. Regarding the BFE parameter, it is possible to conclude that the Dv50 of the coarse lactose contributes positively: the larger the particle size of the coarse lactose, the higher the BFE. On the other hand, the percentage of fine lactose contributes negatively to the same parameter, meaning that when this percentage is increased, the BFE decreases. The particle size of the fine lactose does not have a significant influence on this rheology parameter. Formulation parameters have the same influence on the CBD as they do on the BFE. In Figure 3, the observed values for each variable are compared with those predicted by the model. Figures 3a and 3b, depicting the BFE and CBD respectively, demonstrate the good quality of the predictions.

Regarding the AE parameter, Figure 2 shows that this variable depends mostly on the particle size of the fine lactose and on the percentage of fines, negatively and positively respectively. This means that as the size of the fine lactose increases, the AE decreases, and it increases when the percentage of fine lactose increases. Figure 3c, showing the observed versus predicted values for this variable, shows a higher degree of scatter around the regression line, which was expected given the higher RSDs for this variable and the lower performance of the model, mentioned above.

Unlike AE, the PD across the powder bed does not show a dependence on the size of the fine lactose. Instead, this variable depends heavily on the particle size of the coarse lactose and on the percentage of fines, as can be inferred from Figure 2. This variable increases as the percentage of fines increases and as the Dv50 of the coarse lactose decreases. Figure 3d shows a very good agreement between observed and predicted values for this parameter.

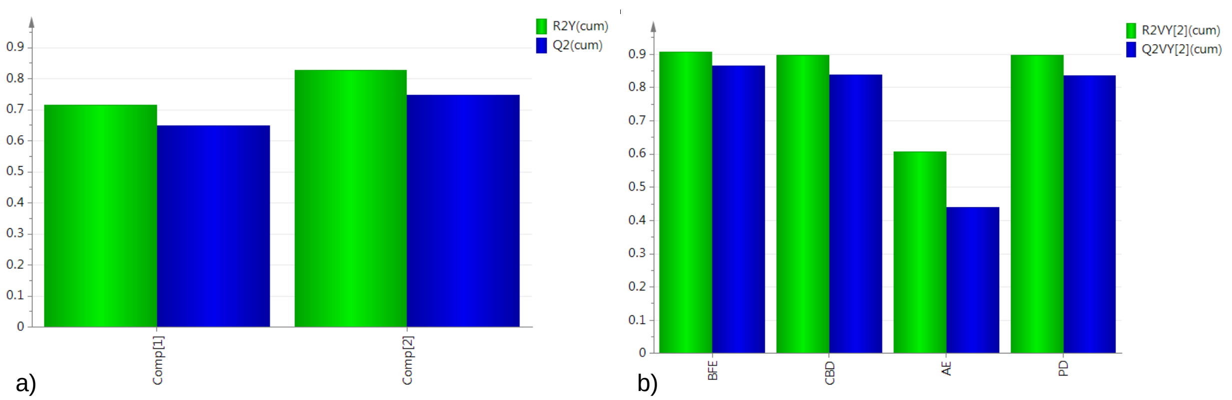

Figure 1 – PLS results: a) R2 and χ2 values for one and two principal components; b) cumulated R2 and χ2 values for each output of the model.

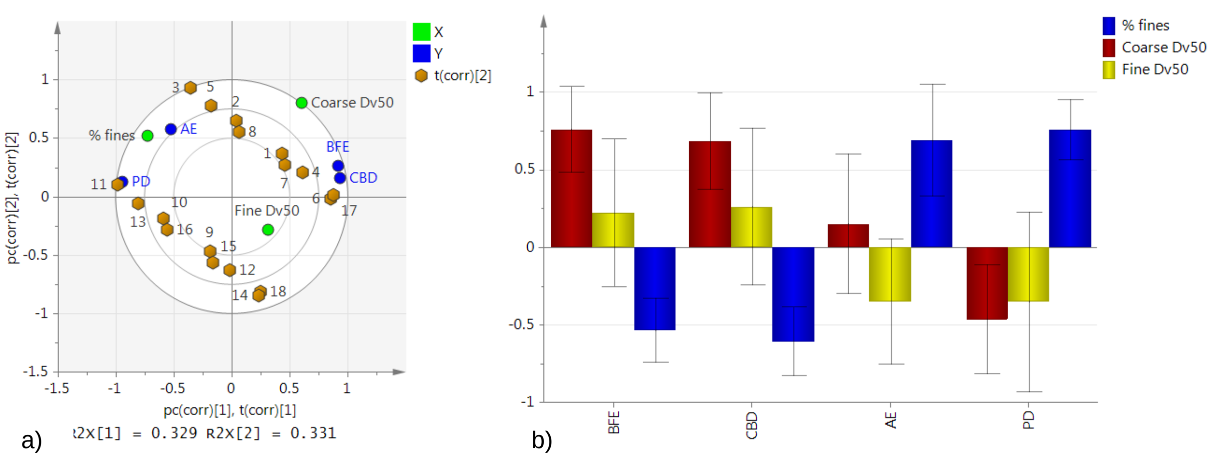

Figure 2 – PLS results: a) biplot showing X variables, Y variables and observations; b) model coefficients overview, with the corresponding error bars.

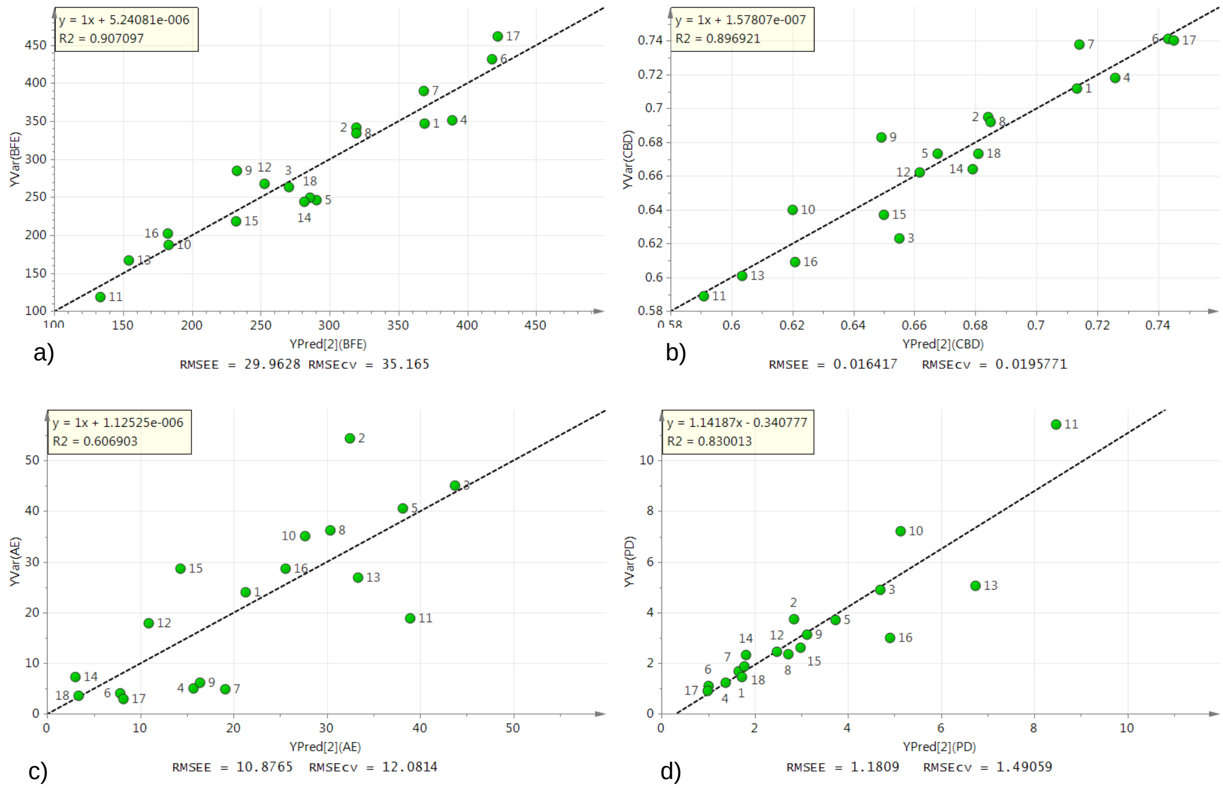

Figure 3 – Observed versus PLS model predicted results for different Y variables: a) basic floability energy (BFE, mJ); b) conditioned bulk density (CBD, g/mL); c) aeration energy (AE, mJ); d) pressure drop (PD, mbar).

The developed model therefore allows the prediction of the rheological properties of any blend of fine and coarse lactose grades, given the composition and particle size of both grades, within the ranges evaluated in this work.

If the AE parameter is excluded from the model, due to its high variability, an improved fitting is obtained, with the global model presenting an R^2 of 0.91 and a χ^2 of 0.84; regardless, the relationships are kept the same.

Conclusion

Rheology data were obtained for 18 blends composed of different coarse lactose, fine lactose and percentage of fine lactose. A partial least squares (PLS) regression was applied to the gathered data and a very good correlation was found between formulation composition and rheology parameters, with an R^2 of 0.83 and a χ^2 of 0.75 for the global model. Results for the individual parameters were also well fitted, with R^2 ranging from 0.61 for the AE (the lowest value given the high RSDs of this specific test) to 0.91 for the BFE. The model allows conclusions to be made about which formulation parameters influence each of the rheology properties of the powder. It was observed that the percentage of fine lactose and the particle size of the coarse lactose govern the BFE, CBD and PD parameters, and the particle size of the fine lactose and the percentage of fine lactose influence the AE. This thorough understanding of the rheology properties of lactose blends is expected to play an important role during the prediction of the capsule filling and device performance, as explored in Part B of this article.

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