Modelling of the microfluidization process for top Inhalation APIs

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SUMMARY

Background: Microfluidization is one emerging size reduction technique in the field of inhalation; previous works [1] have suggested modelling equations for the involved comminution profiles, but evaluation of such mathematical relationships across different compounds is still missing.
Methods: Size-reduction of three compounds, namely fluticasone propionate (FP), salmeterol xinafoate (SX) and mometasone furoate anhydrous (MF), was performed by microfluidization of suspensions using the same model processor and operating conditions. In all cases, the final particle size after processing was within a typical inhalation range (1.5 μm < Dv50 < 2.5 μm). After generating the data, different candidate models were identified through Partial Least Squares (PLS) regressions and, afterwards, fine-tuned by reducing the number of fitting parameters in order to minimize over-fitting phenomena and facilitate a potential mechanistic interpretation of the found relationships.
Results: The obtained results show that the size-reduction profiles of the different compounds, although apparently similar, cannot be entirely captured by previous models [1], requiring more flexible mathematical relationships; additionally, it was also found that the penalty (decrease of R^2 value) associated to the reduction of the number of fitting parameters depends heavily on the pre-set equation structure, a key indicator for the selection of the best performing model.
Conclusions: The intrinsic behaviour of microfluidization processes, across different top inhalation compounds, can be accurately captured, provided that an appropriated model structure is adopted; the suggested equation enables a mechanistic interpretation, where one of the fitting parameters is hypothesized to be related with the physical intrinsic properties of the compounds.

INTRODUCTION

Particle size is one of the key factors for successful pulmonary drug delivery. Conventional crystallization processes lead typically to particles in the size range 10 - 100 μm; consequently, the established way to achieve micron-size crystals is the comminution of particles by a suitable size reduction technique [2, 3]. Given the growing importance of wet media milling methods, the particle size-reduction dynamics of three widely used active pharmaceutical ingredients - fluticasone propionate (FP), salmeterol xinafoate (SX) and mometasone furoate anhydrous (MF) – were obtained by employing a microfluidization process; the generated particle size data was afterwards modelled, in order to determine which mathematical equations are best suited for the description of the involved phenomena.

RESULTS

Microfluidization of FP, SX and MF suspensions was performed using the same processor and operating conditions for size-reducing the APIs to a typical inhalation range. The particle size after *N* passes across the microfluidizer was determined using a laser diffraction method, being the average of three measurements of the same sample. Different models were considered for describing the comminution profile with the number of passes across the microfluidizer, which were randomly generated following a PLS exercise using mathematical functions that could best translate the experimental curve. The best identified models are shown in Table 1. For each experimental point, the median particle size of the APIs based on a volumetric distribution (Dv50) after a *i* number of passes was normalized with the starting raw material $Dv50_{t0}$ according to equation (1):

$$Dv50^* = Dv50_i / Dv50_{t0} \quad (1)$$

The data regression considered the least squares method for determining the coefficient values that would minimize the model error; the final models coefficients and summary of fit for the different pharmaceutical compounds are presented in Table 2, while the prediction profiles and model residuals are shown in Figure 1.

Table 1 – Best models (after a PLS exercise) for description of Dv50* as function of the number of passes *N*.

Model	Equation
#1	$lnDv50^* = alnN + b$, for $N \geq 1$
#2	$lnDv50^* = \frac{a}{N} + b$, for $N \geq 1$
#3	$lnDv50^* = alnN + \frac{b}{N} + c$, for $N \geq 1$
#4	$ln\frac{1}{Dv50^*} = alnN - \frac{b}{N} + c$, for $N \geq 1$

Table 2 – Model coefficients and summary of fit for the four best performing models (see also Table 1).

Model	Fluticasone propionate				Salmeterol xinafoate				Mometasone furoate anhydrous			
	a	*b*	*c*	R^2	*a*	*b*	*c*	R^2	*a*	*b*	*c*	R^2
#1	-0.23	0.02	NA	0.9792	-0.42	-0.35	NA	0.9658	-0.45	-0.08	NA	0.9636
#2	0.95	-0.66	NA	0.7394	7.75	-2.19	NA	0.9291	1.40	-1.27	NA	0.6673
#3	-0.28	-0.26	0.18	0.9893	-0.26	3.37	-1.07	0.9993	-0.59	-0.60	0.33	0.9870
#4	0.48	8.66	-2.44	0.9664	-0.01	4.12	-0.36	0.9972	0.15	3.19	-0.97	0.9892

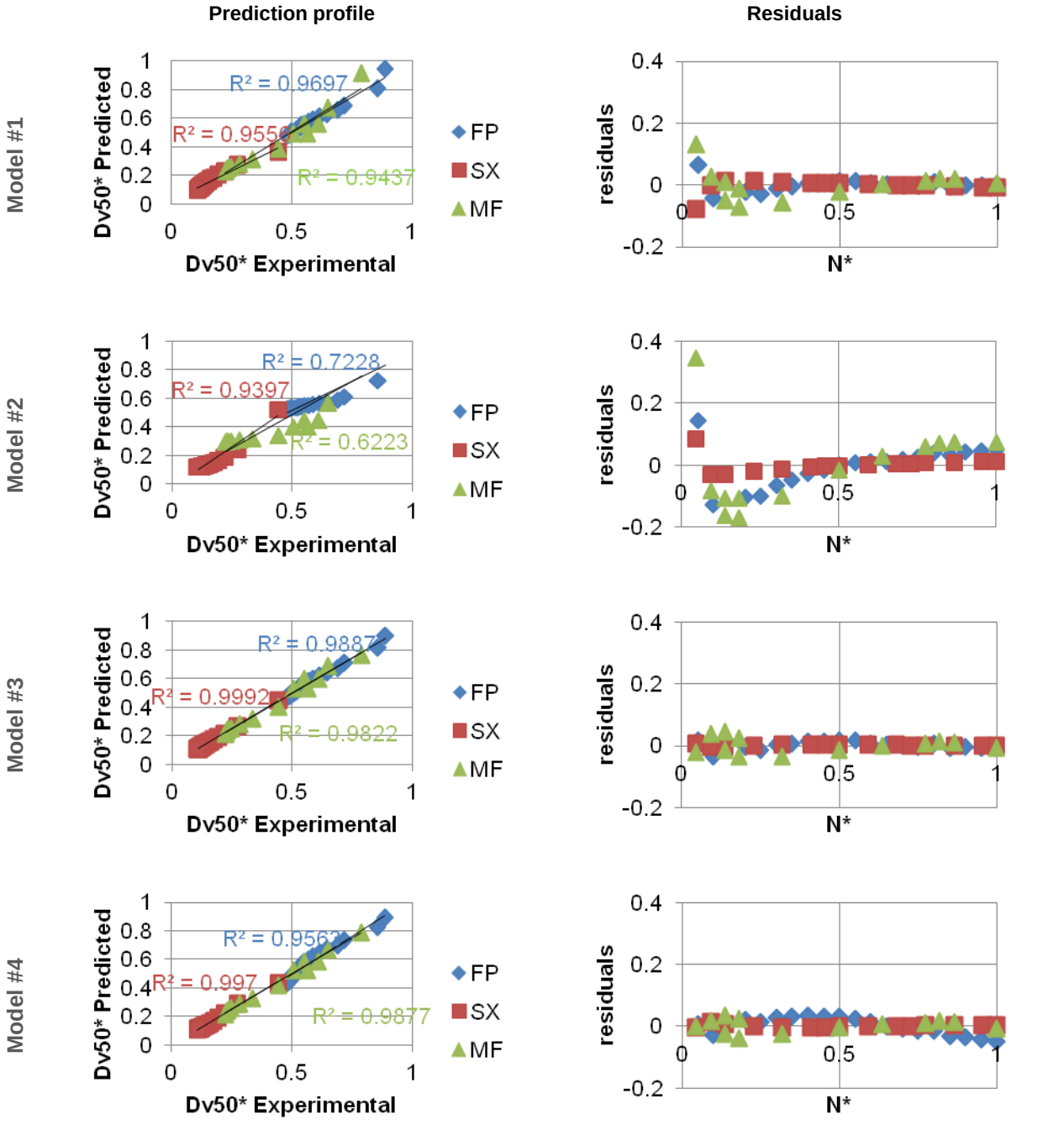

Figure 1. Prediction profiles and residuals for the four different models of *Dv50** during the microfluidization of: fluticasone propionate (FP; blue diamonds), salmeterol xinafoate (SX; red squares), and mometasone furoate anhydrous (MF; green triangles). In the residual plots, the number of passes was normalized over the total number of passes (*N**).

From both the correlation coefficients and the residuals distributions, models #3 and #4 are the ones that better capture the size reduction dynamics across the different APIs; however, immediate classification of models #1 and #2 as poorer performers is not possible, as a direct benchmark would only be feasible if the number of fitting parameters were the same. In fact, models #3 and #4 consider three fitting parameters (against two fitting parameters in models #1 and #2)

and, without evaluating trade-offs between reduction of residuals magnitude and incremental number of model coefficients, no general conclusions can be taken.
Given the above, models #3 and #4 were subjected to a multi-objective optimization process in order to evaluate the penalty on the correlation coefficient (R^2) when the number of model coefficients is reduced. This exercise was conducted by considering the minimization of the objective function (2):

$$\min\left(w_1 \sum_{i=1}^{N} (Dv50^*_{model} - Dv50^*_i)^2 + w_2 (a-b)^2\right) \qquad (2)$$

The weight terms, w_1 and w_2, were set in order to value both objectives evenly, that is, to mathematically express the importance of minimizing the least squares term (which would translate into a better R^2) and, simultaneously the importance of having coefficient "*a*" equalling coefficient "*b*" (which would eliminate an additional fitting parameter). The outcome of this exercise is shown in Figure 2, for the particular cases of FP and SX (the APIs for which the best and worst fits were obtained using both model structures – see Table 2). As shown in Figure 2, and as observed in general for all the remaining cases, there is much less degradation of the overall fit for model #3 when the difference between coefficient "*a*" and "*b*" is minimized, than for model #4. Table 3 shows the summary of fit when "*a*" is equal to "*b*" (meaning that only two fitting parameters were regressed) for models #3 and #4; as can be seen, the particle size reduction profile can be successfully described with only two fitting parameters for model #3, and still with higher correlation coefficients than any other of the candidate models (for all compounds in study).

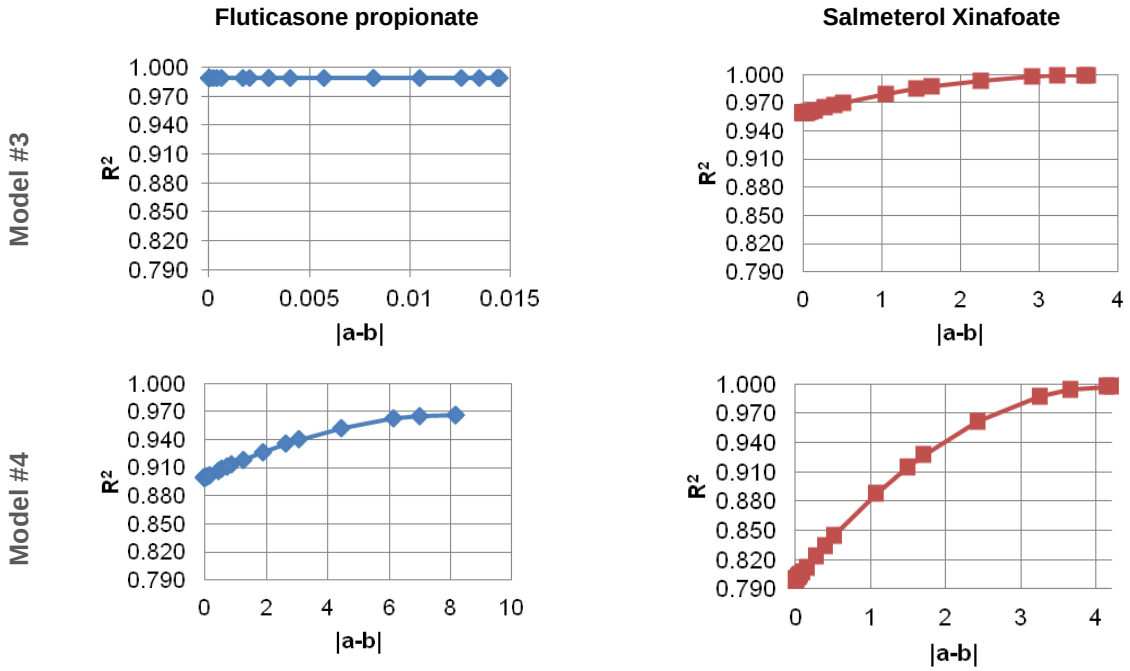

Figure 2. Correlation coefficients of models #3 and #4 as a function of the absolute difference in coefficients, |*a* – *b*|.

Table 3 – Model coefficients and summary of fit for models #3 and #4 when coefficients "*a*" and "*b*" are equal.

Model	Fluticasone propionate				Salmeterol xinafoate				Mometasone furoate anhydrous			
	a	*b*	*c*	R^2	*a*	*b*	*c*	R^2	*a*	*b*	*c*	R^2
# 3	-0.28	-0.28	0.19	0.9892	-0.43	-0.43	-0.26	0.9584	-0.59	-0.59	0.32	0.9870
# 4	1.82	1.82	-6.64	0.8992	0.18	0.18	-1.21	0.7992	0.76	0.76	-2.71	0.9154

The better performance of model #3 is explained by the increased mathematical flexibility obtained through the combination of terms log(*N*) and 1/*N*; these two terms translate different slopes of size-reduction and can therefore better describe, for any compound, the beginning and the end of the comminution profile (even when both terms are forced to depend on the same fitting parameter); additionally, by imposing *a=b,* the value of this model coefficient can be hypothetically related to the intrinsic physical properties of the API, since it is the dictating (and sole) factor for the variation in particle size with the number of passes *N* across the microfluidizer. Qualitatively, MF would be therefore more friable than FP under these experimental conditions, as the determined "*a=b*" value is larger. Similar model interpretations were already proposed elsewhere [1]. Indeed the impact of the API mechanical properties on the micronization process behaviour has already been reported [4]. Future modelling work should therefore include (i) analytical characterization of the raw compounds in terms of hardness / friability; and (ii) exploring alternative experimental conditions (namely pressure drop across the microfluidizer, solids concentration in suspension and/or microfluidizer configurations), so that potential interactions may be identified and, in this way, contribute to a deeper mechanistic understanding of these processes.

CONCLUSIONS

Different models were explored, in an attempt to capture the size-reduction process of different inhalation compounds by microfluidization; the results show that, in order to properly model the obtained size reduction profiles, it is necessary to consider different mathematical terms, as single dependences cannot effectively capture the initial and final stages of the process. The suggested model structure encloses two regressing parameters, where one is hypothesized to be correlated with the physical intrinsic properties of the API in suspension. Additional analytical characterization of the compounds (raw materials) and investigation on the impact of additional microfluidization parameters are recommended in order to deepen the mechanistic understanding of the process and enable some degree of predictability to the obtained models.

REFERENCES

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