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Modeling dispersion of dry powders for inhalation. The concepts of total fines, cohesive energy and interaction parameters

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ABSTRACT

A range of carrier based dry powder formulations consisting of micronized drug, carrier lactose and, in some formulations, lactose fines were produced and tested for dispersibility, i.e. fine particle fraction (FPF). Two different drugs were used, budesonide (BUD) and beclomethasone dipropionate (BDP). A model based on the total amount of fines (TF) and the cohesive energy (CE) of the formulation is proposed, where TF is the sum of added drug, lactose fines and the fines inherent to the carrier. The expression for CE is derived from regular solutions theory and allows calculation of interparticle interaction parameters. The model was able to describe experimental data well, such as the decrease in FPF when the proportion of drug is increased at a constant TF level and the non-linear effects seen when a cohesive drug is added to carrier. BDP and BUD were found to be 5.3 times and 1.8 times more cohesive than lactose fines respectively. The model hence provides a link between the macroscopic behavior of a dry powder formulation and the interaction between the different species at the particulate level.

1. Introduction

Despite intense research, dispersion of dry powders for inhalation is still relatively poorly understood. This is true both for pure micronized systems and for carrier based formulations, the latter also called ordered or adhesive mixtures. In the majority of dry powder formulations, the drug particles are micronized or otherwise processed into particles with a diameter of less than 5–10 μm. Due to the extremely small mass of a single drug particle, gravity has little influence in comparison to the forces exerted by the neighboring particles, causing the drug particles to aggregate with each other and excipient particles present in the formulation. A key functionality of any dry powder inhaler is hence to provide forces that serve to deaggregate the powder and disperse the drug particles into a fine aerosol that can reach the lungs of the patient. In the case of passive dry powder inhalers, this action relies entirely on patient inspiratory force. The mechanisms by which powder dispersion occurs are extremely complex and obviously depend on the detailed design of the inhaler as well as the physico-chemical properties of the formulation. To date only few articles have addressed dry powder dispersion in a more profound and general way (De Boer et al., 2003a,b; Nichols and Wynn, 2008; Visser, 1989).

In this work, some new concepts which are believed to be useful for a more general understanding of dry powder formulation dispersion are introduced. Focused on carrier based formulations, it will be demonstrated how the fine particle fraction of the drug can be modeled based on these concepts. By fitting the model to experimental data, interaction parameters pertaining to drug–drug, drug–excipient and excipient–excipient interactions can be obtained.

Before presenting the model, a discussion around inhaler 'working range' is needed.

It is argued that each dry powder inhaler (DPI) has a 'working range' as regards the formulations. Within this range, the inhaler does its job and disperses the powder into the airstream following general principles and laws (although these laws can be extremely hard to unravel). But if a dry powder inhaler is used with a formulation outside the working range, the dispersion processes are no longer in control and the performance often collapses.

A substantial part of dry powder inhalation research has been directed to "dilute" systems, i.e. formulations consisting of lactose carrier with a very low percentage of drug. In this range the surface properties of the carrier tend to dominate the behavior (Heng et al., 2000; Louey and Stewart, 2002; Young et al., 2005, 2002). The notion of "active sites" has been introduced, debated and refined (Jones and Price, 2006). The performance of such dilute systems is often poor, with fine particle fractions ranging from single digit up to around 20%. It has been shown that a low fine particle fraction generally correlates with a high variation in the lung dose to the patient (Borgström et al., 2006). In addition to this, economical aspects make such dilute systems of limited interest for DPI product development.

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Table 1
Compositions and fine particle fraction data for all twenty-one formulations. The last column indicates whether or not a formulation is included in the modeling.

Exp. no.	Drug type	Lactose type	%Drug (by weight)	% Lactose fines (by weight)	% Lactose carrier (by weight)	Fine Particle Fraction (%)	Included in modeling
1	BUD	Pharmatose	2		98	19.4	X
2	BUD	Pharmatose	2	8	90	37.4	X
3	BUD	Pharmatose	5		95	24.2	X
4	BUD	Pharmatose	10		90	31.1	X
5	BUD	Pharmatose	2	3	95	28.1	X
6	BUD	Pharmatose	5	5	90	31.1	X
17	BUD	Pharmatose	15		85	29.1	
18	BUD	Pharmatose	25		75	14.5	
19	BUD	Pharmatose	2	13	85	41.8	
20	BUD	Pharmatose	2	18	80	44.0	
7	BUD	Respitose A	2		98	15.2	X
8	BUD	Respitose A	2	8	90	36.1	X
9	BUD	Respitose A	5		95	18.3	X
10	BUD	Respitose A	10		90	23.1	X
21	BUD	Respitose A	25		75	16.6	
11	BDP	Respitose B	0.5	9.5	90	32.6	X
12	BDP	Respitose B	2		98	8.0	X
13	BDP	Respitose B	10		90	10.8	X
14	BDP	Respitose B	2	8	90	23.6	X
15	BDP	Respitose B	5		95	5.4	X
16	BDP	Respitose B	5	5	90	12.3	X

An intermediate region with regard to drug load can be identified ranging approximately from 2 to 15%. This range is more appropriate for development of inhaled products, as significantly higher fine particle fractions can be achieved. This range will be the focus of this work.

When higher drug loads (>15%) are applied in ordered mixture systems, a collapse in the FPF is often seen (Louey et al., 2003; see Fig. 5). This is because the physico-chemical properties of the formulations are no longer aligned with the requirements of the inhaler. In addition to suboptimal drug delivery, this also entails a high variability, which makes product development very difficult. This reasoning does not apply to formulations consisting of micronized material only, for which specially designed inhalers are used, e.g. Turbuhaler®.

In summary, this work aims to model the dispersion of carrier based formulations for inhalation, with focus on the intermediate region as regards drug load. It will be shown that the novel concepts introduced and the model itself are useful in providing insight into the principles and mechanisms of dry powder dispersion from a DPI. Experimentally, twenty-one formulations were produced comprising two different lactose carrier grades, two different drugs, budesonide (BUD) and beclomethasone dipropionate (BDP), and optionally micronized lactose fines. Compositions of all formulations are given in Table 1. The formulations were analyzed in a simple prototype inhaler, consisting of an L-shaped cylindrical channel (see Fig. 3 below). The FPF data obtained are included in Table 1.

2. Model

The model deals with binary and ternary formulations consisting of carrier, drug particles with a particle size of less than 10 μm (diameter), and for some of the formulations added fines, also with particle size less than 10 μm. The model may however hold true outside of this scope. It is further assumed that the formulations are within the working range of the inhaler (as discussed above) and that they have good homogeneity. It should be possible to model the dispersion (fine particle fraction) of such formulations as the product of all contributing factors. One problem here is that not all factors are known, and another is that the equation may become overly complicated. Starting out from seven well-known independent critical factors, the following general equation for FPF is obtained:

$$\mathrm{FPF} = F \times G \times H \times P \times J \times K \times L \quad (1)$$

where F represents formulation cohesivity, G the effect of fines, H the influence of the carrier, and P the effect of processing. The remaining factors relate to the inhaler and how the aerosol cloud is generated; J represents a factor for the device, K the flow rate or pressure drop and L represents the properties of the gas phase (essentially the relative humidity). For a dataset generated using only one inhaler at one air flow (pressure drop) in controlled laboratory environment, Eq. (1) reduces to:

$$\mathrm{FPF} = F \times G \times H \times P \quad (2)$$

These factors are discussed more thoroughly below.

2.1. The processing factor, P

It is well known that the FPF is heavily dependent on the processing of the formulation. An efficient, robust and reliable manufacturing process is needed for mixing the very fine and cohesive drug particles with the carrier in order to ensure that the formulation is homogeneous with regards to drug content. As the dose weight may be as low as a few milligrams, this can represent a major challenge. Beyond this, it is known that the mixing process may directly influence formulation performance measures such as fine particle fraction. A decrease in FPF with increasing mixing time was observed for salbutamol sulfate and lactose carrier blended in a high shear mixer (Steckel, 2007), while Jones et al. (2010) reported an increase followed by a decrease at longer mixing times for binary budesonide–lactose blends using a Turbula mixer. In this work, the manufacturing process has been exactly the same for all formulations produced. The processing factor can therefore be set to 1, and so is not considered further in this work.

2.2. The carrier factor, H

Many investigations have been directed to the influence of carrier properties on formulation dispersibility (Chan et al., 2003; Heng et al., 2000; Islam et al., 2004a,b; Larhrib et al., 1999, 2003a,b; Zeng et al., 2000). It has been shown that carrier particle size, size

Table 2
Materials used and key characteristics. Particle size data in this table was measured using Sympatec Helos with RODOS/ASPIROS at 4 kPa. The R2 lens was used for micronized materials and the R3 lens for carriers. The % of particles <9 μm measured by Sympatec (column 8) was recalculated as % of particles by weight <9 μm (column 9) using a calibration curve as described in Section 3.4.

Material	Lot	Denotation	Density (g/cm^3)	D10 (μm)	D50 (μm)	D90 (μm)	%<9 μm symp.	%<9 μm weight
Budesonide	482-04	BUD	1.26	0.52	1.6	4.1	99.9	100[a]
Beclomethasone dipropionate	03220520	BDP	1.36	0.49	1.3	3.1	100	100[a]
Lactose fines	108-01	LF	1.52	0.75	2.9	7.0	96	100[a]
Lactose carriers								
Pharmatose 125 M	10099086	Pharmatose	1.52	15.6	61.1	108	7.4	3.3
Respitose SV003	10134131	RespitoseA	1.52	30.0	57.8	88,0	4.4	2.0
Respitose SV003	10139208	RespitoseB	1.52	27.9	59.0	91.8	4.7	2.1

[a] The micronized materials were assumed to be 100% <9 μm in the modeling.

distribution and shape can affect powder dispersibility. In addition to this, carrier surface properties such as rugosity, purity and crystallinity have been shown to be important and may significantly influence the performance. The majority of these studies has however been performed at very low concentration of drug.

In this work two different grades of lactose carrier have been used, namely Pharmatose 125 M and Respitose SV003. These materials are sourced from the same supplier, factory and manufacturing line, and have similar surface properties and also similar shape and median diameter (VMD). There is, however, a main difference between the two grades; the amount of inherent fine particles, here denoted 'carrier fines', is significantly higher for one grade than for the other (see Table 2). The amount of carrier fines is known to be critical as regards powder dispersibility. It is here suggested that carrier fines have a similar function to added fine particles in the formulation, as long as they are released from the carrier surfaces during the mixing process and hence are available for mixing with the drug and added lactose fines. In order to have independent factors in the model, the carrier fines will be incorporated with the *G*-factor, accounting for the total amount of fine particles in the formulation, and will not be part of the *H*-factor. The *H*-factor therefore can also be set to 1 and will not be considered further.

2.3. The total fines factor, G

Although complex in nature, the dispersal of a fine powder into an airstream relies on fundamental physical principles. The basic particulate features governing such behavior are particle size, shape and density. It is therefore assumed that lactose fines and drug, which both consist of micronized particles of similar size, shape and density, will behave in similar ways as regards dry powder dispersion and should hence be modeled similarly. This is particularly true when the lactose fines are produced by micronization. It is believed that it is the combined effect of the drug and the lactose fines that is of importance as regards the dispersal of a dry powder formulation. To capture this the concept of 'total fines', defined as the total amount of fine particles present in the formulation, is adopted. As stated above, the lactose fines inherent to the carrier should also be included into the total fines as long as they are available for mixing. It is then important that these are measured in a relevant way. In this work, laser diffraction using dry dispersion at high pressure was used to capture the carrier fines (details are given in Section 3.4). It can be assumed that the strong shear forces of the dispersing unit are comparable to those present in the mixing process.

Several investigations have shown that FPF increases with an increased amount of drug in the formulation, as well as with addition of lactose fines (Adi et al., 2006; Dickhoff et al., 2002; Guchardi et al., 2008; Guenette et al., 2009; Kinnunen et al., 2010; Muresan and Hebbink, 2009; Zeng et al., 1998). The relationship is often close to linear.

One observation is that with increasing amount of drug and/or added lactose fines, the amount of aggregates of fine particles on the surfaces of the carrier particles increases. Such aggregates are also visible in the formulations produced in this study (Fig. 1).

Based on the above reported experimental behavior, a linear expression for the effect of the total fines can be assumed:

$$G = k_1 + k_2 \times TF \quad (3)$$

where TF is the fraction of total fines in the formulation and k_1 and k_2 are constants that will be fitted to data.

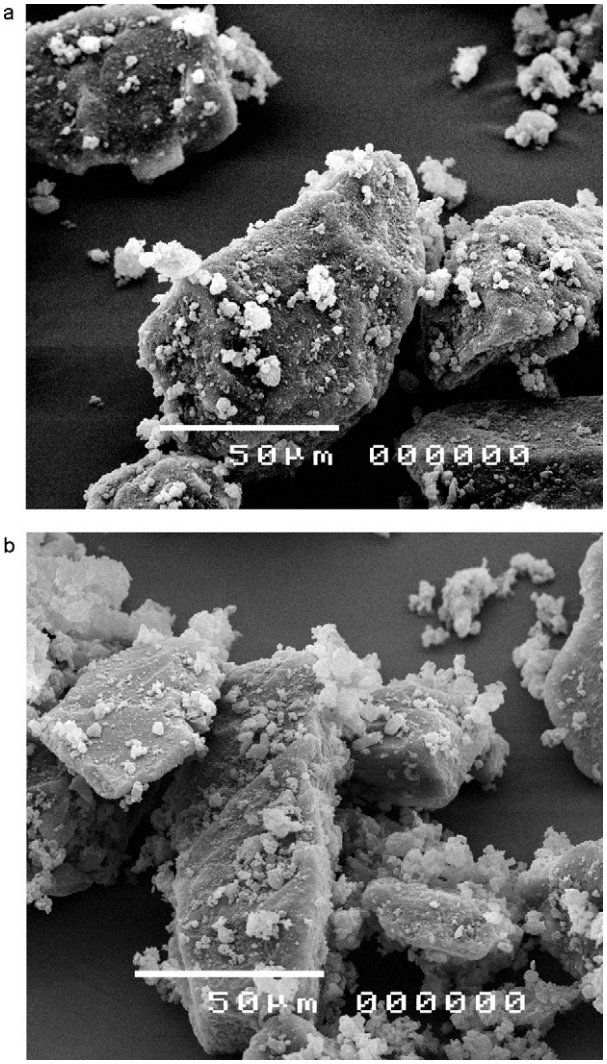

Fig. 1. SEM pictures obtained with JEOL JSM-5200 of formulations containing Respitose SV003 and (a) 5% BUD, (b) 2% BUD and 8% lactose fines.

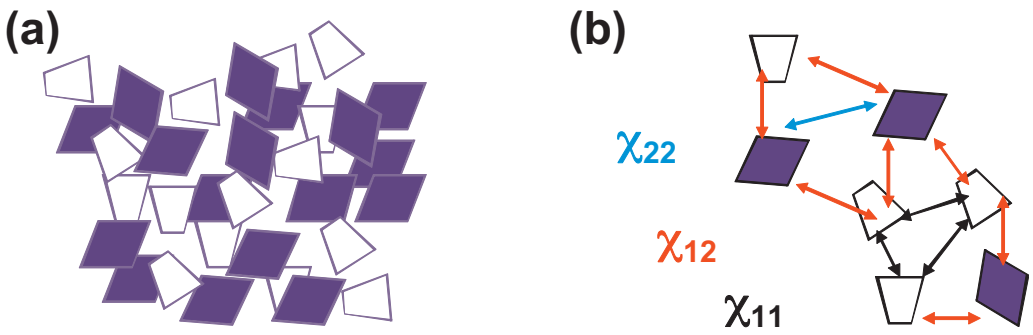

Fig. 2. (a) An aggregate consisting of 2 different species, blue representing the drug and white representing the lactose; (b) expansion to illustrate the interactions between drug–drug (blue), drug–lactose (red) and lactose–lactose (black). In this schematic the species have similar size but different shape.

Compositions of solid formulations are generally given in %w/w. Attention is here drawn to the effect of differences in true density between ingredients. The true density of α-lactose monohydrate is 1.52 g/cm^3. Obviously, if the drug density also is 1.52 g/cm^3, 1.0% w/w corresponds to 1.0% (v/v). But if the drug has a density of 1.00 g/cm^3, a 1.0% (w/w) formulation corresponds to ca. 1.5% (v/v), which means 1.5 times more drug particles (provided the particle size distribution is the same), and hence a significantly higher density of drug particles at the carrier surfaces. This illustrates the need to express TF in volume fraction in Eq. (3).

2.4. The cohesivity factor, F

Cohesion of a powder formulation occurs due to interparticle interactions. These interactions have to be overcome in order to disperse the powder into an aerosol of inhalable particles. The 'cohesive energy', CE, of a dry powder formulation is here defined as the sum of all interparticular interactions in the formulation.

In Fig. 2, interparticulate forces are schematically illustrated for a system of fine particles of drug and lactose. The three types of interactions present are represented as follows:

- χ_{DD} denotes drug particle–drug particle interactions
- χ_{LL} denotes lactose particle–lactose particle interactions
- χ_{DL} denotes drug particle–lactose particle interactions

The theory for regular solution deals with the interaction between neighboring molecules in a solvent mixture (Hildebrand and Scott, 1962; Prausnitz et al., 1999; Wikipedia: Regular solution). If this theory is adopted to a mixture of drug and fine lactose particles, an expression for the cohesive energy can be derived, Eq. (4), in analogy to the enthalpy expression for a regular solution:

$$CE = \Phi_L^2\chi_{LL} + 2\Phi_L\Phi_D\chi_{DL} + \Phi_D^2\chi_{DD} \quad (4)$$

where Φ_L and Φ_D are the volume fractions of lactose and drug, respectively. Replacing Φ_L with $(1-\Phi_D)$ and rearranging gives:

$$CE = \chi_{LL} + 2\Phi_D(\chi_{DL} - \chi_{LL}) + \Phi_D^2(\chi_{LL} - 2\chi_{DL} + \chi_{DD}) \quad (5)$$

It should be noted that this approach assumes random mixing between the individual particles in the mixture. For carrier based formulations, Φ_L and Φ_D will be defined as volume fractions within the total fines (this will be further rationalized in Section 4).

It is intuitive that the higher the cohesive energy, the lower the dispersibility of the dry powder formulation. A simple approach is then to assume that the dispersibility is inversely proportional to the cohesive energy. This means that the *F*-factor will read:

$$F = \frac{1}{CE} = \frac{1}{\chi_{LL} + 2\Phi_D(\chi_{DL} - \chi_{LL}) + \Phi_D^2(\chi_{LL} - 2\chi_{DL} + \chi_{DD})} \quad (6)$$

2.5. The combined model

Starting out from Eq. (2), it is shown that for the set of formulations studied here, both the processing factor *P* and the factor *H* relating to the carrier can be set to 1. Combining the *F* factor, which accounts for cohesive energy (Eq. (6)), with the *G* factor, which accounts for total fines (Eq. (3)), a final expression for the fine particle fraction (FPF) is obtained:

$$FPF = F \times G = \frac{1}{CE} \times (k_1 + k_2 \times TF) \quad (7)$$

where CE is the cohesive energy of the formulation as given by Eq. (5).

In Section 4.2, this equation will be fitted to the experimental dataset for formulations which lie within the 'working range' of the inhaler. The values obtained as well as the significance of the different parameters of the model will thereafter be further discussed.

3. Materials and methods

3.1. Materials

Micronized budesonide (BUD) was sourced from AstraZeneca, micronized beclomethasone dipropionate (BDP) was sourced from Letco/Meridian, USA. Both drugs were crystalline as confirmed by XRD. Particle size and true densities are given in Table 2. Lactose carriers Pharmatose 125 M and Respitose SV003 were sourced from DMV–Fonterra Excipients, Holland. For the latter grade, 2 different batches were used. Particle size data as measured by Sympatec Helos (Sympatec, Germany) are given in Table 2.

Lactose fines were prepared by micronization of lactose monohydrate in a jet mill using nitrogen as the milling gas. The material was then conditioned by exposing the powder to approximately 50% humidity at 25 °C overnight, followed by drying. The particle size is given in Table 2.

3.2. Powder mixing

Dry powder formulations were prepared by mixing drug, and lactose fines where used, with lactose carrier in a Diosna P1-6 (Diosna, Germany) high shear mixer for 1 min at 500 rpm followed by 14 min at 1500 rpm. 200 g batch sizes were produced using the 1.2 l bowl. The chopper was removed before use. Homogeneity was assessed by HPLC analysis of 6 samples of ca. 10 mg. Mean contents were all in the range 93–96% of the nominal value. The relative standard deviation (RSD) was less than or around 3%, with two exceptions where the RSD was 6%.

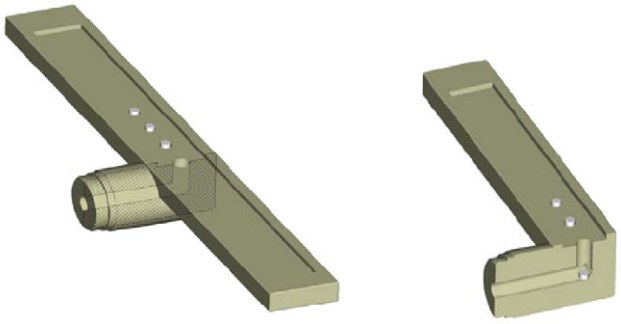

Fig. 3. The device used for fine particle assessment consists of an L-shaped cylindrical channel (diameter 7.0 mm), which is fitted via the USP throat to the NGI. A rectangular support plate with cylindrical holes allows for scrape filling, but in the normal procedure powder was weighed using a spatula and transferred directly through the vertical channel into the bend of the L-shaped channel.

3.3. Fine particle assessment

A simple prototype inhaler made of stainless steel was used, see Fig. 3. Doses of 10 mg were loaded into the device and withdrawn to the Next Generation Pharmaceutical Impactor (NGI) model 170 (MSP Corporation, Shoreview, MN, USA), connected through a USP throat at a flow rate of 77 l/min for 4 s. 2–10 doses were loaded into the NGI (depending on drug load in formulation) and 2–4 NGI tests were performed per formulation. The retention in the prototype inhaler was negligible.

3.4. Determination of carrier fines

Particle size distributions of the carriers used (Table 2) were obtained using Sympatec Helos (Sympatec, Germany) with the R3 lens and the dry dispersion unit RODOS operated at 4 bar. Samples of 0.25 g were prepared in duplicate in test tubes and introduced into the ASPIROS sample holder. The percentage of particles less than 9 μm (obtained directly from the results output sheet) was used as an index of the amount of carrier fines.

Laser diffraction is a robust and repeatable particle sizing method, but may not give accurate values, in particular in this case where the objective is to determine a small amount of fine particles among carrier particles. To resolve this, a calibration curve was prepared by weighing in exact amounts of lactose fines in the concentration range 0.5–2.5% (w/w) to Respitose SV003 carrier, followed by gentle mixing in the test tube. A linear correlation was found between the Sympatec <9 μm value and the amount of added lactose fines (Fig. 4) with a slope of 2.2. This implies that each added percent of lactose fines gives 2.2% increase in the Sympatec <9 μm value. Based on this relation, the fines content could be calculated for the carrier grades used, see column 9 of Table 2.

3.5. Software

All calculations were made in MATLAB 7.11 (The MathWorks, Natick, MA, USA), MODDE 9 (Umetrics, Umeå, Sweden) and Excel 2007 with the Solver add-in (Microsoft Corporation, Redmond, WA, USA).

4. Results

4.1. Experimental results

Compositions of the formulations produced and fine particle fractions, FPF, are given in Table 1. To illustrate the trends observed, FPF is plotted versus formulation composition in different ways in Figs. 5–7.

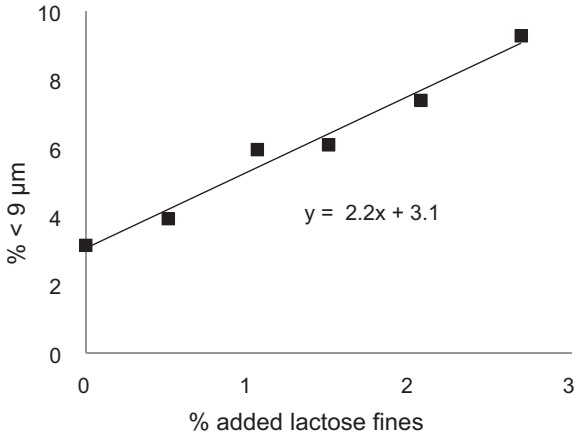

Fig. 4. Calibration curve showing the percentage <9 μm as measured by Sympatec as a function of the amount of added lactose fines to a lactose carrier. It should be noted that the batch of Respitose SV003 used for the calibration is different to the batches used to produce the formulations.

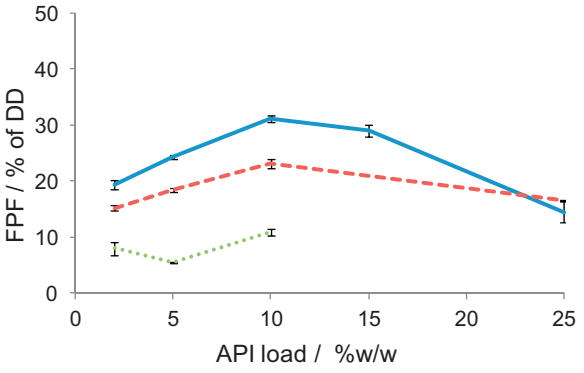

Fig. 5. Fine particle fraction of formulations of lactose carrier and drug only. Solid line refers to BUD/Pharmatose 125 M, dashed line to BUD/Respitose SV003 and dotted line to BDP/Respitose SV003.

Drug and carrier only. In Fig. 5, FPF is plotted as a function of the amount of drug added. For BUD, the carrier Pharmatose 125 M gives rise to higher FPF than Respitose SV003. For both carriers, a linear region where FPF rapidly increases is observed, but at higher drug loads FPF declines. BDP display FPF values which are significantly lower than those for BUD. Surprisingly, the 5% BDP formulation yields a lower fine particle fraction than the 2% BDP formulation.

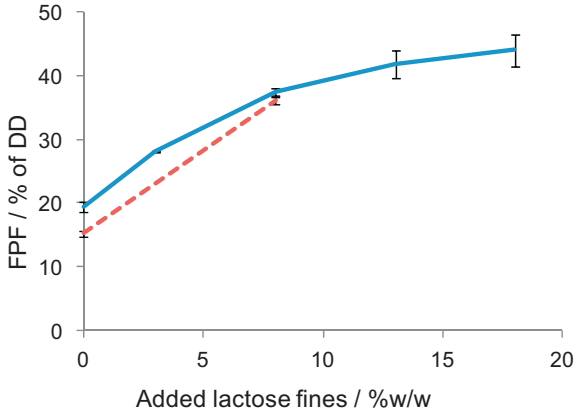

Fig. 6. Fine particle fraction of formulations containing 2% BUD and different amounts of added lactose fines. Solid line refers to BUD/Pharmatose 125 M and dashed line to BUD/Respitose SV003.

Table 3
Fine particle fraction data, weight and volume based composition measures for the sixteen formulations included in the modeling.

Exp. no.	Drug type	Lactose type	Fine particle fraction (%)	%Drug (by weight)	%Lactose fines (by weight)	Total fines (% by weight)	Φ_D (drug weight fraction)	Φ_D (drug volume fraction)	Total fines (% by volume)
1	BUD	Pharmatose	19.4	2		5.3	0.377	0.422	5.69
2	BUD	Pharmatose	37.4	2	8	13.3	0.150	0.176	13.66
3	BUD	Pharmatose	24.2	5		8.3	0.602	0.646	9.24
4	BUD	Pharmatose	31.1	10		13.3	0.752	0.785	15.05
5	BUD	Pharmatose	28.1	2	3	8.3	0.241	0.277	8.68
6	BUD	Pharmatose	31.1	5	5	13.3	0.376	0.421	14.19
7	BUD	Respitose A	15.2	2		4.0	0.500	0.547	4.39
8	BUD	Respitose A	36.1	2	8	12.0	0.167	0.194	12.36
9	BUD	Respitose A	18.3	5		7.0	0.714	0.751	7.95
10	BUD	Respitose A	23.1	10		12.0	0.833	0.858	13.78
11	BDP	Respitose B	32.6	0.5	9.5	12.1	0.041	0.046	12.15
12	BDP	Respitose B	8.0	2		4.1	0.488	0.516	4.33
13	BDP	Respitose B	10.8	10		12.1	0.826	0.842	13.12
14	BDP	Respitose B	23.6	2	8	12.1	0.165	0.181	12.31
15	BDP	Respitose B	5.4	5		7.1	0.704	0.727	7.64
16	BDP	Respitose B	12.3	5	5	12.1	0.413	0.440	12.61

Addition of lactose fines. In Fig. 6, formulations containing 2% BUD, lactose carrier and added lactose fines are compared to batches with added BUD only (at 0% added lactose fines). Again an increase in FPF is seen up to a level of about 10% of total fines, whereafter the FPF starts to level off. Comparing Figs. 5 and 6, it can be observed that addition of lactose fines generally give higher FPF values than addition of a corresponding amount of BUD.

In Fig. 7, batches containing 10% (w/w) of added fines (drug plus lactose fines) and 90% (w/w) of Respitose SV003 are compared. For BDP, a marked reduction in FPF is seen when the drug load is increased, i.e. when the drug fraction within the added fines increases. For BUD, the effect is smaller. It is intuitive that BDP is more cohesive than BUD.

4.2. Modeling results

Only formulations which lie within the 'working range' were included in the modeling. The dataset (Table 3) consisted of FPF data for 16 formulations, 10 for BUD and 6 for BDP. Subscripts "L" for lactose, "B1" for BUD and "B2" for BDP are used to denote the interaction parameters. First, the parameters for F and G were solved for BUD by least squares fitting using the Levenberg–Marquardt–Fletcher (LMF) algorithm (Matlab script by M. Baldac see Reference section) for residuals minimization. The lactose–lactose interaction, χ_{LL}, was used as a reference and set to 1 and χ_{B1B1}, χ_{LB1}, k_1 and k_2 were estimated using experiments 1 to 10. The parameters for G, k_1 and k_2, from the BUD solution were then used to estimate χ_{B2B2} and χ_{LB2} from experiments 11 to 16. The calculations were then repeated, but all 16 experiments were used to give estimates for the six parameters. The robustness of each result was tested by leaving one experiment out and re-fitting the parameters. This was repeated until all experiments had been excluded once, also known as leave-one-out (LOO) crossvalidation. The resulting parameters are presented in Tables 4 and 5.

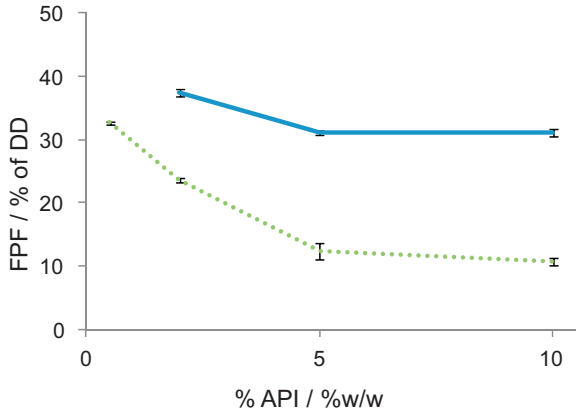

Fig. 7. Fine particle fraction data for formulations with different drug loads, all containing 10% of added fines. Solid line refers to BUD/Pharmatose 125 M and dotted line to BDP/Respitose SV003.

Table 4
The fitted parameters for Eq. (7), sequential approach.

	Mean (LOO)	95% CI (LOO)	%RSD (LOO)
BUD ($n = 10$)			
χ_{B1B1}	1.84	1.74–1.94	7.7
χ_{LB1}	1.40	1.04–1.76	35.9
k_1	13.9	10.7–17.1	32.1
k_2	2.18	2.07–2.29	7.0
BDP ($n = 6$)			
χ_{B2B2}	5.36	4.45–6.27	16.2
χ_{LB2}	3.49	3.16–3.82	8.9

When checking the LOO rounds, one round gave results inconsistent with the other calculations. When the parameters were fitted without experiment 6, the calculated values of χ_{LB1} and k_1 differed by one or two orders of magnitude. Omitting that round led to a drop in the %RSD for χ_{LB1} and k_1 of 10 and 7% respectively. The root-mean-square-error (RMSE) of the fitted data using all 10 experiments was 1.7% FPF, the observed vs. predicted correlation (r^2) was 0.95. There was no obvious outlier in the LOO rounds for BDP. The RMSE of the fitted data using all six experiments was 1.4% FPF, the observed vs. predicted correlation (r^2) was 0.97.

When simultaneously estimating all six parameters, leaving experiment 6 out lead to a different solution for χ_{LB1} and k_1 as previously described. The RMSE of the fitted data using all 16 experiments was 1.6% FPF, the observed vs. predicted data are shown in Fig. 8 ($r^2 = 0.97$).

Table 5
The fitted parameters for Eq. (7), simultaneous approach.

BUD + BDP ($n = 16$)	Mean (LOO)	95% CI (LOO)	%RSD (LOO)
χ_{B1B1}	1.83	1.79–1.87	4.0
χ_{LB1}	1.38	1.31–1.46	9.7
k_1	13.9	13.2–14.6	9.6
k_2	2.15	2.11–2.19	3.3
χ_{B2B2}	5.30	4.99–5.62	11.0
χ_{LB2}	3.27	3.05–3.49	12.6

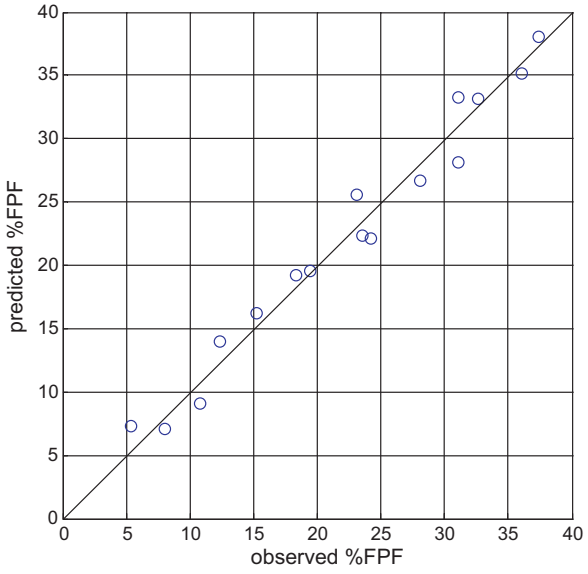

Fig. 8. Predicted vs. observed fine particle fraction data.

Table 6
The fitted parameters for Eq. (7) for model variants i–v.

BUD + BDP ($n = 16$)	i	ii	iii	iv	iv (b)	v
χ_{B1B1}	1.64	1.85	0.11	0	−19.8	1.73
χ_{LB1}	1.39	1.46	0.38	4.86	6.58	1.34
k_1	13.3	14.6/12.9[a]	3.14	4.87	5.56	13.8
k_2	2.19	2.18	0.12	2.98	3.14	2.14
χ_{B2B2}	4.81	5.21	0.05	1.57	−141	4.50
χ_{LB2}	3.47	3.13	1.41	22.2	28.6	3.02

[a] k_1 for BUD/k_1 for BDP.

4.3. Examined variants of models

The models presented in this subsection were all fitted using the Solver add-in to Microsoft Excel 2007. The results using Solver were identical to the results obtained with the LMF algorithm in Matlab for all tested data sets. The following variants were examined:

i. Percent by weight vs. percent by volume.
ii. Drug dependent intercept in Eq. (7) (k_1).
iii. Omitting the lactose–lactose interaction term in Eq. (6).
iv. Using percent of the total composition instead of percent of the total fines.
v. Fitting the exponent of F shown as −1, CE^{-1}, in Eq. (6).
vi. A statistical model with three factors.

i. Estimating all six parameters simultaneously using all 16 experiments with weight data instead of volume data lead to a model with equally good fit compared to the one presented in Table 5; RMSE was 1.6% FPF and the observed vs. predicted correlation (r^2) was 0.97. The fitted parameters are shown in Table 6.
ii. Adding a seventh parameter to be fitted, i.e. separate intercepts for BUD and BDP, also lead to a fitted model comparable to the one in Table 5; RMSE was 1.6% FPF and the observed vs. predicted correlation (r^2) was 0.97. The fitted parameters are shown in Table 6.
iii. Omitting the lactose–lactose interactions term in Eq. (6) drastically changed the model fit; RMSE was up to 4.9% FPF and the observed vs. predicted correlation (r^2) was down to 0.81. The fitted parameters are shown in Table 6.
iv. When calculating the fractions based on the total composition, the fit was still good; RMSE was 1.9% FPF and the observed vs. predicted correlation (r^2) was 0.96. However, dramatic changes in interaction parameters were seen. For example, the χ_{B1B1} interaction was 0 which seems both unphysical and counter-intuitive with respect to the dataset obtained, e.g. the results shown in Fig. 7. Restrictions on the interaction parameters (to be greater than or equal to zero) were then removed leading to a small improvement in RMSE, 1.8% FPF. In this case, see column iv (b) in Table 6, the drug–drug interaction parameters were negative which is not a reasonable result.
v. Again, a seventh parameter was added to the Solver optimizer; the exponent of CE. The exponent was estimated to −1.1 with a RMSE of 1.6% in FPF and the observed vs. predicted correlation (r^2) at 0.97, i.e. the same good fit as for variants i and ii. The rest of the fitted parameters are shown in Table 6.
vi. A statistical model was fitted to the data using multiple linear regression (MLR) in Modde. The factors "drug type", "Φ_D (drug volume fraction)" and "total fines (% by volume)" as listed in Table 3 are close to orthogonal and thus suitable for this type of model. The RMSE and r^2 of the model fit was 2.1% FPF and 0.95 respectively. The size and direction of the model coefficients are shown in Table 7.

The statistical model in vi can be seen as the simplest way to model the data where no assumptions about the underlying physics are made. The fit is somewhat less good than the model described by Eq. (7). Judging from the LOO and sequential vs. simultaneous tests previously described, the better fit for Eq. (7) is not obviously attributable to overfit and this strengthens the case for the theory behind this paper. Further, the number of parameters fitted was five, including the regression constant, for the MLR model and only one more, six, for Eq. (7) without separate intercepts, which again makes it less likely that the latter is significantly overfitted.

5. Discussion

It has been shown that fine particle fractions of carrier based formulations could be fitted to an equation containing two factors; one accounting for the cohesivity of the formulation, the other for the effect of the total amount of fines (Eq. (7)). The model was shown to correlate well to experimental data and was robust as regards prediction. It is believed that the proposed model can provide insight into the mechanisms underlying dispersibility of carrier based formulations from a DPI. The model may also be expanded to incorporate additional factors as outlined in Section 2. Different aspects and implications of the model are now discussed.

5.1. Why include lactose–lactose interactions?

As fine particle fraction is measured on the drug component only, it may be argued that only interactions involving drug particles should be included in the model. This would mean omitting the

Table 7
The scaled and centered model coefficients for model variant vi.

BUD + BDP ($n = 16$)	Drug type BUD	Drug type BDP	Drug volume fraction	Total fines	(Drug volume fraction)^2
Coefficient	6.4	−6.4	−8.6	5.4	9.0
95% Confidence interval	4.9–7.9	−7.9 to −4.9	−11.5 to −5.7	2.9–7.8	2.0–16.0

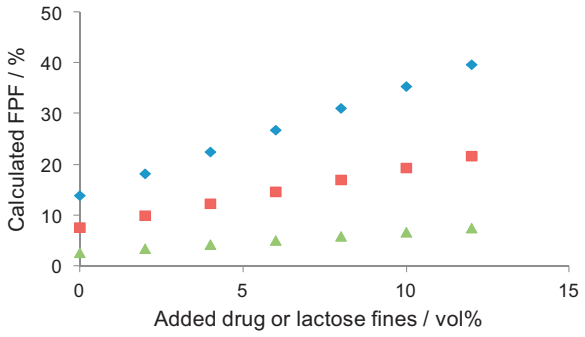

Fig. 9. The effect of addition of different kind of fines to lactose carrier containing no carrier fines, according to Eq. (8). Rhombs refer to addition of lactose fines, squares to BUD and triangles to BDP.

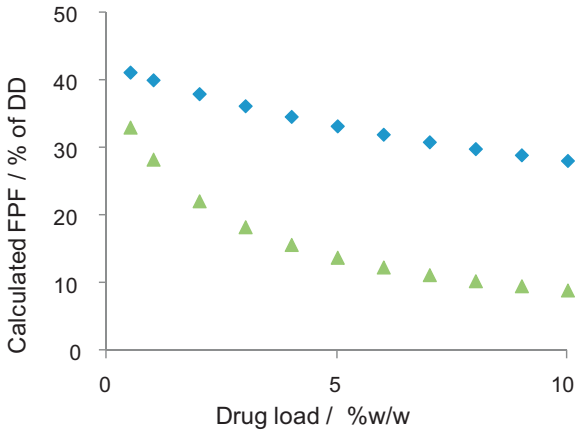

Fig. 10. Calculated fine particle fractions for formulations containing 10% (w/w) of added fines at different drug loads for the systems BUD/Pharmatose 125 M (rhombs) and BDP/Respitose SV003 (triangles).

first term in the cohesive energy expression, Eq. (4), which refers to lactose–lactose interactions, and only consider drug–lactose and drug–drug interactions. However, attempts to model the dataset in this way have led to significantly poorer fits. Apparently, a term referring to the lactose–lactose interactions, χ_{LL}, is essential in the expression for cohesive energy, which is in line with the analogy of this expression to the interaction energy of regular liquid solutions.

5.2. Inverse proportionality between dispersibility and cohesive energy

The assumption that FPF is inversely proportional to the cohesive energy, CE, may be challenged. Model fitting including also the exponent resulted in a value of −1.1, i.e. very close to −1, hence supporting this assumption.

5.3. The use of volume fractions

The model was built using volume fractions. It was shown, however that an equally good fit could be obtained by using weight fractions. It is believed that volume fractions still should be preferred, as this provides a direct link to the theory of regular solutions. Furthermore, as discussed above, the use of volume fractions more correctly captures the total fines effect, as this relates to the density of fine particles at the carrier surface. The difference in density between lactose and BUD may be one reason behind why it is possible to add significantly more lactose fines than BUD (w/w) and still be inside the inhaler working range (compare Figs. 5 and 6).

5.4. The total fines effect

The G factor was estimated to $G = 13.9 + 2.15 \times \mathrm{TF}$, using the simultaneous approach. For the current dataset comprising two different drugs, it was possible to obtain a good fit using a single value of the intercept, k_1, and also for the slope k_2. To better understand the influence of the drug as regards total fines, Eq. (7) is rearranged as follows:

$$\mathrm{FPF} = \frac{k_1}{\mathrm{CE}} + \frac{k_2}{\mathrm{CE}} \times \mathrm{TF} \tag{8}$$

Clearly, both the intercept and the slope are affected by the cohesive energy of the formulation. The predicted effect of addition of different types of fines to a pure lactose carrier (containing no carrier fines) is shown in Fig. 9. CE is here given by the χ-parameter of the fine particles (i.e. χ_{LL}, χ_{B1B1}, or χ_{B2B2}), as there is only one type of fine particles present. As seen in Fig. 9, the higher the interaction parameter, i.e. the more cohesive the drug, the lower the intercept and also the slope.

The intercept should represent the fine particle fraction at infinite dilution of the drug. At high dilution, however, drug to drug particle interactions are statistically unlikely to occur. Instead, interactions between drug particles and the lactose carrier have been shown to be the dominent (Heng et al., 2000; Louey and Stewart, 2002; Young et al., 2002, 2005). As stated in the introduction, the present model is not applicable to very low drug loads. The lower limit for the 'working range' is as yet unknown.

While still not fully understood, it is possible that the increase in FPF caused by the total fines is related to the formation of aggregates of the fines particles, which in turn is due to the increased density of fine particles at the carrier surface. The fact that the best model fit was obtained when volume fractions within the total fines were used for the F-factor (as opposed to volume fractions of total composition) is a further support for the aggregate hypothesis.

A model consisting of two factors, one related to the total amount of fines and the other to the cohesive energy within those fines, suggests a two-step mechanism for powder dispersion; a first step in which aggregates are detached from the carriers, followed by a second step in which they are deaggregated to inhalable particles. To infer from this that carrier particles do not play a role in the deaggregation process would however be an over-simplification. Deaggregation of fine particle aggregates is to a large extent due to the carriers themselves (Louey et al., 2003) and collisions between carrier and aggregates within the inhaler has been suggested as an important break-up mechanism (Ooi et al., 2011).

5.5. The cohesive energy factor and interaction parameters

The χ parameters are here defined in analogy with standard theory for regular liquid solutions. By fitting fine particle fraction data for a set of different formulations, χ parameters were obtained for the interactions between different species. It should be noted that the interaction parameters are relative numbers; here χ_{LL} was set to 1. In Fig. 10, fine particle fractions for BUD and BDP are calculated using the interaction parameters obtained at a level of 10% of added fines. The similarity to observed data (Fig. 7) is unambiguous.

When combining the cohesive energy factor with the total fines factor, also the apparently confusing results relating to addition of BDP to Respitose SV003 can be rationalized. Indeed, a first decrease in FPF is predicted followed by an increase when more BDP is added, see Fig. 11. The explanation is that at low drug loads, lactose carrier fines are diluted with the more cohesive drug particles, leading to an increase in cohesive energy and hence reduced dispersion as given by the F factor. When more BDP is added, the total fines effect (the G factor) becomes more and more dominating leading to an increase in FPF. The agreement between the predicted and the observed pattern for BDP (Fig. 5) is further evidence that the

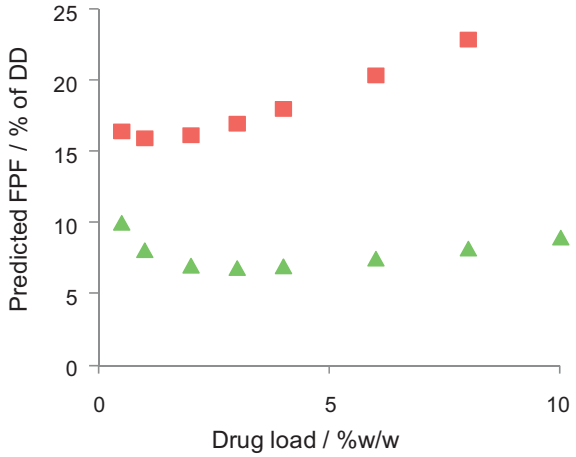

Fig. 11. Predicted FPF when adding drug to lactose carrier. Squares refer to BUD/Respitose SV003, triangles to BDP/Respitose SV003.

carrier fines (as defined and measured in this work) are available in the mixing process. A similar but smaller non-linear effect is also predicted for BUD (Fig. 11). This could however not be detected in the experimental data.

5.6. How to understand the interaction parameters

Obviously, the interaction parameters are apparent parameters, i.e. they reflect how the species behave in the powder mixture. $\chi_{DD,app}$ would be the correct denotation for a drug–drug interaction parameter obtained this way. For a given set of BUD formulations, $\chi_{B1B1,app}$ thus refers to the specific grade and batch of BUD used for manufacturing the formulations. Apart from material properties, particle size and size distribution as well as particle shape, surface energy and roughness are factors contributing to $\chi_{B1B1,app}$. In this work, it was found that the drug–drug interaction parameter was significantly higher for BDP than for BUD. BDP is more hydrophobic than BUD, but there was also a difference in particle size, BDP particles being significantly smaller than BUD particles (see Table 2). It seems likely that both material and particulate properties contribute to the observed difference. With regards to lactose fines, it has been shown that both median size and size distribution profile of the lactose fines play a significant role on the dispersibility (Adi et al., 2006, 2009; Lexmond et al., 2010). It is believed that the concept of formulation cohesive energy and the possibility to derive apparent interaction parameters from experimental data will open the way for further studies addressing the underlying factors related to drug cohesivity and dispersion from a DPI.

5.7. Validity and limitations of the model

As stated in Section 2, a homogeneous formulation is a prerequisite for this model. This is particularly true for the fines and it is assumed that the drug and the fine lactose particles are randomly mixed. Clearly, the degree of mixing will be determined by the mixer and the mixing method used. Furthermore, drug properties as well as the properties of the fines (lactose or other) may affect particulate 'miscibility'. Novel imaging techniques with high spatial solution, such as TOF-SIMS, may provide further insight to this.

The formulation 'working range' which is based on the total fines, TF, should be investigated further. Formulations with 14.2% and 15.0% TF were the highest included in the modeling; the first of these was slightly over-estimated with regards to FPF, the second was slightly under-estimated. The first three excluded formulations had 18.6, 20.0 and 20.8% TF. FPF was over-estimated by at least 5% for all of these, and for the other three excluded formulations the over-estimation was even higher. This is expected because the model does not contain any factor limiting the FPF at high total fines loads. More experimental data may rationalize a second order polynomial for the total fines effect. With such an expression it may be possible to model the maximum attainable FPF. It is pointed out that the formulation working range as well as the attainable FPF level will primarily be determined by the inhaler used.

5.8. Final remarks

It is believed that the interactions dealt with here are predominantly van der Waals interactions (Visser, 1989). It should however be noted that both electrostatic forces and capillary forces can have a large impact on the behavior of dry powder formulations for inhalation. In this work, all raw materials and formulations produced were stored under dry conditions, i.e. at a relative humidity below 30%. No special measures were taken to reduce electrostatic charging and static behavior was neither observed during mixing nor during fine particle assessment.

6. Conclusions

It has been shown that the dispersion of carrier based formulations with total fines in the range from ca. 2 to 15% can be modeled based on two factors; one relating to the 'total fines', the other to the 'cohesive energy' of the formulation. Total fines is defined as the sum of all particles in the formulation in sizes approximately less than 10 μm, including the drug, the lactose fines and the fines inherent to the carrier. The expression for the cohesive energy, CE, of the formulation is derived from regular solution theory for liquids; in essence it is the sum of all interparticular interactions in the formulation.

Adopting the model to fine particle fraction data, it was found that the interaction parameter for BUD, χ_{B1B1}, was 1.8 times higher than for the lactose fines, χ_{LL}. For BDP, χ_{B2B2} was 5.3 times the lactose interaction parameter. The lactose–drug interaction parameters were found to lie between the lactose interaction parameter and the corresponding drug interaction parameter. It is emphasized that the interaction parameters obtained are apparent parameters reflecting how the drug particles behave in the macroscopic formulation system.

The model, combined with an appropriate experimental design, thus enabled quantification of the interaction between different components in the system, which in turn opens the field for studies directed to the factors underlying particle interactions in a dry powder blend. The model equation can be further expanded to include factors relating to carrier properties and processing, and possibly also factors relating to the inhaler, inhalation flow rate and the relative humidity at dose withdrawal.

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