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

Kyrre Thalberg*, Elna Berg, Magnus Fransson

Pharmaceutical Development, AstraZeneca R&D Mölndal, Pepparedsleden 1, 43183 Mölndal, Sweden

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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.

* Corresponding author. Tel.: +46 31 7761698/709 131964; fax: +46 31 7763727.
E-mail address: Kyrre.Thalberg@astrazeneca.com (K. Thalberg).

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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