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Note

The dispersion behaviour of dry powder inhalation formulations cannot be assessed at a single inhalation flow rate

Floris Grasmeijer*, Anne H. de Boer

Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Groningen, The Netherlands

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ABSTRACT

The dispersion performances of inhalation powders are often tested at only one inhalation flow rate in mechanistic formulation studies. This limited approach is challenged by studies showing that interactions exist between inhalation flow rate and the effects on dispersion performance of several formulation variables. In this note we explain that such interactions with inhalation flow rate are, in fact, always to be expected. Because these interactions may greatly affect conclusions concerning the effects of formulation variables and their underlying mechanisms, the utility of future dry powder inhalation formulation studies may benefit from an approach in which dispersion performance is by default tested over a range of inhalation flow rates.

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In mechanistic studies focussing on the formulation of powders for inhalation it is common practice to assess and compare the dispersion performances of powders at a single inhalation flow rate. Mostly a flow rate of 60 L/min is chosen (e.g. Jones et al., 2010; Louey and Stewart, 2002; Zeng et al., 1998), possibly because this flow rate is often considered representative of the flow rates achieved by patients in practice. The time consuming nature of dispersion performance experiments may be an important aspect contributing to this common approach.

Although seemingly rational at first, the approach in which dispersion performance is tested at only one inhalation flow rate may severely hamper the fundamental understanding of dry powder inhalation formulations. Inhalation flow rate or dispersion pressure may quantitatively and qualitatively interact with the way in which other formulation variables affect formulation dispersion performance. This was shown for carrier-free or 'cohesive' formulations (e.g. Behara et al., 2011; Das et al., 2012) as well as adhesive mixtures (e.g. Grasmeijer et al., 2013, 2014, see Fig. 1). Such interactions greatly affect conclusions concerning the effects and working mechanisms of the formulation variables studied.

It follows that for the rational design of a mechanistic formulation study one needs to weigh the benefit of dispersion performance testing over a range of flow rates (i.e. extra information) against the cost of time and effort. For this one needs to assess whether interactions can be expected between inhalation flow rate and the specific formulation variables that are subject of the intended study. It is the purpose of this note to aid in this assessment by providing an understanding of why interactions between inhalation flow rate and formulation variables are likely to occur always.

First, it is important to distinguish between a powder's 'dispersion performance' and its 'dispersibility' or 'dispersion behaviour'. The dispersion performance of a powder is often represented by the fine particle fraction or (sometimes for adhesive mixtures) the drug fraction that is detached from the lactose carrier. It is always related to a specific inhalation flow rate or pressure drop and type of inhaler or disperser and it results from the balance between interparticulate interaction forces and opposing dispersion forces. Increasing the flow rate or pressure drop during dispersion results in a higher air flow velocity through the inhaler or disperser and, therefore, a higher kinetic energy of the airstream. This means that higher dispersion forces may be generated relative to the interaction forces in the powder and that a greater dispersion performance can be expected. In contrast, the dispersion performance as a function of inhalation flow rate will be referred to as the powder's dispersibility or dispersion behaviour throughout this note.

For carrier-free or 'cohesive' powders dispersion concerns the break-up of agglomerates. Cohesive powders are inherently

* Corresponding author at: Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Ant. Deusinglaan 1, 9713 AV Groningen, The Netherlands. Tel.: +31 050 3633286; fax: +31 050 3632500.
E-mail addresses: f.grasmeijer@rug.nl (F. Grasmeijer), a.h.de.boer@rug.nl (A.H. de Boer).

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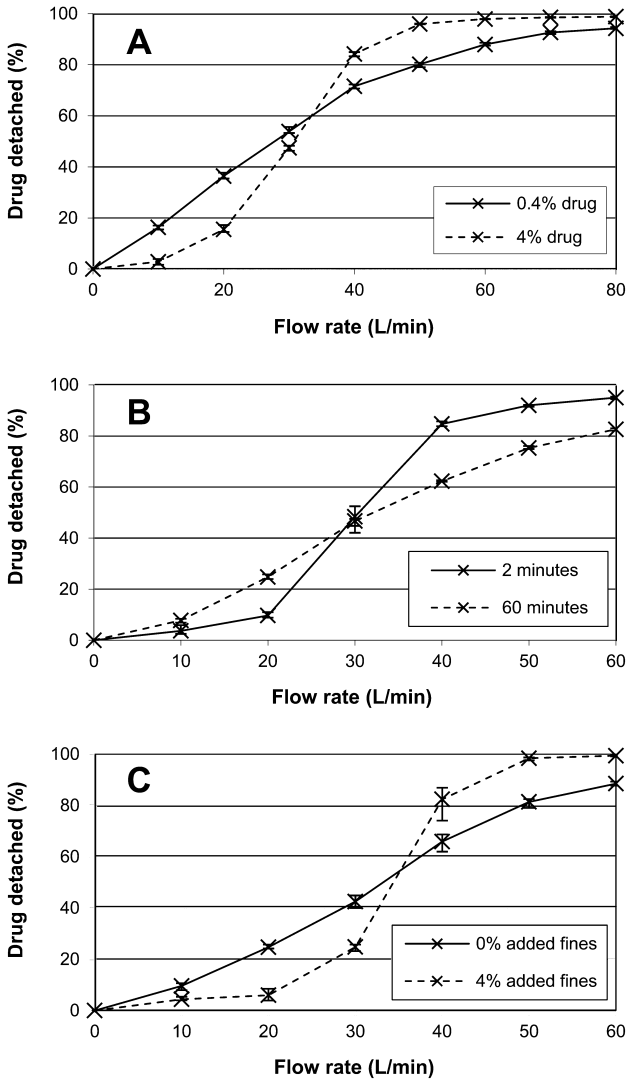

Fig. 1. interactions between the inhalation flow rate and variables in the formulation of adhesive mixtures. (A) Interaction with salmeterol xinafoate content. Data obtained from Grasmeijer et al. (2013, Fig. 6). (B) Interaction with mixing time for mixtures containing 0.4% salbutamol sulphate. Data obtained from Grasmeijer et al. (2013, Fig. 9). (C) Interaction with 4% lactose fines added to 0.4% budesonide mixtures. Data obtained from Grasmeijer et al. (2013, Fig. 3A).

heterogeneous with a distribution of the tensile strength of the agglomerates throughout the powder bed as a result (Das et al., 2012). During dispersion, only the agglomerates with a tensile strength below the dispersion force generated will break up. Therefore, if it is assumed that at a certain flow rate all agglomerates experience more or less the same dispersion force, then the dispersion behaviour of a powder directly relates to its agglomerate tensile strength distribution. Indeed, differences in the width of the agglomerate tensile strength distribution between cohesive powders of milled lactose and Lactohale 300 could explain why the order of their dispersion performance inverted with increasing flow rate (Das et al., 2012). Hence, one cannot assume that a difference in dispersion performance between two cohesive powders at a specific flow rate is representative of the difference in dispersion performance at other flow rates. Doing so would neglect the distributed nature of a primary factor that determines dispersion performance (i.e. the tensile strength of agglomerates). It is not much different from comparing particle size distributions based only on a single percentile value.

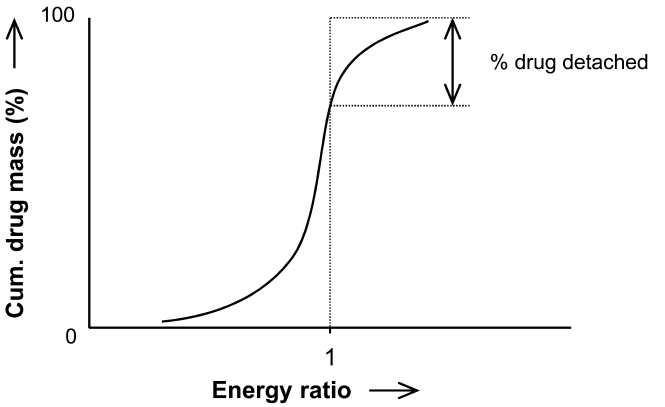

Fig. 2. hypothetical cumulative drug mass fraction as a function of the energy ratio (i.e. energy ratio distribution). The detached drug fraction corresponds with the part of the curve for which the ratio of potential separation energy ($E_{s,pot}$) to binding energy (E_b) ≥ 1. An increase in flow rate results in a shift of the energy ratio distribution to higher values and thus leads to an increase in the detached drug fraction.

A certain analogy exists between the dispersion of cohesive powders and that of adhesive mixtures. The dispersion of adhesive mixtures primarily concerns the detachment of drug particles (including drug and drug/fine-lactose agglomerates) from a lactose carrier surface. Although this process was previously described by de Boer et al. in terms of opposing adhesion and separation forces in the so-called 'force distribution concept' (de Boer et al., 2003), a slightly different description is preferable to better understand the interacting role of inhalation flow rate. The strength of a drug-carrier interaction can be expressed in terms of the minimum amount of energy needed to break it. This 'binding energy' (E_b) is independent of the mode and rate of particle separation for similar end-situations (e.g. equal drug particle displacement and no difference in the degree of plastic deformation) (Israelachvili, 2011). The energy that is equal to the maximum binding energy that can potentially be overcome for a certain drug particle in the mixture and a specific dispersion process is referred to as the 'potential separation energy' ($E_{s,pot}$) in this manuscript. From these definitions, it follows that detachment of a drug particle from the carrier surface occurs during dispersion if its energy ratio $E_{s,pot}/E_b \geq 1$, regardless of the exact underlying adhesion and drug detachment mechanisms. Because of variability of the parameters that determine the magnitude of $E_{s,pot}$ and E_b for individual drug particles throughout the mixture (e.g. drug and carrier particle surface roughness, local carrier surface composition, number of contact points, drug particle shape, size and orientation), these types of energy will exhibit a distribution, and consequently, so will the energy ratio $E_{s,pot}/E_b$. The relationship between the energy ratio and the drug fraction that is detached from the carrier surface is further clarified in Fig. 2, which presents a hypothetical drug mass distribution as a function of the energy ratio (i.e. energy ratio distribution) for an adhesive mixture subjected to a particular dispersion process. A higher flow rate is represented by a shift of the energy ratio distribution curve to higher energy ratio values as it increases $E_{s,pot}$. Hence, the dispersion performance at any flow rate (i.e. dispersion behaviour) directly relates to the energy ratio distribution. The dispersion behaviours of two adhesive mixtures from a specific inhaler are the same if their energy ratio distributions are exactly the same. If two formulations have a different energy ratio distribution as a result of a change in a relevant variable of the formulation process, then the difference in dispersion performance between these formulations theoretically cannot be the same over the range of flow rates that correlates with 0–100% dispersion or detachment efficiency. This is elucidated in Fig. 3 for a number of different imaginary

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