The interplay between variables in the formulation and dispersion of adhesive mixtures for inhalation

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Summary
An insufficient understanding of (statistical) interactions between variables in the formulation and dispersion of adhesive mixtures for inhalation leads to a low utility of studies concerning these processes. Drug detachment from lactose carriers is described in a basic manner to improve the understanding of the interplay between variables. It is suggested that the effect of any variable on drug detachment depends on how it alters the so-called energy ratio distribution during inhalation and on the initially detached drug fraction. Therefore, interactions between the effects of component and process variables on the detached drug fraction and any inhalation variable that alters the initially detached drug fraction (e.g., inhalation flow rate) are always to be expected. In addition, interactions between variables arise if one variable affects the way in which another variable alters the energy ratio distribution. This may occur if these variables have a non-additive effect on drug detachment through the same so-called ‘principal factor(s)’ of the mixture, or if one variable affects the relevance to drug detachment of changes in the principal factors that are caused by another. It follows that multi-order interactions between variables are very likely to occur. Anticipating these interactions will increase the utility of future studies and the efficacy of quality by design approaches to the development of dry powder inhalation products.

List of definitions

- **Component variable**: any variable related to the (physicochemical) properties and relative amount of mixture components (e.g., carrier size fraction, type of drug, drug content).
- **Process variable**: any variable related to the mixing and mixture handling processes (e.g., mixing time).
- **Inhalation variable**: any variable related to the dispersion process (e.g., type of dispersion principle, flow rate).
- **Drug particle**: any particle on the carrier surface that contains drug, including (drug-lactose composite) agglomerates.
- **Binding energy** ($E_b$): the energy needed to separate a drug particle from the surface of a carrier particle.
- **Separation energy** ($E_s$): the net energy with a 100% detachment efficiency that is maximally directly or indirectly transferred to a carrier-bound drug particle (assuming infinite binding energy) from the kinetic energy of the air stream through the inhaler.
- **Energy ratio**: the ratio of separation energy to binding energy ($E_s/E_b$) for a carrier-bound drug particle.
- **Carrier surface site activity**: the inverse of the energy ratio of a certain drug particle after minimal compression to that carrier surface site and at a defined dispersion effort (i.e., flow rate or pressure drop).

Introduction

Despite intensive research efforts over the past decades, the exact mechanisms by which formulation variables exert their effect on the dispersion performance of adhesive mixtures for inhalation are to a large extent unknown. One cause that has been identified is an insufficient understanding of (statistical) interactions between the variables that are involved [1, 2]. In a study on the relationship between drug content, mixing time, blending order and the effect of added lactose fines Jones et al. concluded that “the effect of a variable on the fine particle fraction is not consistent between different levels of another variable” [3]. More recently we have shown with a series of drug detachment experiments that multi-order qualitative and quantitative interactions between variables such as inhalation flow rate, drug content, mixing time and carrier size fraction exist [4, 5]. Not anticipating such interactions leads to a low utility of individual studies. To increase the understanding of the interplay between variables we first describe drug detachment from lactose carriers in a most basic way, avoiding the complex details of adhesion and separation mechanisms involved. The resulting view on drug detachment is then further developed into a schematic model that describes the interplay between the different types of variables defined. Finally, some recommendations for future research are presented.

Energy ratio distributions

The strength of a certain interaction between a drug particle and the carrier surface may be expressed in terms of the 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) [6]. In order for any drug particle to be detached from the carrier surface its binding energy has to be overcome by the separation energy ($E_s$). Hence, detachment of drug particles from the carrier surface occurs if their energy ratio $E_s/E_b > 1$, regardless of the exact underlying adhesion and drug detachment mechanisms. If $E_s$ > $E_b$ (i.e., the energy ratio > 1), the energy difference $E_s - E_b$ may result in kinetic energy of the detached particle, which for agglomerates can add to further dispersion. Because of variability of the parameters that determine the magnitude of $E_s$ and $E_b$ for individual drug particles (e.g. drug and carrier surface roughness, local carrier surface composition, number of contact points, drug particle shape and size), both types of energy will exhibit a distribution throughout the mixture, and therefore, so will the energy ratio $E_s/E_b$. The relationship between energy ratio and the detached drug fraction is further clarified in Figure 1.
The effect of a change in any variable on the detached drug fraction ultimately depends on how it alters the energy ratio distribution and on the initially detached drug fraction (i.e., the detached drug fraction before the variable under investigation was changed). This is illustrated in Figure 2. Two major implications follow from recognition of the above:

- Because the magnitude of the effect of a variable on the detached drug fraction cannot be equal over the entire range of initially detached drug fractions (not even in the most extreme situation as presented in Figure 2, situation D), interactions between the initially detached drug fraction and the ('primary') effect of component or process variables on the detached drug fraction are always to be expected.

- Qualitative or quantitative interactions between variables arise if one variable affects the way in which another variable alters the energy ratio distribution. These interacting ('secondary') effects have to be dependent on the initially detached drug fraction too, because of the same reasons as mentioned for primary effects.

A further understanding of the interplay between the different types of variables follows from a consideration of the way in which component and process variables may change the energy ratio distribution.

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Figure 2: different effects on the detached drug fraction. Axis titles of individual figures are as shown in Figure 1 and have been omitted for the purpose of clarity. Solid lines represent hypothetical energy ratio distributions in the starting situation, dashed lines the hypothetical energy ratio distributions after changing a certain component or process variable. Situations differ in the initially detached drug fraction (low, intermediate, high), the way in which the energy ratio distribution is changed (situations A-D) and the shape of the energy ratio distribution in the starting situation (situations A-C versus situation D). Different changes in the energy ratio distribution and different initially detached drug fractions may result in a different sign (+ or -) or magnitude (length of arrow) of the effect on the detached drug fraction, representing qualitative and quantitative interactions, respectively. Even for a linear energy ratio distribution that is shifted without changing its shape, the effect cannot be the same in magnitude over the entire range of initially detached drug fractions (situation D).

Figure 1: hypothetical energy ratio distribution.
**Principal factors and effects**

Component and process variables may alter both the separation and binding energy distribution by changing ‘principal factors’ of the mixture. At least three principal factors are regularly used in literature to explain the effects of component and process variables, and they may be summarised as:

- the particle size distribution of the drug particles as they are detached from the carrier surface;
- the degree of compression of the drug particles onto the carrier surface; and
- the activity distribution (see further) of occupied carrier surface sites.

Other factors, such as the fluidisation behaviour of the powder [7], may play an important role as well. A change in the detached drug fraction during inhalation through a change in one of the three principal factors listed will from here on be referred to as particle size effects, press-on effects and distribution effects, respectively.

**Particle size effects**

Examples of particle size effects are changes in the detached drug fraction through the (de-)agglomeration of the drug on the carrier surface during mixing or the co-agglomeration with a ternary component (e.g. lactose fines). Positive correlations between drug particle size and drug detachment from carrier particles have been presented in the past [8, 9]. Such findings are in agreement with the fact that the binding energy is generally proportional to the drug particle diameter ($E_b \propto d_{drug}$), whereas the separation energy may be proportional to a higher power of $d_{drug}$ depending on the predominant type of separation force generated during inhalation. For lift and inertial separation forces the separation energy will be proportional to $d_{drug}^2$ or $d_{drug}^3$, respectively, whereas for drag forces (Stokes regime) it will only be proportional to $d_{drug}^{-1}$ [10]. Consequently, the energy ratio will be positively related to $d_{drug}$ or $d_{drug}^{-1}$ for lift and inertial forces, whereas it will depend on particle size to a lesser extent when drug detachment is caused by drag forces. It follows that if a variable causes a change in the size distribution of the drug particles as they are detached from the carrier surface, the particle size effect (i.e., the change in the detached drug fraction) depends on:

- the exact change in the size distribution of drug particles as they are detached from the carrier surface;
- the predominant type of separation forces; and
- the initially detached drug fraction.

The first two factors together determine the change in the energy ratio distribution during inhalation. Interactions between a variable causing a particle size effect and any other variable that alters one of the above three factors can be expected. Examples are the carrier size fraction, which affects the agglomeration potential of the drug [11]; the dispersion principle, which determines the predominant type of separation force; and inhalation variables such as the flow rate through the inhaler, which may to great extent determine the initially detached drug fraction.

**Press-on effects**

Frictional and inertial forces which act on the drug particles during the mixing process may serve as press-on forces when they have a vector component directed towards the carrier surface. These press-on forces increase the binding energy and thus lower the detached drug fraction by increasing the contact area between interacting particles and by reducing their separation distance [12]. Any process or component variable that alters the degree of compression of drug particles onto the carrier surface, for example by changing the effectiveness of press-on forces or the number of press-on events, may thus affect drug detachment. An example may be the drug content relative to the capacity of carrier surface irregularities to offer shelter to drug particles from press-on forces. The press-on effect of a variable (i.e., the change in the detached drug fraction) also depends on 1) the change in the energy ratio distribution that results from a change in the variable and 2) the initially detached drug fraction. As for particle size effects, interactions can be expected between a variable causing a press-on effect and any other variable that changes (one of) these two factors. Examples may be the mixing time and mixing intensity, which determine the number and magnitude of press-on events, respectively, and thus their potential to be altered; and again the flow rate through the inhaler.

**Distribution effects**

A definition of carrier surface site activity solely in terms of binding energy is flawed if one wishes it to be directly related to drug detachment. It does not take into account any effect of the binding site on the potential separation energy. Site activity is therefore defined as the inverse of the potential energy ratio of a drug particle at a particular binding site after minimal compression at a defined dispersion effort (i.e., flow rate or pressure drop). The distribution in activity of occupied carrier surface sites consists of two aspects: the activity distribution of the carrier surface sites and the physical distribution of the drug over these carrier surface sites. A change in either one or both of these aspects is considered a
distribution effect if it results in a change in the detached drug fraction during inhalation. Examples may be changes in the carrier surface morphology; coating of the carrier surface with 'force control agents' [13]; altering the drug redistribution by changing the mixing time; altering the type of drug; or the saturation of active carrier surface sites with an increasing drug or lactose fines content in the mixture [3, 14]. The change in the detached drug fraction resulting from distribution effects, like any effect, depends on the change in the energy ratio distribution and the initially detached drug fraction. This means that interactions may be expected between all variables that influence carrier surface site activity, the distribution of drug over the carrier surface and inhalation variables determining the detachment efficacy.

The coherence of variables

The different principal effects are not likely to occur in isolation when a certain variable in the formulation process is changed. Instead, any change in the detached drug fraction will be determined by the sum of the different principal effects. An interacting variable causes a different outcome of this sum for an equal change in another variable. This may be the result from physical changes in the powder mixture; when changes in the principal factors caused by the variable are dependent on the interacting variable (as would be the case for interactions between component and/or process variables). Alternatively, the changes to the principal factors caused by the variable may remain equal when the relevance of these changes to drug detachment is altered by the interacting variable (as would be the case for interactions between component or process variables and inhalation variables). This conception of the interplay between variables in the formulation and dispersion of adhesive mixtures is schematically presented in Figure 3. According to this view, multi-order interactions between variables are more likely to be a rule than an exception.

The above implies that future research concerning the dispersion performance of adhesive mixtures for inhalation may benefit from an approach in which attention is focused on:

- the development/optimisation of sensitive methods to measure or monitor the principal factors of the powder mixture;
- establishing the relationship between principal factors and drug detachment or dispersion performance under different inhalation conditions (especially the dispersion principle and inhalation flow rate);
- determining the relationship between component and process variables and the principal factors of the mixture; and
- rationally designing studies by anticipating (and using) interactions between variables.

Conclusions

Multi-order interactions between variables in the formulation and dispersion of adhesive mixtures for inhalation are very likely to occur. Anticipating these interactions may increase the utility of future studies and the efficacy of quality by design approaches to the development of dry powder inhalation products.

References