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Importance of particle size and shape on the tensile strength distribution and de-agglomeration of cohesive powders

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ABSTRACT

Purpose: The purpose of the study was to understand the role of particle size and shape changes in modifying agglomerate strength distribution and de-agglomeration of cohesive lactose powders.
Methods: The relative de-agglomeration of three lactoses of different particle size distributions (Lactohale 201 or LH201, Lactohale 210 or LH210 and Lactohale 220 or LH220) was determined from laser diffraction particle sizing of the aerosol plume at different air flow rates. The agglomerate strength distributions were estimated by Monte Carlo simulation using the primary particle size, work of cohesion and tapped density distributions determined by laser diffraction, inverse gas chromatography and tapping apparatus, respectively. The morphology and particle shape parameters were determined by scanning electron microscopy and the Morphologi G3.
Results: The estimated agglomerate strength correlated well with the de-agglomeration of all lactose samples at different air flow rates. While the work of cohesion of the lactose samples was not significantly different, the packing fraction was dependent on the proportion and shape of intermediate-sized, cohesive particles between 5.4 and 14 μm. For example, while the proportion of particles <5.4 μm was similar for all lactose samples, the proportion of intermediate-sized, cohesive particles increased in the order of LH201 < LH210 < LH220. The intermediate-sized, cohesive particles were more elongated than the <5.4 μm fraction and the extent of elongation of the lactose samples increased in the order of LH220 > LH210 > LH201.
Conclusion: The study reinforced the role of agglomerate strength distributions in understanding de-agglomeration of cohesive materials. Modification of particle size distributions and shape characteristics contributed to the agglomerate strength changes in the lactose samples. The study enhanced the fundamental understanding of powder de-agglomeration and provided strategic approaches that could be used to improve inhalation product performance.

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1. Introduction

Dry powder inhaler formulations often contain micron-sized drug particles (usually <5μ in size) mixed with large, free-flowing lactose and cohesive fine lactose. Due to high adhesion/cohesion of these micron size particles, the drug is agglomerated alone, with fine carriers, with large carriers or with both fine and large carriers resulting in complex multi-particular agglomerates [1]. However, for effective drug delivery to the deep lung/alveolar region, the agglomerates need to be de-agglomerated and dispersed to particles <5 μm [2]. De-agglomeration of powders was found to be influenced by the agglomerate strength which was indirectly measured by air shear pressure using an Aerosizer® [3,4] or by the mechanical strength measured using a dual column physical testing machine [5]. Agglomerate strength (σ) can be calculated using the Eq. (1) [6]:

$$\sigma = 15.6\left(\frac{\rho^4 W}{d}\right) \quad (1)$$

where 'd' is the particle diameter, 'ρ' is the packing fraction (volume of particles/volume of aggregates) and 'W' is the work of adhesion or cohesion of particles. In fact, real powders are heterogeneous in nature having a distribution of particle size, a distribution of work of cohesion and a distribution of packing fraction resulting in a distribution of agglomerate strength [7]. While the de-agglomeration and dispersion of powders at a particular flow rate may relate to a single, average value of agglomerate strength [5], the complex de-agglomeration behavior of cohesive micronized powders (<5 μm) at a range of flow rates is better explained by the agglomerate strength distribution [8]. According to Eq. (1), for the same material where the work of cohesions of different powders is similar, the agglomerate strength, and therefore, the de-

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agglomeration will vary depending on the differences in particle size and packing fraction.

The packing density and packing fraction of powders are influenced by particle size distribution [9,10] meaning the agglomerate strength and therefore, the de-agglomeration of powders will be influenced by particle size distribution. The influence of particle size of lactose on drug dispersion has been studied; however, the focus of these studies has been on either the free-flowing larger carrier particles or on the very small micronized particles usually less than about 5 μm. For example, the dispersion of the drug was either decreased or remained unchanged with increasing particle size of large carriers [11–14]. However, Islam et al. also showed that it is fine lactose (FL), not the carrier lactose size, which was important in increasing de-agglomeration of salmeterol xinafoate (SX) [13]. The FL, usually of size <5 μm and either associated with carrier lactose or additional to the formulation, improves dispersion through either passivation of the 'active sites' [15,16] or by the formation of 'mixed agglomerates' of drug and fine lactose particles which are less strong than drug alone agglomerates [1,17]. However, the role of intermediate sized cohesive lactose (i.e., mean particle size is generally in the range of 5–15 μm which is larger than the micronized lactose particles used to enhance aerosolisation) and the mechanism of changing dispersion performance was less explored. An increase in the dispersion of salbutamol sulphate (SS) was found when only 1.5% w/w of lactose of volume mean diameter (VMD) 15.9 μm was added to a mixture of SS and coarse sieved lactose (VMD, 90.8 ± 5.0 μm) [15]. However, in that study, the lactose sample was not completely free from fines (<5 μm) raising the question of whether the result was due to fines or intermediate size lactose. In another study, the dispersion of SX from SX-FL binary mixtures was higher using FL of VMD 7.9 μm than using FL of VMD 3 μm [3]. Using particle size-shear pressure profiles of the powders, they argued that the formation of more open packed structures of the mixture containing FL of VMD 7.9 μm enhanced the aerosolisation in comparison with the mixture containing FL of VMD 3 μm. In the FL of VMD 7.9 μm, 90% of particles were less than 14 μm. Conventional carrier lactose powders used in inhalation formulations have a broad distribution of particle size including fine cohesive fraction (<5 μm), intermediate size semi-cohesive fraction (for example, 5–14 μm) and larger, free-flowing particles. It is, therefore, important to understand the key particle fractions providing the greatest impact on de-agglomeration and to give focus to the role of intermediate size fractions of carrier lactose and the mechanism of dispersion change. It is now possible to determine the agglomerate strength distribution directly from particle size distribution, tapped density distribution and work of cohesion distribution determined by laser diffraction, tapping apparatus and inverse gas chromatography, respectively [7]. Moreover, various particle shape parameters such elongation and circularity can be analysed capturing 2-dimensional (2D) images of the 3-dimensional (3D) particles by the Malvern Morphologi G3® [18]. These shape parameters can give a useful indication about the particle shape which may have effect on packing and de-agglomeration [19].

It is hypothesized that the intermediate size cohesive lactose fraction will create a more open-packed structure of the cohesive powder bed resulting in more facile de-agglomeration and faster achievement of the peak de-agglomeration. Therefore, this experiment was designed to study the influence of intermediate sized lactose fraction on de-agglomeration and to understand the mechanism. The de-agglomeration of the three lactose of different particle size distributions having similar work of cohesions and similar proportion of fines (<5.4 μm) but differing proportions of intermediate size fractions was examined at different air flow rates. The work of cohesion distribution, particle size distribution, and packing fraction distribution were determined and the agglomerate strength distribution was calculated from these parameters using a Monte Carlo simulation. The shape parameters of agglomerates were also examined. Understanding the roles of these intermediate size semi-cohesive lactose fractions will help better design powder formulations or to develop carrier lactose particles that can give improved efficiency.

2. Materials and methods

2.1. Materials

Three lactose samples: Lactohale 201® (LH201), Lactohale 210® (LH210) and Lactohale 220® (LH220) supplied by DFE Pharma, Netherlands were used as received. GC grade hexane, heptane, octane, nonane, decane, dichloromethane and ethyl acetate (all from Sigma-Aldrich GmbH, Steinheim, Germany) were used for surface energy analysis.

2.2. Methods

2.2.1. Pre-conditioning of powders

In order to confirm that powders have been exposed to similar mechanical processing prior to investigation, each powder was pre-conditioned by a standardised hand mixing experiment that has been developed and validated in our laboratory [20]. Five grams of each powder in each batch was mixed in a glass jar for five minutes using three ceramic balls (10 mm diameter). At the end of every 30 s mixing, the jar was tapped both horizontally and vertically to release the powder stuck on jar's cones and wall. The mixing was conducted by gentle shaking so that no particle size reduction occured; this was confirmed as no statistically significant difference ($P > 0.05$) was observed in primary particle size distributions before and after pre-conditioning.

2.2.2. Work of cohesions calculation

Non polar, polar and total surface energy distributions were determined using a finite dilution experiment with inverse gas chromatography (IGC, Surface Measurement Systems Ltd, London, UK) according to a literature method [21,22]. In brief, approximately 0.6 g of lactose was packed in pre-silanised glass columns (300 mm × 3 mm internal diameter) by tapping for four minutes using a tapping apparatus (Surface Measurement Systems Ltd, London, UK). The powder filled columns were closed at both ends with silanised glass wool and conditioned for 2 h at 303 K to remove surface impurities. A series of alkanes such as hexane, heptane, octane, nonane and decane were used to determine non-polar surface energy (γ^{NP}), and two polar probes such as dichloromethane and ethyl acetate were used to determine polar surface energy (γ^{P}). All these probes were passed through the column at concentrations of 0.03, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.8, 0.94 p/p^0 (where p denotes the partial pressure and p^0 the vapour pressure). Helium flowing at 10 sccm (standard cubic centimetres per minute) was used to carry the probes in to the column. A flame ionization detector was used to detect retention times. The retention time for methane run at a concentration of 0.1 p/p^0 was regarded as the dead time, where there was no interaction between probe and sample. Retention volumes were calculated from retention times. The Brunauer–Emmet–Teller (BET) surface area was determined from hexane adsorption isotherms, and the surface coverage (n/n_m) was calculated from the adsorbed amount (n) and monolayer capacity (n_m, the number of moles of the probe adsorbed for monolayer coverage). At each surface coverage for each probe, the net retention volume (V_N) was calculated. The γ^{NP} was the slope ($2 N_A \sqrt{\gamma^{NP}}$) of a plot of $RT\ln V_N$ against a $\sqrt{\gamma^{NP}}$ of alkanes [23]. The γ^{P} was calculated from acidic (γ^{+}) character determined from interaction with a monopolar basic probe, ethyl acetate, and basic (γ^{-}) character determined from the interaction with a monopolar acidic probe, dichloromethane as per van Oss concept [24,25]. The total surface energy (γ^{T}) was calculated by summing up the non-polar (γ^{NP}) and polar surface energies (γ^{P}) [26]. The work of cohesion (W) was calculated from the non-polar and polar surface energies [27].

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