Mechanistic time scales in adhesive mixing investigated by dry particle sizing

Duy Nguyen [a], Anders Rasmuson [a], Ingela Niklasson Björn [b], Kyrre Thalberg [b,*]

[a] *Department of Chemical Engineering, Chalmers University of Technology, SE-412 96 Gothenburg, Sweden*
[b] *Astra Zeneca Pharmaceutical Development R&D Mölndal, SE-431 83 Mölndal, Sweden*

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ABSTRACT

This study exploits the mechanisms governing blending of adhesive mixtures, i.e. random mixing, de-agglomeration and adhesion, and their relative importance to achieve mixing homogeneity. To this end, blending of micronized particles (fines) with carrier particles was carried out using a high shear mixer. Dry particle sizing using laser diffraction coupled with a strong powder dispersion unit was employed to measure the fines content in samples collected during mixing, and hence to assess blend homogeneity. The method was also employed to evaluate the relative strength of the agglomerates present in the fines. Particle sizing using a non-destructive imaging technique was used to monitor changes in particle size during blending. It could be shown that the de-agglomeration of the fine-particle agglomerates is the slowest mechanism and hence the rate-limiting step as regards achieving a homogeneous adhesive mixture. Consequently, a longer mixing time is needed for blending of larger agglomerates. Being fast, simple and reproducible, the laser diffraction technique was shown to be an efficient method for measurement of fine particle content and homogeneity of a mixture, while the non-destructive image analysis was able to give relevant information on the rate of de-agglomeration of the fine-particle agglomerates as well as on the size of the resulting carrier-fine particle assemblies.

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1. Introduction

The mixing in which fine particles are attached onto the surfaces of carrier particles has successfully been employed to produce homogeneous pharmaceutical formulations, both in the case of very potent APIs and as regards dry powder formulations for inhalations (Vikas Anand Saharan et al., 2008). The mixing process was first described by the concept of ordered mixing where mixing rate obeys first-order kinetics (Hersey, 1975), i.e. same as random mixing, but was later described as a dynamic equilibrium process between adhesive and non-adhesive mixings using the 'total mixing' concept (Staniforth, 1981). The term adhesive mixing, was later recommended (Staniforth, 1987). Adhesive mixing is applied to improve homogeneity of pharmaceutical dosage forms as well as to alter the surface properties of several products in a wide range of industrial applications (Jiang et al., 2006; Kale et al., 2009; Swaminathan and Kildsig, 2002). It has been reported that mixing homogeneity is a function of material properties such as particle size (Sundell-Bredenberg and Nystrom, 2001), particle shape (Wong and Pilpel, 1988), and surface properties (Buckton, 1997; Podczeck, 1998) and also depends on composition, addition of other components (Jones and Price, 2006) and mixing time (Bosquillon et al., 2001; Jones et al., 2010).

The mixing process itself is obviously a key unit operation in the formulation of an adhesive mixture. Although the effects of material properties on product performance have been well documented, the mixing dynamics have not received much attention (de Boer et al., 2012). Therefore, there is still a need to investigate mixing mechanisms and dynamics, in order to provide better understanding of the overall process. The aim of this work is thus to estimate the time scale of the mechanisms governing the mixing process as well as their relative importance as regards achieving a homogeneous mixture.

Spherical mannitol pellets with a median diameter just above 200 µm and micronized lactose monohydrate with a median size of 4 µm were selected for the experiments (details are given in Section 3.1). The latter component can be regarded as representing drug particles, e.g. in a pharmaceutical dry powder formulation for inhalation. Since such fine particles spontaneously forms agglomerates during processing and handling, the study also deals with the influence of fine-particle agglomerates on the mixing behaviour.

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* Corresponding author. Tel.: +46 70 9131964; fax: +46 317763727.
E-mail address: Kyrre.Thalberg@astrazeneca.com (K. Thalberg).

In addition, the application of two different dry particle sizing techniques is reported. In order to assess the content and content uniformity of the fine particles in the blend, laser diffraction combined with a powerful powder dispersing unit was applied. By means of a calibration procedure, the exact fine particle content of a sample could be determined. The method was also used to measure relative strength of the fine-particle agglomerates. As a complement to this, a non-dispersing particle size method was applied to monitor the disintegration of the fine-particle agglomerates and the formation of fines-carrier aggregates during mixing.

2. Mixing mechanisms

It has been documented that the mixing of fine particles with carrier is achieved via a combination of random mixing and adhesive mixing (de Villiers, 1997). Four different mechanisms can be distinguished in this process, as is illustrated in Fig. 1. The first one governs the distribution of assemblies, e.g. the mixing between carrier particles and fine-particle agglomerates, and can be described by the concept of random mixing developed by Lacey (1943). The second mechanism is de-agglomeration of fine-particle agglomerates which occurs as a consequence of mechanical collisions during blending (Ikegami et al., 2003; Kale et al., 2009). It has been reported to occur rapidly during the random mixing stage (de Villiers, 1997). Adhesion is the third mechanism implying the binding of fine particle fragments onto the carrier surface by adhesion forces, e.g. van der Waals forces (Nyström and Westerberg, 1986). The last mechanism deals with redistribution and exchange of fine particles between carrier particles (Alonso et al., 1989; de Boer et al., 2012, 2003). Finally, press-on forces acting during mixing may cause the compression of fine particles onto the carrier surfaces (Podczeck, 1996).

For a given fines-carrier combination, the homogeneity of the mixture and the properties of the final blend are functions of the above described mechanisms, which in turn depends on the type of mixer and the process parameters applied. For instance, the dispersion performance of adhesive mixtures for inhalation was found to be affected by the balance between de-agglomeration, re-distribution and compression mechanisms (Grasmeijer et al., 2013). The present work focuses on studying the time scales of the mechanisms governing the high shear mixing process, in particular the steps of random mixing, de-agglomeration and adhesion of fines.

3. Material and methods

3.1. Material

D-Mannitol pellets (Nonpareil 108-200) supplied from Freund (Japan) was used as model carrier, and have a narrow size distribution in the range of 150–250 µm (D_{50} = 212 µm). Micronized lactose monohydrate from AstraZeneca was used as fines, thus representing the drug component in a pharmaceutical adhesive blend. The fines have a median size (D_{50}) of 3.8 µm.

3.2. Sieving of fines

Due to high cohesion, micronized particles often exist in the form of self-agglomerates with a very broad size distribution. This was also the case for the micronized lactose fines used here. To investigate the effect of agglomerate size on mixing dynamics, the material was gently sieved using sieves of mesh sizes; 0.71 mm, 1.0 mm, 1.4 mm, and 2.0 mm, to obtain five size fractions of fines-agglomerates.

3.3. High shear mixing

The mixing experiments were performed in a MiPro high shear granulator (Procept, Belgium) installed with a 1.9 l vessel and a 3 bevelled-blades impeller, and was used without the chopper. A moderate impeller speed of 500 rpm was used in all experiments. A total of 260 g of material with 5% w/w of fine-particle agglomerates was loaded in each experiment. The agglomerates were placed as a horizontal layer in the middle of the powder bed at start. The mixer was stopped after 5, 15, 30, 45, 60, 75, 90 and 100 s to withdraw samples for analysis. At each time point, approximately 7 g was removed for analysis. Experiments were carried out for all 5 size fractions of fines to evaluate the influence of agglomerate size on the mixing behaviour. Triplicate experiments were carried out for the 1.4–2.0 mm fraction.

3.4. Sizing of primary particles

Particle sizing of primary particles was used for characterization of starting materials. Laser diffraction using Sympatec HELOS equipped with the RODOS dispersing unit was employed. R5 and R2 lenses were used for sizing of carrier and fine particles, respec-
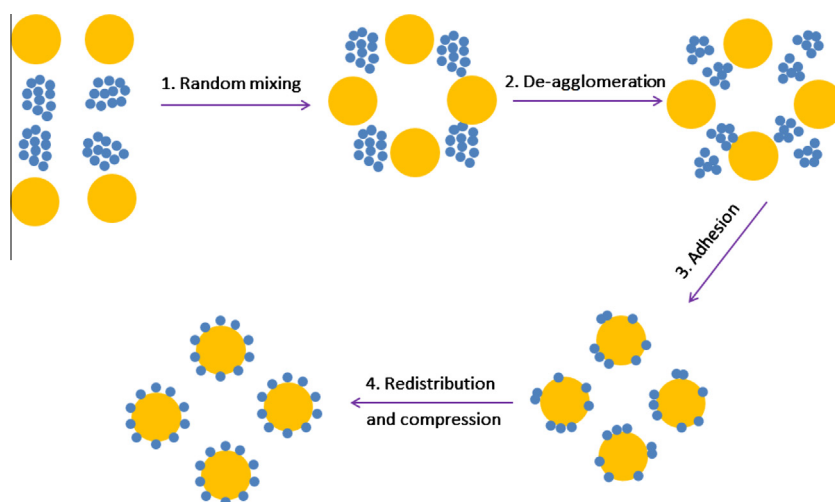

Fig. 1. Schematic representation of the four mixing mechanisms.