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# A study of the redistribution of fines between carriers in adhesive particle mixing using image analysis with coloured tracers

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ABSTRACT

Understanding the dynamics and kinetics of mixing mechanisms, i.e. random mixing, de-agglomeration, adhesion, and redistribution, is critical in order to achieve a structure of interest in adhesive particle mixing. In this work, the redistribution of fines between carrier particles, one of the key mechanisms in establishing a homogeneous mixture, was investigated. Coloured carriers (tracers) and image analysis utilizing CIELCH colour space are used as a tool to assess the dynamics of such a mechanism via the evolution of the colour of blends. It is found that, in a high shear mixer, redistribution quickly reaches a pseudo-steady state within a time scale that is of the same order of magnitude as that of random mixing. Considering all the governing mechanisms necessary to achieve an adhesive mixture, it is concluded that the de-agglomeration of fine-particle agglomerates is the rate-limiting step. This work also demonstrates that the redistribution of fines is influenced by the structure of fines on carrier surfaces resulting from processing conditions. This finding supports the fact that beside material properties, blending conditions, e.g. mixing speed and time, are crucial as regards the structure of adhesive mixtures for inhalation.

## 1. Introduction

Dry particle mixing with the adhesion of fine constituents onto coarse constituents, i.e. adhesive particle mixing, is beneficial both for handling properties and for obtaining a high degree of uniformity of a solid dosage form [1]. Although this mixing approach has been successfully applied in industrial processes, e.g. in the formulation of dry powder for inhalation, there still remains several unknown aspects which make formulation development a trial-and-error process [2]. With the addition of fine constituents, the particle mixing mechanism evolves from a so-called random mixing, which obeys the law of probability, to a series of mechanisms across length scales caused by complex particle–particle interactions [3]. As illustrated in Fig. 1, these mechanisms, in order of decreasing length scales, are, (i) Random mixing which distributes all assemblies over a mixer, (ii) De-agglomeration of fine-particle agglomerates, (iii) Adhesion of fines on carrier particles, and (iv) Re-distribution of fines between carrier particles [2,4–6]. In fact, each of these mechanisms plays a significant role in achieving a homogeneous mixture [7]. Additionally, understanding their time scales is important since sufficient energy input is required to form a structure of interest and to avoid damage caused by excess energy [8,9]. Previous research has found that the de-agglomeration of fine-particle agglomerates is the rate-limiting step in achieving an adhesive mixture, i.e. the de-agglomeration time scale is substantially larger than the time scales of the random mixing and the adhesion mechanism [4]. The time scale of the redistribution of fines between dissimilar carriers has also been documented [10]. This time scale was found to be one order of magnitude larger than the time scales of other mechanisms reported in the research by Nguyen et al. In addition to the fact that these studies were conducted using different types of mixers and materials, the reported time scale of such a redistribution mechanism was determined for an extreme case in which a large difference in surface energy was present. A detailed evaluation of the redistribution of fines between similar carriers and the relative magnitude of the time scale of this mechanism to that of other mechanisms is therefore needed. This will improve the understanding of adhesive particle mixing and contribute to a better control of relevant applications, e.g. dry powders for inhalation.

Although computer simulation has achieved great progress in modelling particulate flows, [11–13], there are still limitations in providing a detailed description of flows with complex particle – particle interactions, such as those in adhesive mixing, at an affordable computational cost. Using computer simulation to investigate adhesive mixing in a complex mixer is therefore not feasible in practice. This study aims to propose a simple tool to assess the time scale of the redistribution of fine particles in a high shear mixer and evaluate its contribution to the total mixing time required to attain an adhesive mixture. To this end, CIELCH colour space is used to analyse images of samples which are manufactured by blending adhesive mixtures composed of lactose fines and D-mannitol carriers with coloured carrier particles. These

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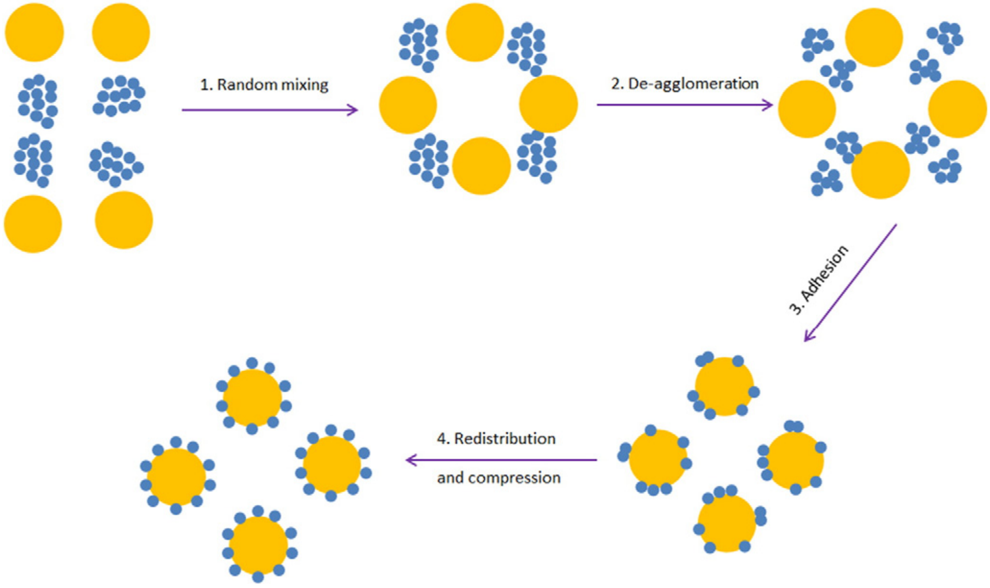

**Fig. 1.** Schematic description of adhesive mixing mechanisms, (1) random mixing, (2) de-agglomeration, (3) adhesion, (4) redistribution [4].

tracer particles were produced by coating primary carriers (D-mannitol) with a thin layer of Rhodamine B. The underlying idea is that when fine particles (white) migrate from the primary carriers (white) in prepared adhesive mixtures to tracer carriers (dark pink), the colour of the samples consisting of those assemblies will change. Keeping track of this change gives information on the dynamics of the transfer of fines.

## 2. Material and methods

### 2.1. Material

D-Mannitol pellets (Nonpareil 108–200, Freund, Japan), with a narrow size distribution in the range of 150–250 μm ($D_{50} = 212$ μm), were used as the model carrier. Micronized lactose monohydrate from AstraZeneca was used as the fine particles, representing the drug component in a pharmaceutical adhesive blend. The fines had a median size ($D_{50}$) of 3.8 μm. The size distribution of fines and primary carriers are reported in Table 1.

Mannitol carriers coated with a thin layer of Rhodamine B were used as tracers.

**Table 1**
Size distribution of primary material.

| | Size distribution (μm) | | | | % Volume lower than 5 μm | % Volume lower than 11 μm | % Volume lower than 50 μm |
|---|---|---|---|---|---|---|---|
| | $D_{10}$ | $D_{50}$ | $D_{90}$ | Span | | | |
| Fine lactose | 1.17 | 3.83 | 8.51 | 1.91 | 70 | 99 | 100 |
| Carrier | 134 | 212 | 254 | 0.56 | 0.09 | 0.2 | 1.4 |

**Table 2**
Prepared adhesive mixtures.

| | Initial adhesive mixture | | | | | |
|---|---|---|---|---|---|---|
| Blend | Mixture | Fines content (%) | Mixing speed (rpm) | Mixing time (min) | Tracer (%) | Mixing speed (rpm) |
| 1 | A | 5 | 500 | 3 | 20 | 500 |
| 2 | B | 10 | 500 | 3 | 20 | 500 |
| 3 | C | 5 | 1200 | 4 | 20 | 500 |

### 2.2. High shear mixing

All mixing experiments were performed in a MiPro high shear granulator (Procept, Belgium) equipped with a 1.9 l vessel and a three-bevelled-blades impeller (without a chopper).

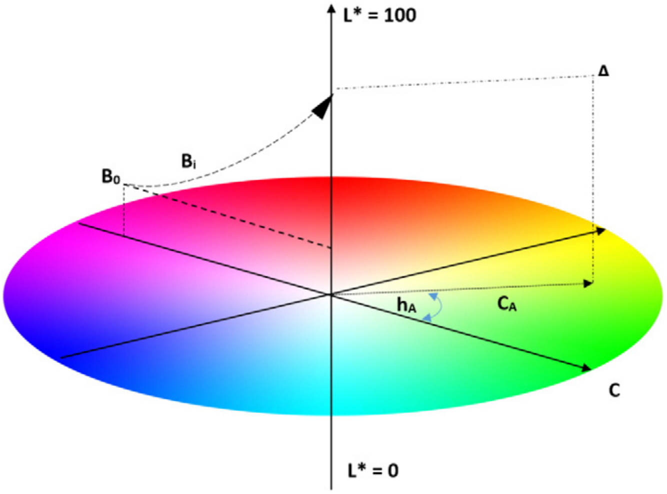

**Fig. 2.** CIELCH colour space, $B_o$–$B_i$ is the expected path of the redistribution of fines.

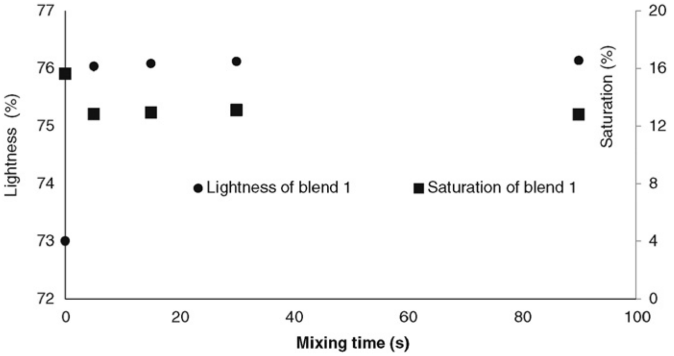

**Fig. 3.** Changes in the lightness and saturation of blends during mixing.