Powder Technology 270 (2015) 461–469

Contents lists available at ScienceDirect

Powder Technology

journal homepage: www.elsevier.com/locate/powtec

Pharmaceutical dry powder blending and scale-up: Maintaining equivalent mixing conditions using a coloured tracer powder

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ARTICLE INFO

Available online 4 May 2014

Keywords:
Mixing
Powder
Dispersion
Deagglomeration
Tracer
Pharmaceutical

ABSTRACT

The identification and optimisation of operating conditions and selection of an appropriate mixer for the manufacturing of pharmaceutical dry powders is extremely challenging, and has relied largely on empirical trial-and-error approaches. A novel extension to a previous method has been proposed, which can be used to quickly and effectively evaluate the progression of a dry powder mixing using a mixing-sensitive coloured tracer powder. A series of lactose powders (white) with 1 wt.% sub-micronised iron oxide tracer (dark red) by weight were blended with three different mixing technologies under a range of processing conditions. Measurement of the hue and hue intensity of the powder blend as a function of time shows two distinct mixing behaviours: dispersion of tracer aggregates through the bulk powder (increase in blend hue intensity) and tracer deagglomeration into primary particles (hue transition from red to orange). The colourimetric values of samples taken at blending times of up to 1 h were assembled to create a series of formulation-specific colour curves which were able to clearly distinguish and group mixers into low and high intensities given their range of values along the same formulation curves. This iron oxide tracer method provides the basis for a novel quantitative approach for ensuring equivalent blending conditions between mixer types, scales and operating conditions for a given formulation. The approach also shows the potential to identify conditions which may cause unintentional and undesirable particle attrition during powder blending.

1. Introduction

1.1. Pharmaceutical manufacturing of dry powder inhaler (DPI) blends

In the pharmaceutical industry, product homogeneity is an extremely important factor in powder mixing due to the small scale of powder used per dose [1], and the health and financial implications of not achieving sufficient uniformity. To achieve product consistency and hence safety, precise mixing is desired, which is often very difficult to achieve in practice due to the size, shape and physical property differences between powders used to create pharmaceutical formulations [2]. Manufacturing difficulties are further compounded for dry powder inhaler (DPI) formulations as they require not only good blend uniformity but also a specific blend structure to enable effective drug delivery [3]. In the blending of pharmaceutical formulations, shear forces are required to ensure that the often small percentage (1–2 wt.%) of large cohesive drug particle clumps are de-agglomerated and dispersed throughout the bulk excipient [4]. In many batch manufacturing processes, an excess of energy is required to ensure that all drug aggregates across the bulk experience the required forces to ensure that they are sufficiently de-aggregated and dispersed throughout the entire powder mass. In some cases this can result in significant damage to the large excipient particles through the generation of cracks on the particle surfaces [5,6] and even unintentional milling and attrition of the powder particles [7,8]. Such particle damage can alter the surface properties of the excipient particles and can affect both product performance and product shelf-life [9].

Dry powder inhaler (DPI) product testing uses several representative samples and requires complex and intensive laboratory analysis. Data on the content uniformity and product performance (e.g. fine particle fraction) are obtained post-blending, and if unsatisfactory, can require the entire drug blend to be disposed of. Surface defects, particle damage and milling are not quantified as part of the standard release testing and are usually only investigated if significant changes in product performance are observed after weeks or months of stability testing. Their specific quantitative measurement is also challenging and no standard methodology exists. The determination of best mixing conditions for a given mixer and scale takes a considerable length of time and can impact the release of new products. This can also discourage pharmaceutical companies from changing mixing technologies and scales to meet changing volume requirements, effectively lowering corporate flexibility, adaptability and ultimately inhibiting cost benefits of scaling.

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http://dx.doi.org/10.1016/j.powtec.2014.04.069
0032-5910/

The current state of knowledge in multi-particulate powder flow is lacking due to the complexity of inter-particulate interactions and powder flow in general [10]. Whilst computer simulations of particle interactions have come a long way in being able to model powder flow in different mixers for relatively simple systems [11–15], their use in industrial processes is currently limited due to the complexities of setting up parameters for specific formulations (complex particle sizes, shapes and interaction parameters). In addition, the computational demands of simulations are very high due to the large numbers of very fine particles involved in DPI blending. These factors make computer simulations of powder blending impractical in most cases for industrial DPI process development. Even considering the anticipated advancements in computational capacities in the next decade, it is expected that industrial DPI powder blending processes will require a combination of experience and experimental approaches.

It would therefore be beneficial for industry to have a simple and cost-effective means of assessing powder blending, and to provide a better quantitative understanding of the influence of operating conditions on powder mixing in different mixers. This would allow for better predictions about the extent of mixing (both required intensity and mixing time) and shift determination of the best operating conditions from the traditional trial-and-error approach to a more holistic and efficient process that has flexibility to be applied to a variety of situations including scale-up and transfer between blender types, rather than being product specific.

The use of a placebo blend containing low-dose coloured tracer instead of the drug as a preliminary testing method would allow the blending process to be quickly and simply analysed through colour change of the blend as it is mixed. Such a tool may also provide insight into specific mixing behaviours of powders within different mixer types. This is the goal of this paper.

1.2. Introduction to colour theory

The colour change of powder blends containing iron oxide can be measured through the use of a colourimeter, which can evaluate and compare colours in a typically 3-dimensional colour space. Whilst there is a multitude of colour spaces [16], the most commonly used is the CIE (1976) colour space due to its ability to quantitatively compare the difference between colours [17]. In the CIE colour space each particular colour has a unique position defined by either Cartesian (L^*, a^* and b^*) or cylindrical (L^*, C^* and h) coordinates (Fig. 1).

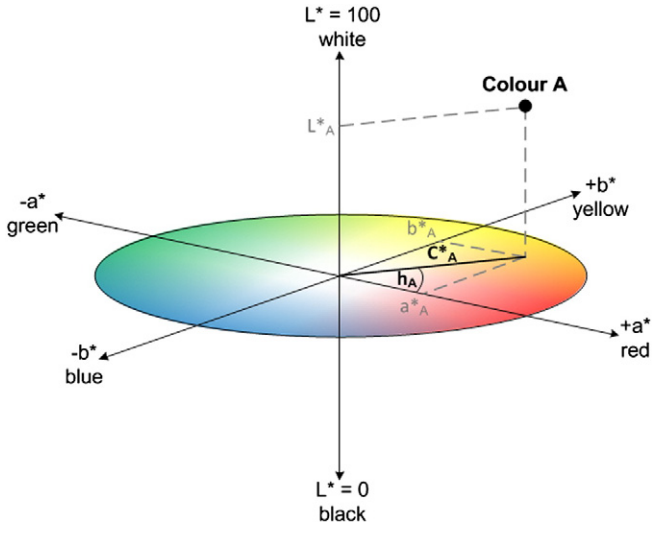

Fig. 1. Schematic of CIE (1976) colour space showing both Cartesian L^*, a^*, b^* and cylindrical L^*, C^*, h coordinate systems for a given colour measurement.

In the CIE colour space, L^* values serve as the degree of tint (white) and shade (black) in a colour, with values ranging from purely white ($L^* = 100$) to purely black ($L^* = 0$). Values along the L^*-axis are termed as achromatic (without hue). In the Cartesian space a^* and b^* values denote a colour's comparative position in terms of red-versus-green (a^*) and yellow-versus-blue (b^*). In the cylindrical space, a colour's hue (hue angle, h) and hue intensity (Chroma, C^*) can be determined through mathematical manipulation of the a^* and b^* values. The CIELCH space has been selected for this work in preference to the more commonly used CIELAB space as it is assumed that the change in hue and hue intensity exclusively indicates pigment de-agglomeration and dispersion respectively (refer to Section 1.3).

1.3. Previous colour tracer studies

The colour change of iron oxide as it is mixed has been observed in other studies, including its use to analyse the extent of mixing in cosmetic manufacturing [18] and for the validation of operating conditions prior to main experiments [19,20]. Of particular interest to this project are the previous works of Satoh and co-workers, who extensively investigated the change in colour of iron oxide pigment in a white bulk powder (calcium carbonate) using different mixers and mixing conditions [20–24]. Satoh and co-workers began with an initial study to characterise mixer types based on process intensity [20] by adding red iron oxide powder (5 wt.%) to white calcium carbonate and measuring the colour change during mixing in various processes. The colour change was primarily compared by a "degree of dispersion" (*DoD*) factor, which was the ratio of powder lightness and blend lightness in the CIE colour space (i.e. L^*-values). Using the *DoD* factor, Satoh et al. [20] were able to classify powder blending equipment based on the shape of curves generated when *DoD* values were plotted against mixing time (t). For each process a distinct family of curves were observed. Satoh and co-worker's study was useful but used only a single dimension of the colour space — the lightness L^* (or relative "whiteness") of the powder blend.

During our preliminary experiments in this current work using 1 wt.% submicronised iron oxide (hematite) tracer in a placebo formulation of inhalation grade lactose, a two-stage colour change in the blend was observed. The formulation initially changed from a pale pink (after very little mixing) to a deep red with increasing mixing time. However, we also observed a secondary colour change from red to orange at long mixing times and/or high intensity mixing. The observation can be explained as illustrated in Fig. 2. As the hematite tracer is environmentally and thermally stable [25], which is also consistent with literature for hematite [26], we conclude that the change in hue is purely due to a physical effect caused by the exposure of primary tracer particles [27]. Coloured solids show one or more absorption bands in the visible spectrum, and the width, profile, and position of absorption bands affect the observed colour. With decreasing particle size (higher surface area) of a coloured powder the position and profile of absorption bands can shift, thereby changing the observed colour. This therefore implies that the change in hue from red to orange indicates that the iron oxide tracer is in an increasingly de-agglomerated state (Fig. 2).

For clarity in this work, "dispersion" is defined as the mixing of tracer aggregates throughout the lactose matrix without any change in the aggregate size or population (Fig. 2a–b), whilst "de-agglomeration" is defined as the breakup of tracer aggregates into smaller aggregates and or primary particles (Fig. 2b–c).

1.4. Proposed process curves

Through colour analysis of an iron oxide blend (i.e. analysis of the blend's C^* and h values), the degree of dispersion and the de-agglomeration can be measured simultaneously and independently in the 3-dimensional CIE (1976) colour space (Fig. 3).