ANALYSIS OF DRY POWDER MIXING PROCESSES USING A FINE COHESIVE PIGMENT

David Barling\textsuperscript{1,2}, Assoc. Prof David Morton\textsuperscript{2}, Assoc. Prof Karen Hapgood\textsuperscript{1}

\textsuperscript{1}Department of Chemical Engineering, \textsuperscript{2}Monash Institute of Pharmaceutical Sciences
Monash University
Melbourne, VIC 3800, Australia
david.barling@monash.edu

ABSTRACT
A novel extension to a previous method has been proposed to evaluate the nature of dry powder mixing processes using a mixing sensitive colouring agent. The method proposed measures the change in the colour (hue) and colour intensity of the powder blends over mixing time.

To evaluate the extent of fine particle dispersion and de-agglomeration, cohesive and free flowing lactose (white) and cohesive micronized iron oxide (dark red) were blended as a bulk and tracer respectively. Measuring the change in hue and intensity of micronized iron oxide in a lactose bulk enables the analysis of two distinct mixing behaviours, namely the de-agglomeration of the pigment (transition from red to orange) and the dispersion of a given sized aggregate through the bulk material (increase in the intensity of the blend’s hue). Blends were manufactured using two different types of powder mixers at a range of processing conditions.

Samples were withdrawn from the mixers at regular time intervals and the hue and intensity analysed using a colourimeter. Hue values were assembled to create a series of process specific curves. The colourimetry data was able to clearly separate and group the mixers into low and high levels of shear and/or mixing intensity over a range of conditions, and suggests that the gradual dispersion and de-agglomeration can be monitored independently using this method. These initial results suggest that the iron oxide tracer method could provide the basis for a novel quantitative approach to producing equivalent powder blends as a function of mixer type, scale and operating conditions.

INTRODUCTION
The mixing of dry powders is a fundamental process that dates back thousands of years (Kaye, 1997) and has been utilised by many industries including chemical, food, ceramic, metallurgical and pharmaceutical (Chandratilleke \textit{et al.}, 2009). Powder mixing is typically employed to ensure that two or more solid substances are evenly dispersed amongst one another, but can also be used to coat and form agglomerates and enhance certain physical properties such as bulk density, flow properties and dissolution rates (Kaye, 1997).
In the pharmaceutical industry, product homogeneity is an extremely important factor in powder mixing due to the small scale of powder used per capsule or tablet (Muzzio et al., 1997). The poor distribution of drug particles within the bulk material can lead to adverse and potentially harmful health effects to consumers. For this reason, a very fine degree of mixing is desired, and very difficult to achieve often due to the size, density and physical property differences of the powders used to create pharmaceutical formulations.

Due to stringent regulations in pharmaceutical manufacturing, the effects of poor blending are typically not seen by the customer, but rather in the rejection of product at the manufacturing site. Such waste of material can prove to be both financially costly and time consuming to industry, inherently raising the cost of pharmaceutical products on the market and decreasing production. In addition to the selection of appropriate mixing technology, there are several other factors that influence the blending of dry powders. These include the chosen operating conditions, particle properties and mixer design (Ngai, 2005). Powder flow throughout many powder mixing technologies, particularly high shear/vertical axis mixers, is not well understood and the influence of the chosen operating conditions are not well known (Knight, 2004). As such the determination of the best mixing conditions in a given vessel, including fill height, operating speed and mixing time is a purely trial-and-error approach.

It would be beneficial to industry to gain a better understanding of the influence of operating conditions on powder mixing in different mixing processes. 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 haphazard trial-and-error approach to a more holistic and accurate process that has flexibility to be applied to a variety of situations rather than being product specific.

Many pharmaceutical formulations comprise of a bulk excipient (typically lactose which is white in colour (Willing et al., 2001)) and a pharmaceutical active ingredient (typically crystalline and making up 1-2% by weight of the formulation (Wagner et al., 2009)). Other powders may also be present, which aide in product flow, granulation and compression properties or in drug delivery (Rhodes, 2008). Current testing of blend homogeneity in such formulations involves the sampling of powder at various regions of the mixer and analysing their drug concentration through appropriate analytical means (Muzzio et al., 1997). This method is slow, labour intensive and does not allow for simple analysis of the entire blend, nor does it allow for quick analysis at the time of mixing.

The use of a coloured pigment as a preliminary testing method, and when used as a substitute for the pharmaceutical active, may hold benefits in allowing an entire blend to be quickly and simply analysed through the blend’s colour change as the level of mixing increases. Analysis of a colour tracer such as iron oxide may also provide key information on mixing mechanisms such as the de-agglomeration pathways of cohesive powders as the colour change in the blend has multiple dimensions.

**Iron oxide and colour change**

As iron oxide is mixed amongst a bulk powder, a colour change in the powder blend can be observed. In the case of a mimic pharmaceutical formulation, the iron oxide replaces the active ingredient (typically 1-2% w/w) and is blended with lactose. The dispersion of the relatively small amount of red pigment in the white lactose shows a significant colour change in the blend, where the formulation changes from an initial pale pink (little mixing) to deep red (good mixing) as the pigment is dispersed throughout the lactose powder. The iron oxide is typically present as aggregates of micron or submicron particles. A further change from red (mostly
intact aggregates, little breakup) to orange (good breakup) can be observed as the pigment is de-agglomerated within the lactose matrix (Fig. 1).

![Fig. 1: Schematic of iron oxide pigment dispersion (a-b) and de-agglomeration (b-c).](image)

This colour change of iron oxide when de-agglomerated has been observed in other studies (Lim, 2003, Satoh et al., 1993, Tsugita et al., 1985) and was attributed to the exposure of unhydrated yellow primary particle surfaces within the hydrated red agglomerates.

For clarity in this work, “dispersion” is defined as the mixing of pigment aggregates throughout the lactose matrix without reduction in the aggregate size (Fig. 1a-b), whilst “de-agglomeration” is defined as the breakup of pigment aggregates into smaller aggregates and or primary particles (Fig. 1b-c).

**Colour theory**

Colour analysis of blends containing iron oxide can be conducted through use of a colorimeter, which measures that reflectance pattern of electromagnetic radiation emanating from the powder sample using a particular light source (Chong, 1988). The reflectance pattern can then be interpreted to enable evaluation and comparison of the sample in a 3-dimensional colour space.

Colour information can be acquired and conveyed in several different ways (Chong, 1988, Billmeyer and Alessi, 1981, Hunter and Harold, 1987a, Hunter and Harold, 1987b). Of the many colour spaces defined in literature (Billmeyer, 1987), the most commonly used is the CIE (1976) L*a*b* (CIELAB) colour space. This colour space is widely used in colour analysis due to its ability to quantitatively compare colours and is included in the *US Pharmacopeia* since 1985. Each particular colour has a unique position in the 3-dimensional CIELAB colour space defined by its Cartesian coordinates L*, a* and b* (Fig. 2).

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*=-100). Values along the L*-axis are termed as achromatic (without hue). a* and b* values denote a colour’s comparative position in terms of red-versus-green (a*) and yellow-versus-blue (b*).

As well as analysing the degree of tint (L*) in this project, a* and b* values can be discussed in terms of the colour they produce (hue, h), and hue intensity (Chroma, C*).
A mathematical interpretation of the colour perceived by a human eye is defined by the hue angle \( h \) which in the case of iron oxide pigment can be used to express the degree of de-agglomeration (Eqn. 1).

\[
h = \tan^{-1} \left( \frac{b^*}{a^*} \right) \quad \text{(Eqn. 1)}
\]

The degree of a colour’s hue saturation \( C^* \), is defined as the length of a line perpendicular to the \( L^* \)-axis to the colour’s value in the CIELAB colour space (Fig. 2) and is an expression of the degree of pigment dispersion (Eqn. 2).

\[
C^* = \sqrt{a^{*2} + b^{*2}} \quad \text{(Eqn. 2)}
\]

Values of \( C^* \) and \( h \) help to enable comparison between colours and make the CIELAB colour space widely recognised as the international standard for quantifying colour (Chan, 2006).

**Previous work in iron oxide colour change**

Several studies have previously used iron oxide pigment to analyse the extent of mixing.

A study of colour changes in cosmetic foundation powders containing different iron oxide pigments (Tsugita et al., 1985) was devised to analyse the change in colour of white-based formulations when applied to a surface by hand.

Lim (2003) used iron oxide pigment in their mixing process as a preliminary scoping tool to determine the mixing time at which sufficient mixing had occurred. The change in blend colour in the 3-dimensional CIELAB colour space was analysed over time until a constant blend colour was achieved.

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 (Iwasaki and Satoh, 2002, Iwasaki et al., 2003, Satoh et al., 1993, Satoh et al., 1994, Satoh et al., 1998, Sugai et al., 1997).
Satoh and co-workers began with an initial study to characterise mixer types based on process intensity (Satoh et al., 1993). They tested the novel method of 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” ($\eta$) scale, which was the ratio of various powder and blend’s $L^*$-values and directly proportional to measured voltages of the photometer.

Using the $\eta$-factor, Satoh et al. (1993) were able to classify powder blending equipment based on the shape of curves generated when plotted against mixing time ($t$). For each process a distinct family of curves were observed (Fig. 3).

![Fig. 3: Relationship between degree of dispersion ($\eta$) and mixing time ($t$) for three types of mixing processes - rotary screw (A), high speed and shear type (B) and rotary vessel with impeller (C) (Satoh et al., 1993).](image)

An extension study also analysed $\eta$-curves around high shear mixers (Sugai et al., 1997), in which $\eta$ was linked to blade speed, chopper speed, mixing time and fill level.

It is implied from the previous studies of Satoh and co-workers that the pigment disperses through the lactose but does not de-agglomerate, in which the use of only the $L^*$-values to analyse the blend is reasonable. However, since de-agglomeration and dispersion are likely to occur concurrently in most real mixing processes, it would be more accurate to express the quality of the blend in terms of both dispersion and de-agglomeration, as the blend’s lightness $L^*$ decreases with pigment dispersion but increases with blend de-agglomeration. Thus, $L^*$ is not sufficient for understanding the balance between dispersion and de-agglomeration.

**Novel approach to this study**

Through colour analysis of an iron oxide blend (i.e. analysis of the blend’s $a^*$ and $b^*$ values), the degree of dispersion and the de-agglomerate can be measured simultaneously and independently. The $a^*$ value represents the redness of the colour, and the $b^*$ value represents the yellowness. Based on the hypothesis in Fig. 1, if a line drawn between two consecutive samples in the $a^*-b^*$ plane passes through the origin, iron oxide is only being dispersed through the powder, but if the line intercepts the $a^*$-axis, then de-agglomeration has also occurred. In this manner we can gain more information from the iron oxide blends than previously attempted, namely through utilisation of the entire CIELAB (1976) colour space.
rather than the $L^*$-axis alone. This concept is a new and novel extension of the previous colour work, in which only the lightness of the blends ($L^*$) were used as an analytical tool.

**DESCRIPTION OF EXPERIMENTAL SETUP**

**Blending equipment**

Two different batch mixers were used in this study to simulate different mixing processes, namely a low-shear tumbler and a range of vertical axis high-shear mixers.

**Formulations used**

Two formulations were used in this study due to limitations in lactose. Both formulations comprised of 1% (w/w) iron oxide (Ferroxide™ micronized high-purity red iron oxide, Rockwood Pigments, Australia) and 99% (w/w) lactose. Formulation 1 comprised of 1% (w/w) iron oxide, 19% (w/w) fine lactose (Lactohale LH230, DMV-Fonterra, Germany) and 80% (w/w) coarse lactose (Respitose SV003, DMV-Fonterra, Germany). Formulation 2 comprised of 1% (w/w) iron oxide mixed with 99% (w/w) of a single lactose (Lactohale LH200, DMV-Fonterra, Germany). Particle size distributions for each formulation’s lactose components and raw iron oxide pigment were collected using laser diffraction (*Malvern Mastersizer Scirocco 2000, Malvern Instruments Ltd, UK*) (Fig. 4).

![Particle size distributions of lactose in each formulation and raw iron oxide pigment using laser diffraction](image)

Fig. 4: Particle size distributions of lactose in each formulation and raw iron oxide pigment using laser diffraction

**Experimental design**

Tumbler blends using Formulation 1 were manufactured in a 0.3 litre Turbula ‘figure-eight’ tumbler at five different rotational speeds (34, 49, 72 and 101 rpm).

A high-shear mixer blend was also created using Formulation 1 at 235rpm and using a lab scale (KG5 high shear mixer, 1 litre bowl) mixer. Due to limitations in materials, Formulation 2 was used for the other three scales of high-shear mixer (25, 65 and 100 litre mixers). The 65 litre mixer was operated at two different impeller speeds (200 and 400rpm) whilst the 25 and 100 litre were operated at a single arbitrary speed (600 and 200rpm respectively).
For all mixers, small samples (approx. 10g) of the blends were sampled as a function of mixing time and the colour of the blends analysed.

Tumblers and the 1 litre high shear mixer were analysed after completing up to 60min of mixing time, all other high shear mixer blends were analysed up to 23min.

**Measurement of blend colour**

The blend’s colour values were recorded in the CIELAB (1976) colour space using a benchtop colourimeter (ColorFlex EZ 45/0, HunterLab Inc., USA). Samples of blend were taken at set time intervals and recorded using a large transparent sampling cup (approx. 6cm in diameter and 3.5cm high). Average values were recorded from four readings taken through 90° rotations of the sampling cups.

**RESULTS**

The change in the powder blend colour values over time shows the generation of different curves in the $a^*$-$b^*$ plane of the CIELAB (1976) colour space (Fig. 5).

![Fig. 5: Distinct curves formed from analysis of changes in $a^*$ (red) and $b^*$ (yellow) values over time for tumbler and high shear mixer (HSM) processes.](image)

For the same process, $a^*$ and $b^*$ values increase over time and appear to follow a curve which is unique to the mixing process and independent of process scale and intensity, similar to the findings by Satoh and co-workers.

The curves generated for tumbler and 1L HSM bowl versus the larger scale (25-100 L capacity) high shear mixer processes are different, suggesting that there are differences in the mixing mechanics and quality of the blend after mixing.
The initially constant slope of the tumbler and 1L mixer lines represents a constant hue, suggesting that their mixing was largely dispersion-based. Towards the end of the mixing, the tumbler blend begins to turn slightly orange and slope of the line increases, as the $b^*$ value (representing yellowness) starts to increase relative to the $a^*$ value. This implies that dispersion dominated the mixing process until near the end of experiments, when some de-agglomeration began. The small scale (1 litre) high shear mixer appears to show the same properties as the tumbler curve, however at the end point a slightly higher level of de-agglomeration is achieved.

For the HSM blends, the slope of the line is much higher, indicating that the iron oxide powder are being dispersed and de-agglomerated simultaneously. This implies more vigorous and effective mixing of the iron oxide through the powder blend.

DISCUSSION

Abilities of iron oxide pigment

The use of iron oxide as a coloured tracer agent appears to be a beneficial in gaining more information about a given mixing process and set of operating conditions, and provides a quick and cost-effective means of preliminarily scoping effective process technology, scale and operating conditions. Pharmaceutical industries constantly require the upscale or resizing of manufacturing processes due to varying demands for their products and limitations in the availability of process equipment on site. There is certainly potential with such a system to analyse coloured blends in different processing equipment and gain a quick feel for the design space of a piece of equipment, and the appropriate conditions between process scales to ensure the same level of fine particle dispersion and de-agglomeration. This would save time and resources for industry.

Of particular interest in this work is the fact that the large scale high shear mixers generated a single curve in the $a^*$.-$b^*$ plane, despite having a significantly wide range of scale (25-100L) and being dimensionally dissimilar (i.e. with different length and height ratios) both in the vessel and impeller. It is unclear at this stage why each process was able to fall on a single curve, but the result shows promise in enabling process design between two mixers of the same type to ensure mixing equivalence despite having dimensionally dissimilar mixers.

The lab scale (1L) high shear mixer curve may not have fallen onto the curve of the larger scale high shear mixers due to the mixer’s unusual impeller and non-standard design. Whilst the 25L, 65L and 100L contain fairly standard three-bladed impellers, the 1L impeller is a completely different design, similar to a short and fat toothed gear. The 1L impeller also occupies a much larger proportion of the free space in the mixer and would have had a significant influence on the powder flow.

From preliminary results the iron oxide tracer appears to have potential to provide information about the dominant mixing kinetics (i.e. whether de-agglomeration or dispersion are driving the process) over any given time period and set of operating conditions given the slope of a process curve generated in the $a^*$.-$b^*$ plane. However, a slightly different grade of lactose was used in the large scale HSM (Formulation 2) compared to the lactose used in Formulation 1, which was blended in the tumbler and 1L mixer. Although the particle size distributions were very similar, the different mixing curves could be attributed either to the different mixing processes used or simply to the differences in the powders being blended. Given the large
physical differences in the tumbler, 1L mixer and the larger scale high shear mixers, we expect the differences observed in Fig. 5 are due to the different powder flows and particle interactions generated by the differences in mixer design. However, further experiments using a single formulation are planned in the future.

**Sensitivity and limitations of iron oxide**

Whilst iron oxide appears to be an effective means of analysing mixture quality and mixing behaviour there may be some limitations to its use, namely as an effective pharmaceutical active mimic and its sensitivity to atmospheric conditions.

Whilst iron oxide does not have the same adhesion/cohesion properties of organic active pharmaceutical ingredients, the mixing behaviours viewed are believed to be similar to those of pharmaceutical active powder of similar particle size and de-agglomeration mechanism. As red iron oxide also has a similar particle size to many drugs (of ~0.1-1 µm) it is thought that it makes a good particle substitute for a wide range of active ingredients.

The colour values of iron oxide pigment have been observed to be sensitive to relative humidity (during mixing) and post-mixing storage conditions (relative humidity, temperature) and time. The degree of sensitivity is not currently known and appears to be slow change over several days but would be an important factor in the viability of this method. The influence of each was mitigated in this work by ensuring that all blending occurred in a specific relative humidity range (40-60%) and that samples were analysed quickly after manufacturing, typically within 30 minutes.

**Future work in pigment analysis**

As these preliminary findings have shown promise, the next logical step is to test the sensitivity of the iron oxide pigment to relative humidity, temperature and time. It would also be beneficial to analyse blends manufactured in other processes and process conditions to observe the versatility of the pigment and to conduct further studies on the influence of powder formulation on the process curves generated. Analysis of the pigment interactions with bulk powder would also help to determine whether iron oxide is an effective mimic of pharmaceutical active powders.

**CONCLUSION**

In this study several blends of lactose and iron oxide pigment were manufactured in both tumbler and vertical-axis high shear mixers at different scales and operating conditions to analyse the mixing behaviour and mixture quality over time. From analysis of the CIELAB (1976) colour values, two distinct curves were generated for each type of mixer which appear to be independent of process intensity and scale. These process curves are able to identify the quality of the blend both in terms of the degree of pigment dispersion and pigment de-agglomeration and ultimately have the potential to be used as a time and cost effective means of assessing a given process and set of operating conditions to ensure the desired degree of mixing and enable effective process scaling. Current findings are only preliminary however and further testing is required to ensure that the use of iron oxide is valid in simulating the mixing of pharmaceutical powders and providing robust results.
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