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Transforming Pharmaceutical Manufacturing Advanced Techniques for Enhancing Powder Mixing Productivity Revealed

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Abstract

In the production of pharmaceuticals, powder mixing is an essential step that guarantees the consistency of powder formulations (drugs and excipients) prior to their conversion into capsules or tablets. Currently, an empirical trial-and-error methodology is extensively relied upon for powder mixing process modifications and scale-up.

The goal of this thesis is to replace this haphazard approach more methodical design-based one. Prior studies have demonstrated that the combination of 1% red iron oxide tracer and 99% lactose powder causes a characteristic color change, going from pink to red and finally to orange. Similar color points in tumbler, high shear, and mechanofusion mixers have been validated by spectrophotometric measurement, and this color shift has been seen in a variety of mixer types (for example, the blend color at 45 minutes in a tumbler matches that at 20 minutes in a high shear mixer). This thesis aims to explore the potential of the color tracer method and its applicability in the pharmaceutical industry. The accuracy of the color tracer method was reviewed in the first chapter, showing its resilience with little variation in color when mixed. Additionally, it was found that 0.5–1% was the ideal concentration and that various mixer types—such as tumblers and high shear mixers—produced color endpoints that were constant and made for useful comparisons. Furthermore, different lactose types were found to display their distinct color curves. Testing various iron oxide tracers, such as the red, purple, black, and yellow varieties, was covered in detail in the second chapter. Because of its stability at mixing temperatures, small particle size for efficient powder coverage, low concentration requirements, and wide color range during mixing, red iron oxide turned out to be the best option. This chapter also shed light on the peculiar color change of the red iron oxide-lactose mix, explaining that it is caused by the orange color of the individual red iron oxide primary particles, which gives rise to the final orange blend. Previous studies on iron oxide color particles revealed that the characteristic orange hue is caused by the size and shape of the particle scattering particular light wavelengths. The third chapter expanded the application of the color tracer method by testing it with various white organic excipient powders besides lactose, including HPMC, MCC, mannitol, and PVP. These excipients displayed similar blend color changes but exhibited their unique color curves, demonstrating the versatility of the color tracer method.

The fourth chapter investigated the possibility of predicting the mixing time point for content homogeneity in the Ventolin formulation using the color tracer approach. The comparison of equivalent blend color points from two distinct mixers—high shear and tumbler—was used to arrive at this conclusion. The color tracer method may be a workable way to scale up mixing procedures, according to the results.

In conclusion, the findings in this thesis provide strong support for the adoption of the color tracer method in powder mixing within the pharmaceutical and solids mixing industries. This innovative approach has the potential to revolutionize the scale-up process and move away from the traditional trial-and-error method.

Keywords: Spectrophotometric, Excipients,Red Iron Oxide, Mixer, HPMC, Mannitol, PVP, etc.

Introduction:

Blending of dry powder is an essential step in many manufacturing industries including food, construction, mining, chemical, agriculture, and pharmaceutical. In pharmaceutical production, the blending step involves mixing drugs with excipients (e.g., diluent, flow agent, etc.). These blends are then made into dosage form (i.e. filled into capsules or tableted). If mixing is not performed correctly, it can cause content uniformity issues, particle and powder damage, and drug delivery issues, which results in discarded batches, reduced production rate, and poor economic performance (Muzzio et al., 2004). Mixing of powder formulations is mainly repetitive and based on empirical work, which limits the expansion of production lines, preventing reductions in production costs, and limits understanding of failed batches. Research in the pharmaceutical industry aims to reduce Mixture and process variability and improve scale-up production, which would be achieved by enhancing design and optimization. a Color tracer method for pharmaceutical blending, using red hematite iron oxide as a tracer (Barling et al., 2014). The investigation showed that mixing iron oxide (1% w/w) with lactose (99% w/w) produced a pink -> red -> orange Color curve. It also showed the same Color curve for different mixers; however, the time to reach a Colorpoint on the curve differed for each mixer tested, and the time to reach a Colorpoint depended on the mixer type, geometry, and speed. The Color tracer approach would then be examined to determine whether it might be improved and applied in the pharmaceutical sector. This effort would significantly impact the development of a design strategy for large-scale pharmaceutical mixing. The research for this thesis would first look at the precision of the Color blend and fine-tuning of iron oxide concentration, then identify the best Color tracer and explain the behavior of the Color change in the blend, then expand the applicability of the method to others excipient powders, and finally test whether the Colorpoint can identify equivalent mixing points for a formulation in various mixers.

Objective:

- To test the robustness and limits of the iron oxide tracer method to strengthen its use in the pharmaceutical industry
- To investigate different colored iron oxides as tracers to understand Color change behavior in Color blending and assess the requirements of an optimal Color tracer
- To blend other excipient powders besides lactose to test if similar Color curves are produced and therefore extend the application of the Color tracer method
- To investigate the tracer method's suitability in determining content uniformity for a particular asthma inhaler formulation and assess the method as a predictor tool for content uniformity for different mixers
- To develop a general method involving the Color tracer method that helps determine content uniformity with drug-excipient blend formulations and also with scale-up mixing.

Materials and Methodology:

This first section of the review covers mixing and powder analysis; this includes:

- Mixing behavior, mixers, and scale up
- Powder behavior and formulations
- Powder mixing analysis
- Color measurement and tracer work

The second section of the review covers dry powder inhalers (DPIs), a type of powder formulation medication; this includes:

- Inhaler devices
- DPI formulation
- DPI behavior
- DPI mixing

The last section covers the general research focus of the experimental chapters in this thesis.

Mixture

The purpose of dry powder mixing is to achieve a homogenous mixture. There are three main definitions of mixtures with varying homogeneity: perfect, random, and segregating mixtures.

Perfect Mixture

The goal of mixing is to achieve a perfect mixture. This means that a sample taken from the Mixture should have the same proportion of particles as the overall mixture concentration, making the Mixture completely homogeneous. A perfect mixture cannot be achieved.

Random Mixture

In the pharmaceutical industry, random mixtures are more achievable; a random mixture is where the probability of selecting a particle is the same at any position and equal to the proportion of particles in the overall Mixture,In industry, determining if a blend is mixed depends on the sample size and the required mixture quality. For example, A 3g dissolvable vitamin and mineral powder in a sachet, a 500mg aspirin tablet, and a 26mg capsule of asthma medication have different sample sizes, affecting the required degree of homogeneity of the powder blend. Real standard deviation (RSD), also known as the coefficient of variation, is a calculation that assesses the variability of the powder blend about its mean. In the pharma industry, RSD determines if a powder blend is mixed .

Segregating Mixture

A segregated mixture is when the overall Mixture is not well mixed; it can be caused by the powder properties and handling of the blend. If a powder has segregated, the medication (i.e., tablet or capsule) may comprise a variable amount of drug, causing an unpredictable effect and resulting in adverse consequences for the patient. If the blend powder experiences segregation during production, it would mean the batch has failed specification, which would cause a financial loss to the pharmaceutical company.

Sampling:

To assess how well a formulation is mixed, samples are taken and analyzed for homogeneity. There are

two golden rules for sampling:

- The powder should be in motion when sampled.
- The whole moving stream should be taken for many short increments.

These rules ensure that a good representation of the powder has been sampled.

In industry, however, sample thieves, who break the golden rules, are commonly used for sample collection. Sample thieves entail long cylindrical tubes that can collect samples at different positions and variable depths of the powder bed; these are discussed in detail and their associated sampling errors are discussed .

Mixing of Particles

The three different mechanisms of solids mixing are diffusive, convective, and shear; these are describe as:

- **Diffusive mixing** - the random scattering or spreading out of particles in a mixture, which is controlled by the freedom of the individual particle in response to agitation and shear.
- **Convective mixing** - the movement of particles from one location to another in the bulk of the Mixture, which is determined by the geometry of the mixer (e.g., baffles, paddles, and mixing vessel).
- **Shear mixing** - the movement of layers of particles moving over each other.
- In contrast to the three main mechanisms,considered diffusive and convective mixing the two main mechanisms, and shear mixing a combination of the two.

Comparison of Liquid and Gas

It is essential to state that the mixing of solids and powders differs from liquid and gas mixing. Noted natural phenomena that occur in liquid and gas mixing but do not occur in solids mixing:

- Molecular diffusion does not occur in solids mixing.
- Mixing of different components causes segregation in solids mixing.
- Sampling of solid mixes would be of much poorer quality (molecular size).

The dynamics of powder mixing are considered deterministic chaos, which limits predicting powder mixing from underlying principles; this is essential in understanding mixing processes.

Mixing Process and Design

stated three critical factors to consider when mixing particulate powders: the type of mixer and its design, the desired characteristics for the Mixture, and the mixing mechanism and required mixing rate.

Mixer Selection

Many different factors need to be considered in the selection of a mixer: mixture quality, particle segregation, particle modification, sensitivity of powder to shear, low or high energy input mixer, mixer temperature, number of mixing stages, continuous or batch process, mixer cost, and ease of cleaning. The major types of mixers in the pharmaceutical industry are the tumbler, rotating element blenders, and high-shear mixers.

Tumbler Mixers

Tumbling mixers mix by moving a shell or enclosed vessel around on its axis: the particles roll in rand-

om motion down a sloping surface as the vessel is rotating. These mixers are generally used for free-flowing powders and are considered not to blend cohesive powders well.Tumbling mixers are common in industry.they are advantageous due to their ability to achieve uniform blends and that they are easy to clean (minimal or no internal parts) ,Common vessel designs of the tumbling mixer are the V and Y mixer, dual cone blender, and zig-zag mixer.

Rotating Element Mixers

Rotating element mixers, also known as convective mixers, comprise a vessel and an internal rotating element, which performs the principal mixing. These mixers blend free-flowing or moderately cohesive powders. Common rotating element blenders are the ribbon, paddle, orbital screw, and the vertical screw mixer.

High Shear Mixer

The high-shear mixer (HSM) mixes by exerting a high shear on the powder, allowing for a more intense mixing, which makes it helpful in breaking down cohesive agglomerates .The high-shear mixer is used for blends that require a high degree of homogeneity. However, this type of mixer is considered challenging to empty and clean.

Continuous Blending

Some mixers can be modified for continuous blending (processing); this is accomplished by adding an inlet and outlet to the mixer for the inflow/outflow of the powder. Continuous blending can achieve more significant production rates from smaller blenders; however, most pharmaceutical production is still done with batch blenders because it allows for better control.

Scale-Up of Mixing

Scale-up of powder mixing is a difficult task, which is made more difficult with the bit of knowledge in this area .The issue with scale-up work is that it is mainly based on empirical work and simple scaling parameters . Another significant issue is that larger volumes of powder can cause much more significant compression than lab-scale volumes, affecting flowability. Factors that need to be considered for any scaling up of a mixing process, according to and Alexander and, are mixer speed (rotation), particle velocities, powder cohesion, order of ingredients added, fill level, mixing time, and mixer geometry. Using a lab-scale mixer with the same or similar geometry to the intended scale-up industrial mixer is also suitable.

Segregation

Segregation is a significant issue in the pharmaceutical industry and can cause homogeneity issues. Mixing or handling of powders can result in segregation and occurs because of a difference in powder properties.Early mixing experiments have shown that different colored sand particles with the same particle size mixed well , but a binary mixture of two different sized particles showed segregation; this was shown with different mixers: a vibration plate and a y- mixer . It was concluded that particle size, density, and shape are the main factors affecting segregation, with particle size being the most significant stated that there are four primary mechanisms of segregation:

- **Percolation** - where smaller particles move through gaps between larger particles, which results in segregated particle layers due to particle size.
- **The angle of repose** - where particles of a smaller angle of repose flow over particles with a larger angle of repose, resulting in segregated particles.
- **Trajectory segregation** - where a particle mixture is projected horizontally into the air, and different-sized particles' velocities decrease at different rates, with larger particles reaching greater distances; this causes the like-sized particles to group together in piles.
- **Elutriation segregation** - when a powder mixture comprising particles of different sizes is charged into a hopper or storage vessel, and the air in the container is pushed upwards. The velocity of the air flowing upwards is faster than the terminal velocity of smaller particles, displacing the smaller particles, which settle on top of the larger particles.

In the pharma industry, it is essential to achieve a homogenous mixture. Therefore, the particle size should be the same to avoid segregation and achieve random mixtures.

Cohesive Powders:

Cohesive powders are less likely to segregate than free-flowing powders, and the mixing process of a cohesive powder is usually slower due to the lack of particle mobility however, the final equilibrium mixture is of higher quality. Due to their nature, cohesive powders can experience some segregation due to agglomerates forming during the mixing process these larger agglomerates then segregate from the bulk powder. Fine powders are generally cohesive.

Particle Interactions

Particle interactions within the powder affect how particles flow in the mixer; this affects the bulk properties of the powder and, therefore, the mixing process. The primary particle forces that affect particle interactions are Van der Waals, capillary (moisture), and electrostatic forc

Van der Waals Forces

Van der Waals (VdW) forces are the attraction forces between the surface dipoles of interacting powder particles. VdW forces are significant between particles with a separation distance of up to 40nm.

Capillary Forces

Water molecules in the air adsorb onto the hydrophilic surface of particles; if there is enough water on the particle surface, liquid bridges form between particles and, therefore, form capillary forces. Capillary forces increase with higher humidity.

Electrostatic Forces

The electrostatic force results from the electric charges of interacting particles; the particles can be attracted or repulsed from each other. The production of these electrical charges is termed 'triboelectrification' due to the three mechanisms that induce electrostatic forces: contact, sliding, and friction of adjacent particles.

Mechanical interlocking

Mechanical interlocking is when particles during the mixing process are forcefully pushed together. The-

se particles interlock, altering their interacting surfaces, resulting in the contacting particles having large interactive forces.

Force Measurement & Analysis

Atomic force microscopy is a probe technique used to measure interacting particle forces. Demonstrated the different adhesion/cohesion forces that can be experienced by different materials in blends (lactose, salbutamol, and budesonide). Ratios were used to describe and quantify the adhesive (lactose-drug)/cohesive (drug-drug) balance and then to compare the different interacting forces between like and different materials.

Ordered Mixters

Recognized that the rate-determining step of mixing cohesive powders with very fine particulates is the breakdown of agglomerates into individual particles rather than randomizing particles. Furthermore, mixing of a small percentage of micronized sodium bicarbonate fines 3% w/w with coarse sucrose (420-710µm) showed, after prolonged mixing, uniform distribution and low % RSD values. This type of mixing was identified as ordered mixing, producing a non-segregating uniform powder blend (ordered Mixture) comprising both fine and coarse particles. It assumes that the fine particles are spreading on the surface of the coarse particles, and there would be numerous fine particles per coarse particles.

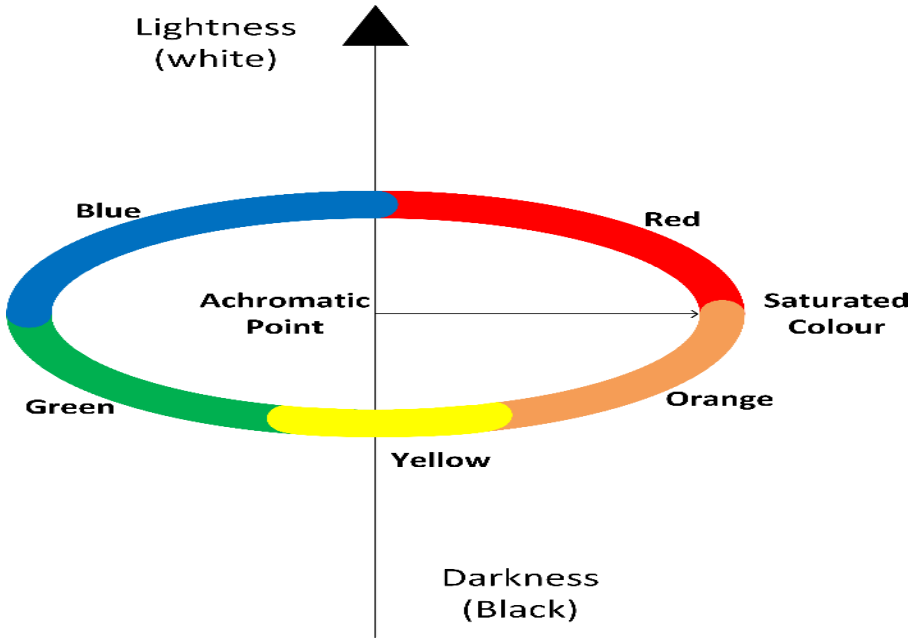

Figure 1 - Simplified CIELChcolor space

Colour Measurement

To understand color measurement, it is necessary to understand how color is categorized. Color measurement is based on how the average human perceives color ,humans have trichromatic color vision because there are three different types of cone cells (color receptors) in the human eye, The CIE (Commission Internationale de l'Eclairage/International Commission on Illumination) is an authority on light, color, and illumination. The CIE has produced color models. One of the first color systems produced, a tristimulus system. It categorizes color with the coordinates XYZ (RGB). XYZ are additive

primaries: red (700nm), green (546.1nm), and blue (435.8nm), which are similar wavelengths to the cones of the human eye, besides red which ranges 560-580nm.

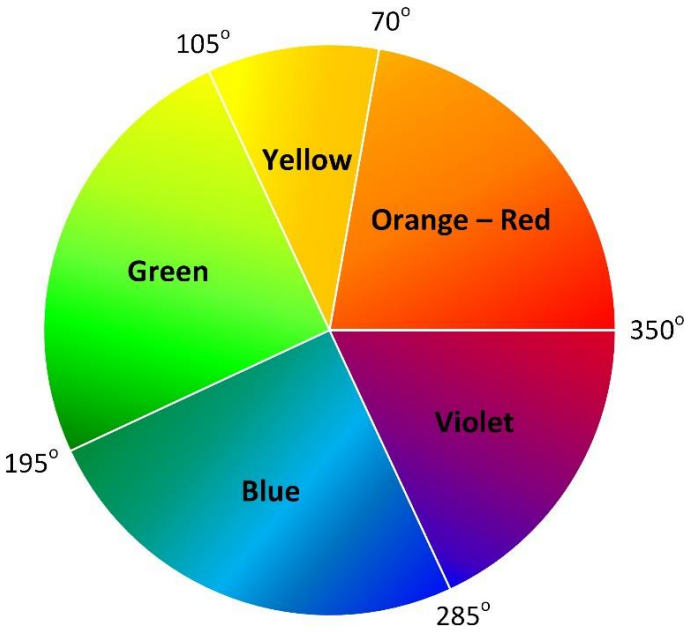

Figure 2 - Colour interpretation of the hue circle

Dispersion and Deagglomeration:

Barling linked the change in chroma (color intensity) with the dispersion of the tracer in the bulk powder and the change in hue (color) with the deagglomeration of the tracer into smaller agglomerates and primary particles.

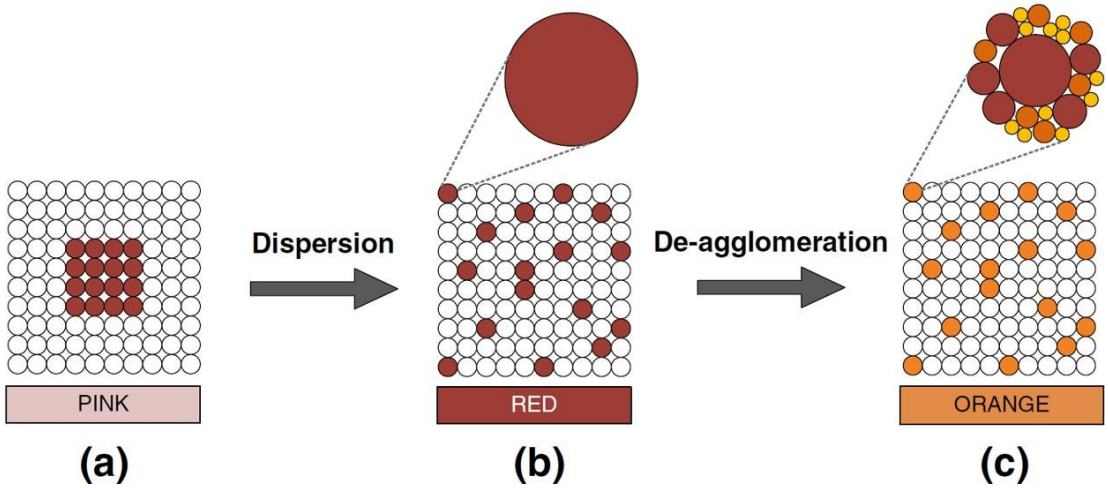

Figure 3 - Schematic of iron oxide pigment dispersion (Barling, 2015)

Barling further developed the color tracer method by identifying three different mixing regions and finding a relationship between color and mixing mechanisms.

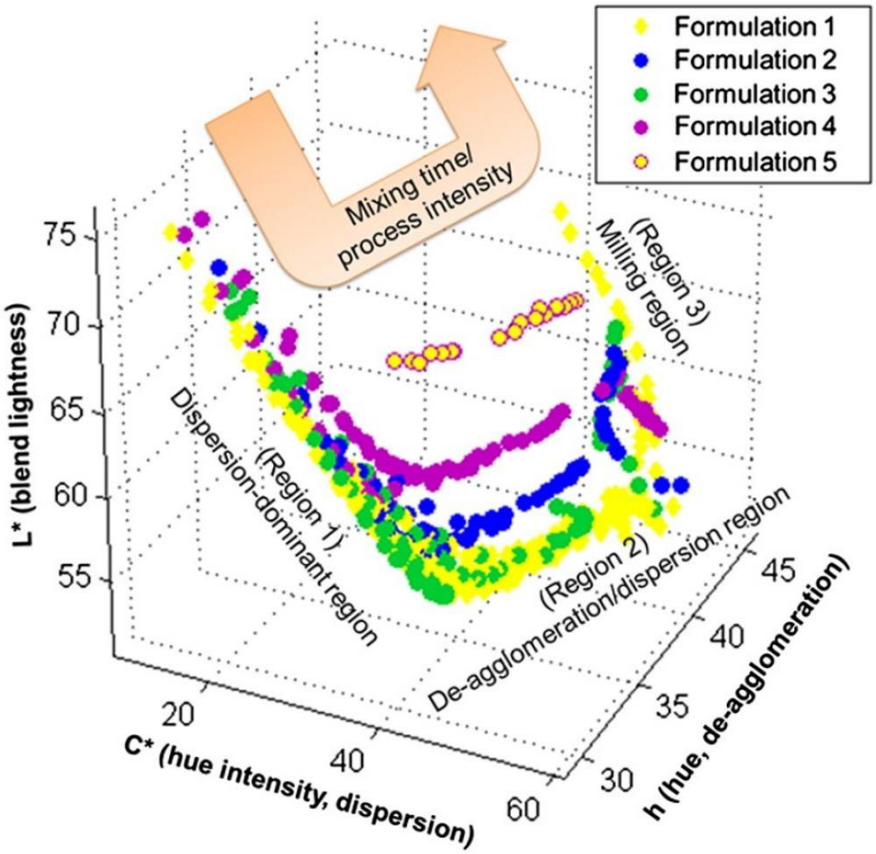

Figure 4 - The three color regions of mixing

The first region of mixing is the dispersion-dominant region. This region experiences mainly tracer dispersion, resulting in a sharp change in the blend's lightness, an increase in chroma, and little or no change in hue; this region has similar curves for different mixers. The second region is the deagglomeration/dispersion region, where there is both dispersion and deagglomeration of tracer, and therefore a change in chroma and hue. The third region is the milling region, where the upper limit of deagglomeration and dispersion has been reached. There is also significant energy input (i.e., mechanofusion) in this region so that there is damage and breakage of the bulk lactose particles; this creates new unexposed white surfaces on the lactose, increasing lightness and variable chroma and hue.

Pharmaceuticals and Dry Powder Inhalers

Powder blending is essential in the production of pharmaceuticals, as drug particles are mixed with excipients to make appropriate doses for drug delivery. The production of dry powder inhaler (DPI) blends a complex process, which requires the powder formulation to be homogenous (general dosage weight ~1-40mg and also has the appropriate characteristics for aerosolization when inhaled.

This project investigated the color tracer method, which involves mixing a small concentration (1%) of iron oxide tracer with a bulk excipient, taking samples, and measuring the color; this method was performed with different mixers. Characterization of tracers, bulk powders, and API was necessary to understand their properties and give a clearer picture of their mixing behavior. This section covers the equipment, experiments, sampling, and characterization that were performed throughout the project; this includes:

- Mixing equipment
- Mixing and sampling of iron oxide blends

- Colour testing
- Characterisation of powders

There were some variations to the experiments and sampling methods within some of the chapters, as stated in the chapter. The chapter states and covers any equipment used for a particular study.

Mixing:

Equipment

The mixing equipment used in this project were the Turbula T2C, Turbula T2F (*Willy A Bachofen AG Maschinenfabrik, Switzerland*), and the KG5 Granulator (*Key International, USA*). These mixers were selected due to their everyday use in industry, The Turbula is a low-shear tumbler mixer, has no stationary internal parts, and uses the figure eight mechanism, which causes the contents to spread over each other , A closed vessel is placed inside the cage tightened, and moved in a figure-eight motion to disperse the powder. In these experiments, glass jars were used as
Containers, The Turbula T2C was used for lactose blending

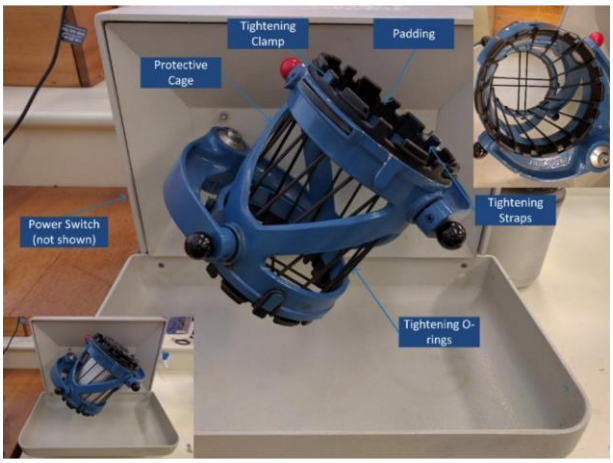

Figure 5 - Turbula T2C

The T2F is the newer model of the T2C with the exact mechanism but with different speeds: the T2C goes up to 90rpm, and the T2F goes up to 101rpm; otherwise, both Turbulas are very similar mixers. The Turbula T2F was used for excipient blending and for the content uniformity study in Chapter 7.

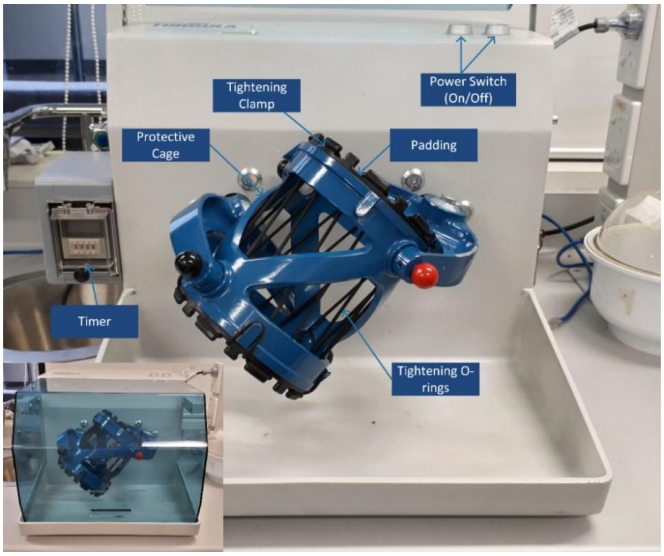

Figure 6 - Turbula T2F

MixingEquipment	MixerType	Blade	MixerSize(L)	PowderMass(g)	SpeedRange(rpm)
TurbulaT2C	Figure-eighttumbler(lowshear)	N/A	1	300-400	20-90
TurbulaT2F	Figure-eighttumbler(lowshear)	N/A	0.5	50	43-101
KG5 Granulator	High shearmixer	Threebladeimpeller	1	200-650	50-750

Table 1 - Mixing Equipment

Timing of Sampling

The time intervals for sampling the powder were every thirty seconds from 0-1 minute, every minute from 1-5 minutes, every 2.5 minutes from 5-15 minutes, every 5 minutes from 15-30, and then every 15 minutes from 30-60 minutes. Previous work found these mixing time intervals to be an efficient way to show the significant color change All blends were mixed for at least 30 minutes. If there was sampling After 60 minutes, the sampling rate was every 15 or 30 minutes until 2 hours. Afterward, the sampling rate became every hour.

Time	Sampling Rate	Number of Samples
0 -1minutes	Every30seconds	2
1-5 minutes	Every1minute	4
5 -15minutes	Every2.5minutes	4
15-30minutes	Every5minutes	3
30-60minutes	Every15minutes	2

Table 2 - Time and Number of Samples taken per Blends

Colour Testing:

Color Flex EZ

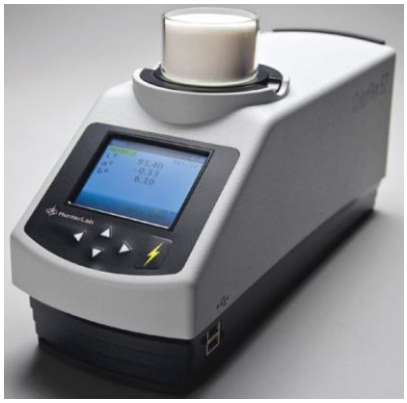

Figure 3 - ColorFlex EZ (Hunter Associates Laboratory, 2013)

The Color Flex EZ (Figure 3) was used to measure the color of the samples.The bench top spectrophotometer measures color by sending a beam of light to the sample and measuring the reflected light The properties of the ColorFlex EZ spectrophotometer are shown in Table-3

Properties	Specifications
OperatingTemperature	10 -40°C
Lightsource	PulsedXenon
Geometry	45°Illumination/0°Viewing
PortDiameter	31.8mm
ViewDiameter	25.4mm
SpectralData	Range:400-700nm ReportingInterval:10nm
SpectralResolution	≤3nm
Illuminants	D65
ColourimetricRepeatability	ΔE*≤0.05CIEL*a*b*onwhitetile
ColourScales	CIEL*a*b, HunterLab, CIEL*C*h,CIEYxy,CIEXYZ

Table 3 - Key Properties of the ColorFlex EZ Spectrophotometer (Hunter Associates Laboratory, 2013)

Result and Discussion:

This chapter tested the tracer color method's applicability and its limits. This was done by testing the following:

- Colour tracer precision
- Mixing color range
- Iron oxide tracer concentration range
- Colour behavior for different lactose grades

shows the high precision and reliability of the mixing color curve due to the low variability with both the HSM and tumbler mixer.

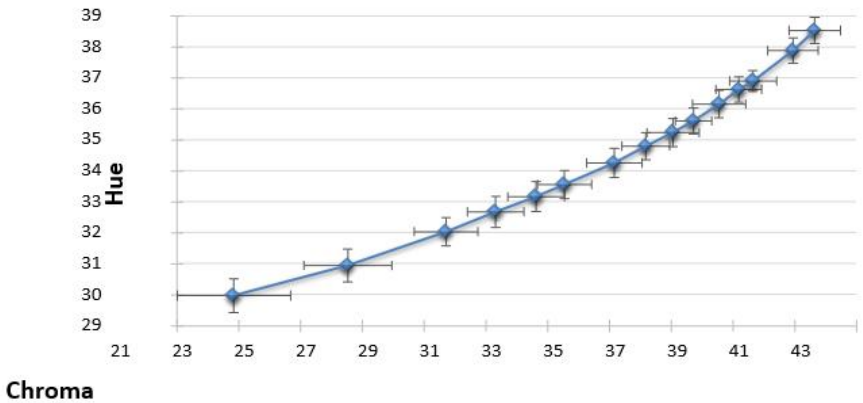

Figure 4 - Repeated runs of 1% iron oxide with lactose at 185rpm in an HSM (7 Runs) for 60 minutes (Figure-4)

Showed that there is an extensive color range for both high shear (HSM) and low shear (tumbler) mixers, with both the tumbler and HSM reaching the same color endpoint. This indicated that the tracer color method allows for comparing relative mixing energy input.

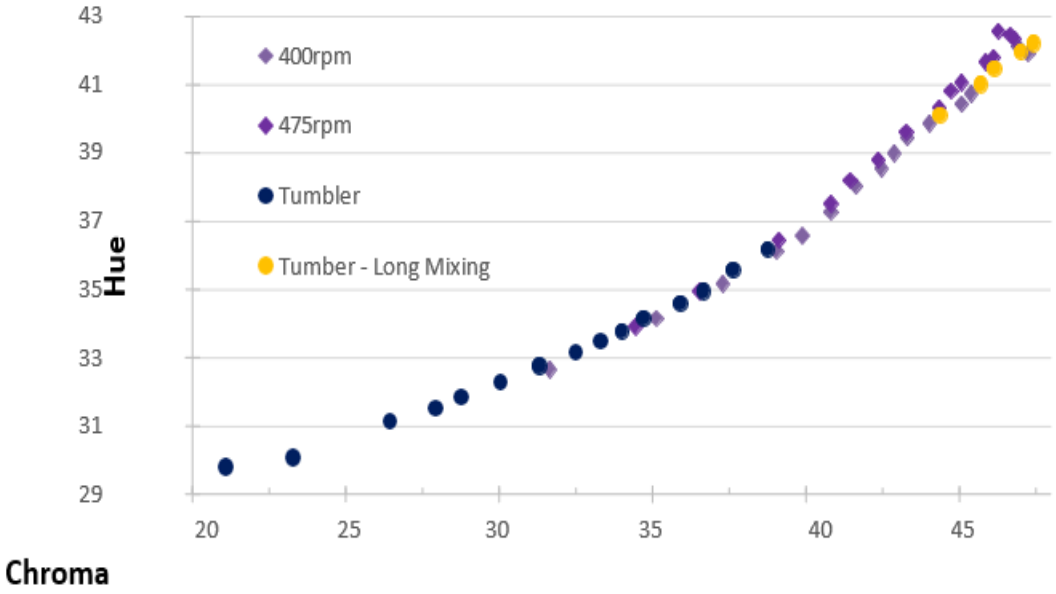

Figure 5 - Mixing and color endpoint for tumbler and HSM (Figure 5)

Figure 5 indicates the necessary tracer concentration for a significant color mixing range (0.5-1%).

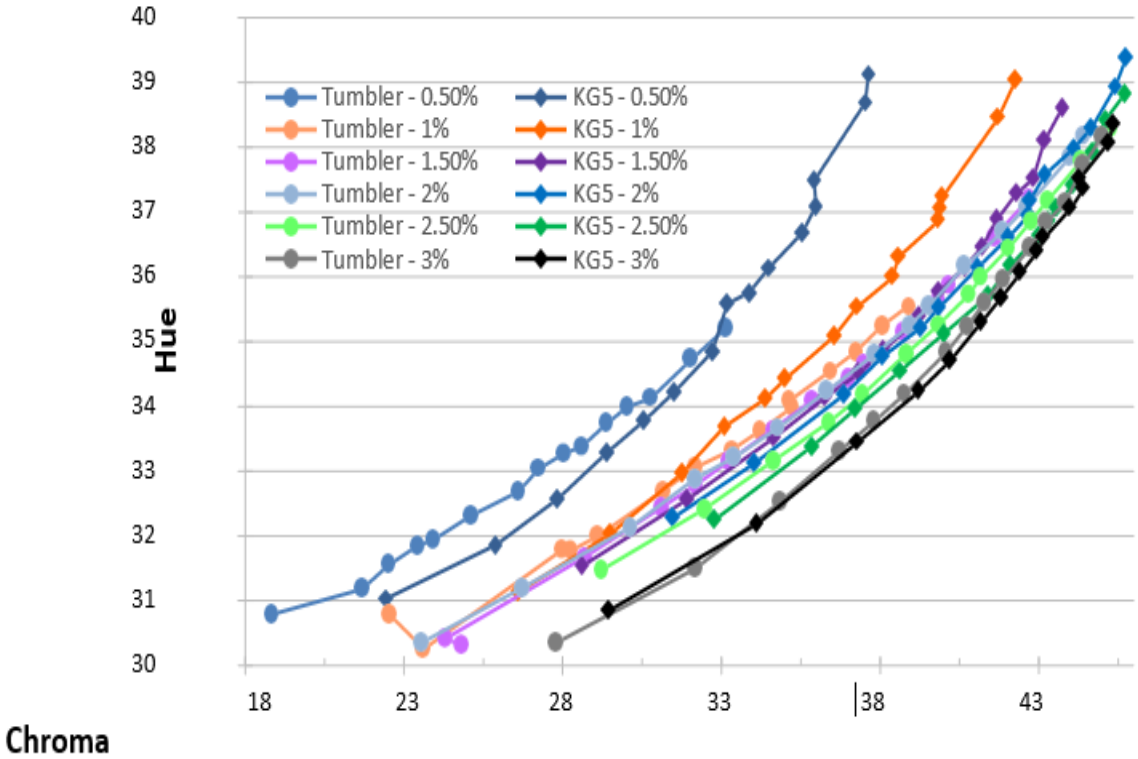

Figure 6 - Both high shear and tumbler mixing of different iron oxide concentration

Overall, this work showed the precision, extensive mixing color range for different mixers, tracer concentration limits, and the ability to use the method with different lactose powders.

The tracer method showed that the uniformity color point was similar for both mixers, as shown in Figure 7

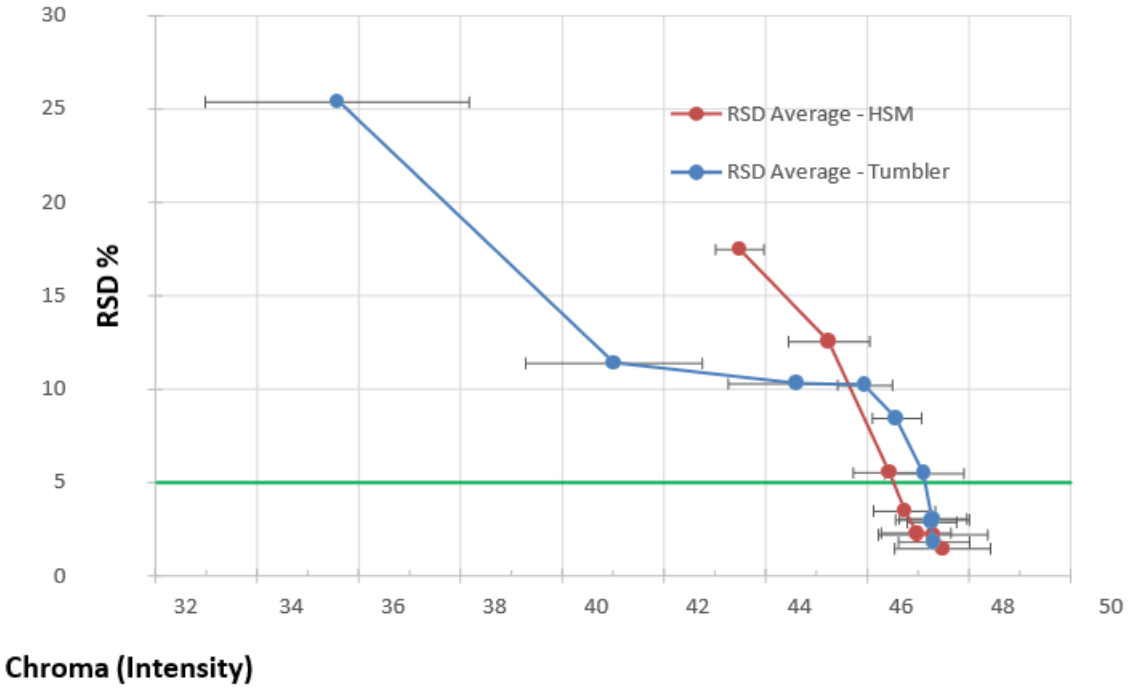

Figure 7 - Average RSD (HSM & tumbler) vs. chroma point

Formulations from different blends attained content uniformity around the same general color point (46.5 – 47.2).

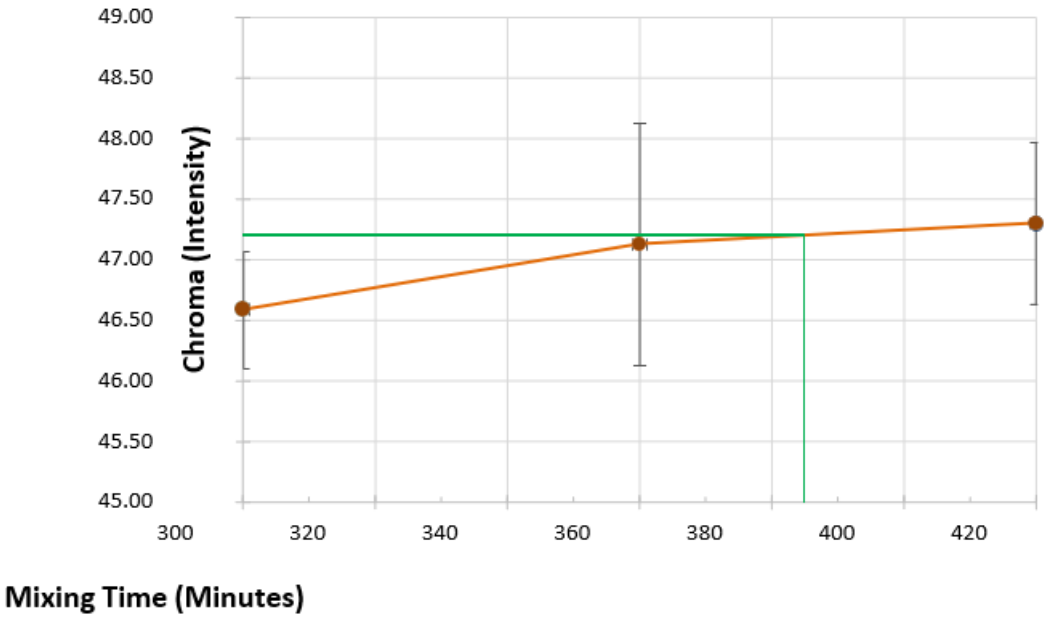

Figure 8 - Tumbler Colour Curve (300-420 minutes)

The work from Chapter 7 indicated that the color tracer method could be used to determine mixing time for a wide range of mixers. This was shown with the CU mixing point for the tumbler and HSM being 385 and 50 minutes, respectively

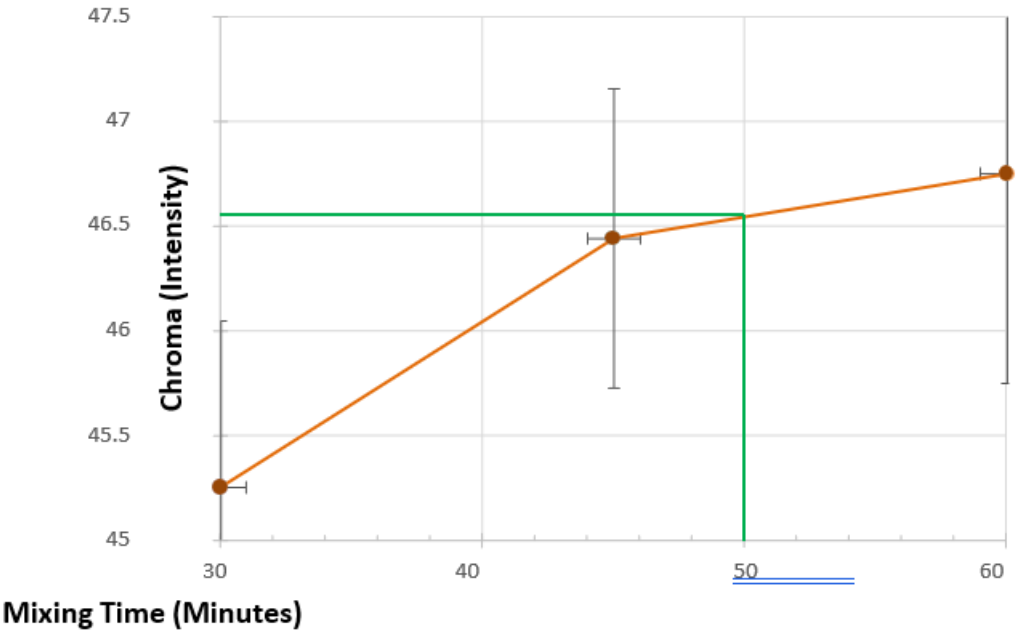

Figure 9 - HSM color curve (30-60 minutes)

Conclusion:

Mixing in the pharmaceutical industry is a critical step in medication production and is mainly based on a trial-and-error approach. This approach implies there is missing knowledge and understanding in mixing and content uniformity. Therefore, the focus of this work was to improve pharmaceutical powder mixing, scale up, and develop a design approach to mixing in manufacturing.

Previous work has shown mixing 1% red iron oxide, and lactose produces a pink to red to orange blend over time. Mixing this formulation in different mixers produces the same color curve, but the same color points were reached at different times; the time to reach a color point depends on the type of mixer and mixing speed. This led to investigating whether this could be useful in the pharmaceutical industry, especially in comparing mixer energy input and, therefore, predicting content uniformity using equivalent color points from different mixers.

This project investigated and developed the color tracer method and tested its application. This work showed the color tracer method to be robust, precise, extensive, and applicable to various pharmaceutical powders. It also identified the optimal color tracer and explained its blend colorbehavior. The work also developed the method and tested if it could predict the content uniformity mixing time for the Ventolin formulation.

Overall, the work showed that the tracer method could be applied to mixing different powder formulations in the pharmaceutical industry. This development could change pharmaceutical manufacturing by moving from the trial and error approach to a design approach, especially from lab-scale to industrial mixing. This change would improve the mixing stage by reducing the risk of content uniformity issues, particle damage, and medication performance. Therefore, it would improve efficiency in terms of time and money and allow for more flexibility in process manufacturing.

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