

# Quantifying Agglomerates in Pharmaceutical Powder Blends using X ray micro CT

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## Aims

Pharmaceutical dosage uniformity is an essential attribute of a safe and efficacious drug product. For dry products (e.g. tablets), powder blending processes are designed to produce a homogeneous mixture of active pharmaceutical ingredient (API) with other constituents (excipients). Homogeneity is compromised if the API powder form contains large resilient agglomerates that survive during the blending process. This is especially true for low-dose drug products where a single agglomerate may account for an appreciable percentage of the entire dose. Unfortunately, no effective analytical methods are available to detect the rare occurrence of API agglomerates. X ray micro CT on the other hand was successfully used to visualize and measure the survival of agglomerates in powder mixtures during blending operations. This technique shows promise as a potential replacement for traditional HPLC techniques for measuring blend uniformity.

## Method

For some formulations, the API and the excipients tend to have similar X ray attenuation properties and cannot be readily distinguished by X ray CT. Therefore, red iron oxide powder was used as a surrogate for API in these experiments. Red iron oxide ( $\text{Fe}_2\text{O}_3$ ) is supplied as a fine, cohesive powder containing agglomerates of varying sizes that can be broken with a spatula or compression with fingers but do not break from standard tumble-bin blending operations.

Excipient powders were mixed with red iron oxide (0.5 wt%) at 15-L scale in a tumble bin equipped with an intensifier bar. The intensifier bar rotates at high speeds inside the tumble bin and aids the blending process by breaking and dispersing agglomerates. Two intensifier bar speeds were used: 2000 and 3477 RPM. Powder samples were collected after different numbers of rotations of the tumble bin (e.g. 5, 10, 15, 20 rotations).

For each sample, approximately 10 grams of powder was placed in a plastic container and analyzed by X ray CT. The 10 gram samples were equivalent to more than 70 individual dosage units.

X ray CT details:

Instrument	Skyscan 1172
X ray Settings	100 kV 100 $\mu\text{A}$
Filter	Aluminum 0.5 mm
Projection image size	1000 x 524
Pixel Size	34 $\mu\text{m}$
Exposure Time	316 msec
Scan Time	15 min (with 8 fold frame averaging)

The size of the agglomerates of interest was greater than 150  $\mu\text{m}$  so, coupled with the large sample size and the need for rapid analysis, 34  $\mu\text{m}$  was determined to be the appropriate pixel size.

A sample that contained no iron oxide (placebo) was used to calibrate the dynamic range for the reconstructions of the X ray CT scans. Image segmentation of the agglomerates was accomplished simply by using a global gray scale threshold. The threshold was set by using the "placebo" sample again and selecting the lowest value which just excluded all pixels within the placebo.

Individual 3D object analysis was then performed on the binarized reconstructed slices.

## Results

Examples of X ray projections for samples obtained after different numbers of tumble bin rotations are shown in Figure 1. The attrition in the number of agglomerates is clear by visual inspection of the images.

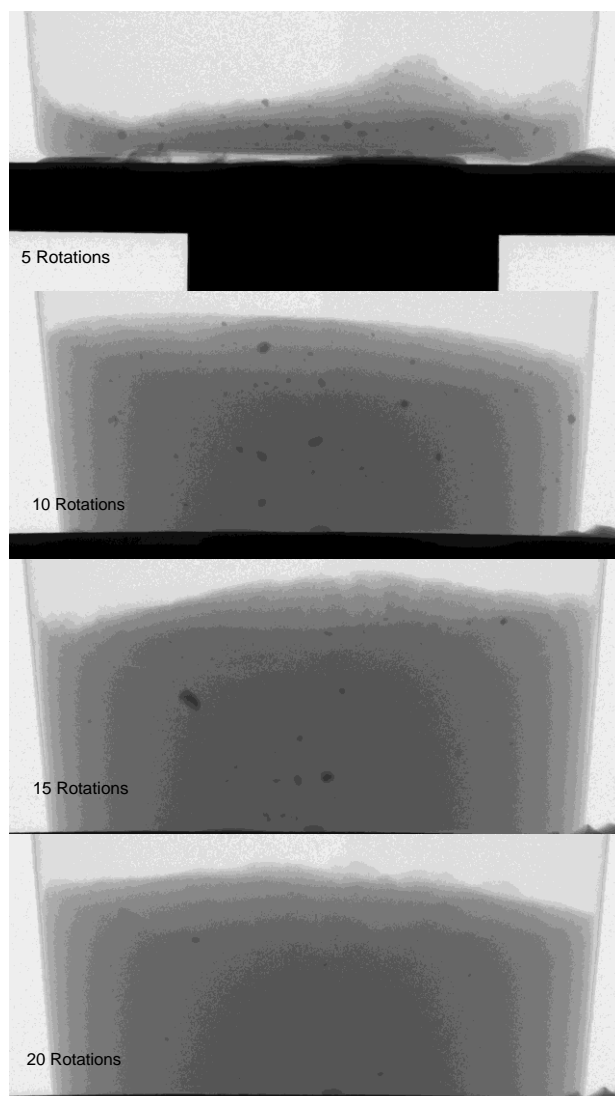


Figure 1: X ray projections of sample cups containing powder collected from tumble bin blender after 5, 10, 15, and 20 rotations with an intensifier bar speed of 2000 RPM. The cups are  $\sim 3\text{cm}$  in diameter. Dark pixels represent higher attenuation.

A 3D volume rendering of a typical reconstructed data set is shown in Figure 2. This is an initial sample of the powder that has been tumble-bin blended without using the intensifier bar, and so the agglomerates are large and numerous.

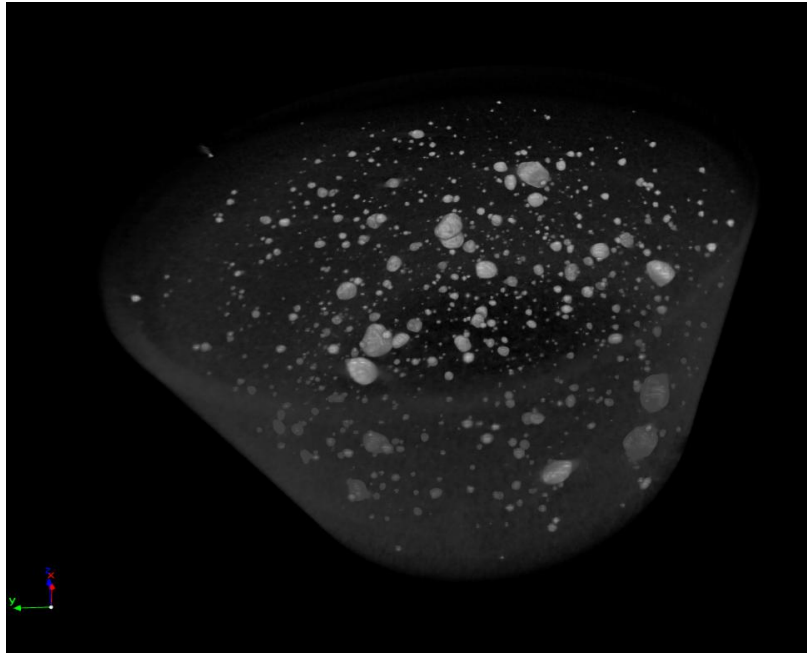


Figure 2 Volume rendering of X ray CT of agglomerates in a sample prior to with intensifier bar blending.

Data were collected for blending runs using two intensifier bar speeds. After reconstruction and processing, the 3D individual object analysis results were exported to Excel and the distribution of size and number of the particles and their relationship with tumble bin rotations for one of the intensifier speeds is shown in Figure 3. The fact that the lower size range particles do not increase in frequency indicates that agglomerates are reduced to particles smaller than the lowest measurable size range throughout the blending process.

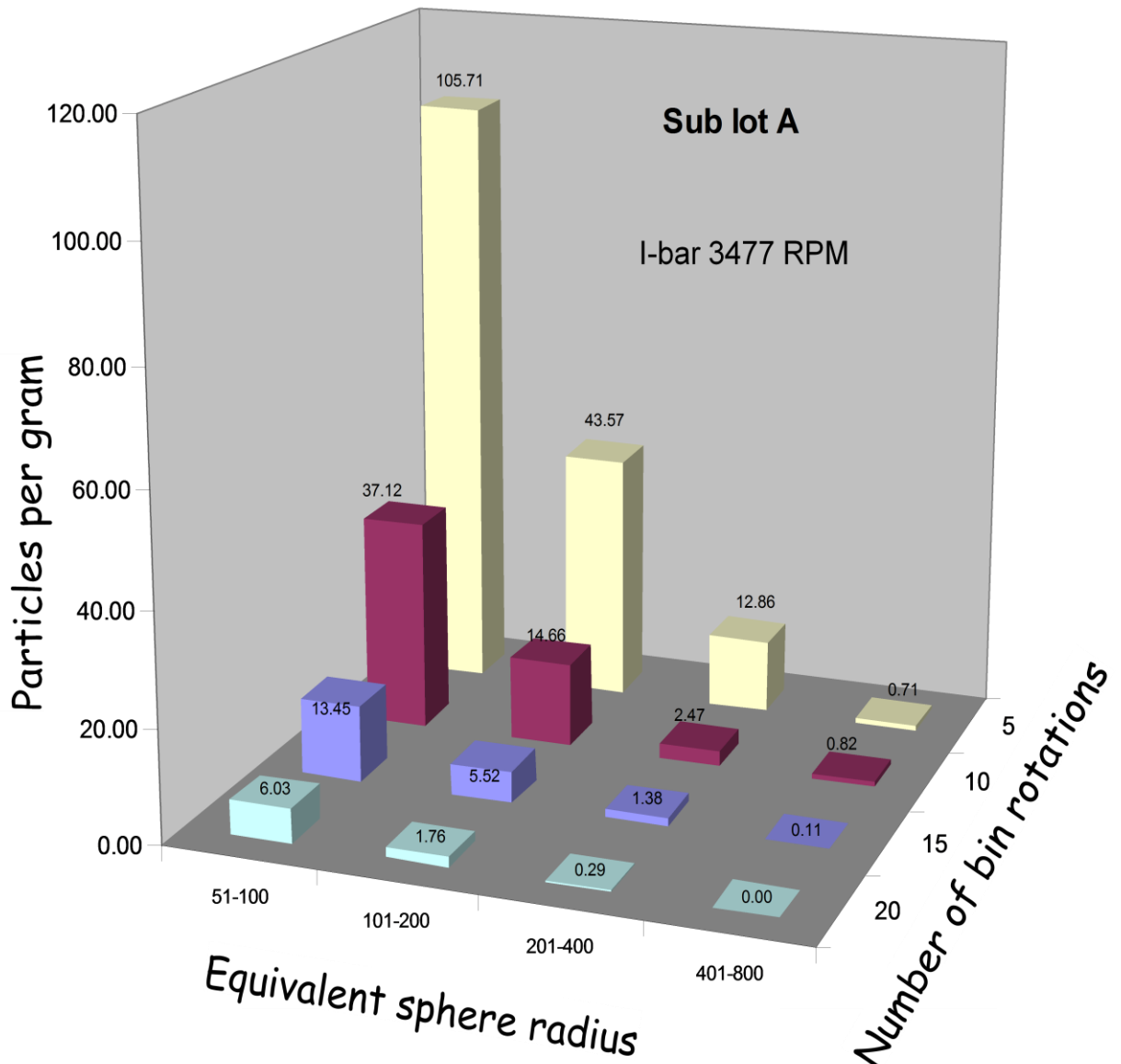


Figure 3. Histogram of the concentration of iron oxide agglomerates during blending at 3477 rpm intensifier bar speed.

Figure 4 shows the number of particles greater than 150 μm on a log scale plotted against the number of bin rotations. The two lines represent the data for the two intensifier bar speeds. The kinetics of blending with an intensifier bar has been modeled as an ideal-mixing problem (see Figure 5). The main assumptions are that the I-bar mechanically disintegrates agglomerates and continuously throws uniformly mixed powders onto a cascading surface of powder inside the tumble bin. The disintegrated powders are thus incorporated into the cascading non-disintegrated powders in a uniform way (nearly ideal mixing). A precise model predicting the kinetics of agglomerate disintegration based on the I-bar speed, volume-rate of powder flow, etc., was not developed. Instead, the basic elements of an ideal mixing model were used to predict log-linear behavior of surviving agglomerates over time.

The correlation coefficients for the lines fitted to the data points show that agglomerate survival measured by X ray micro CT is consistent with this model. An additional point was added based on agglomerates counted in an X ray radiograph of a 826 g sample in which 70 agglomerates were detected. It should be noted that 826 g is equivalent to more than 6000 individual dosage units. Detection by traditional HPLC techniques would impractical.

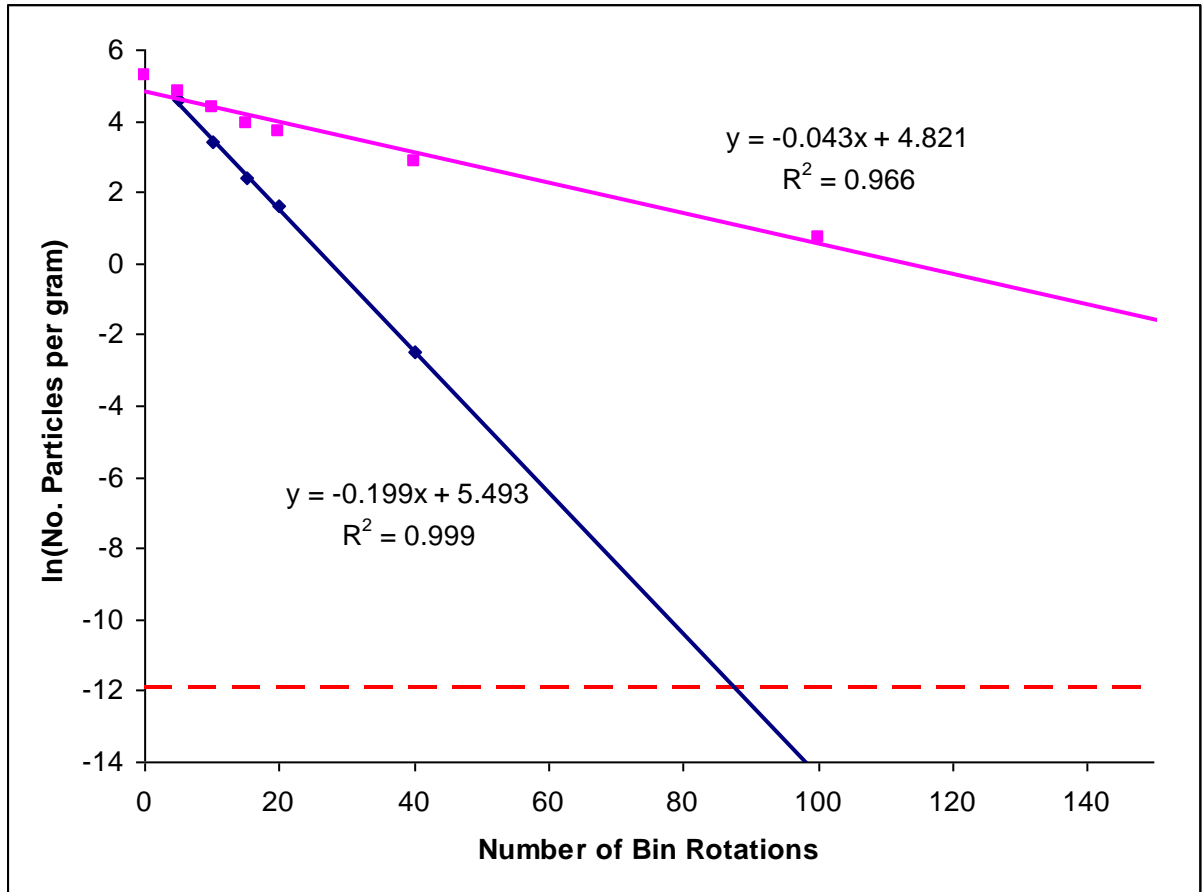


Figure 4: The number of  $\text{Fe}_2\text{O}_3$  agglomerates remaining per gram (larger than  $150 \mu\text{m}$ ) versus the number of bin rotations (note the logarithmic vertical scale). The pink data points indicate agglomerate survival at an I-bar speed of 2000 RPM. The blue data points represent an I-bar speed of 3477 RPM. The blue data point at 40 rotations represents 70 agglomerates measured in 826 gm of powder (using a single X ray radiograph). The horizontal dashed line indicates survival of one agglomerate in one million dosage forms.

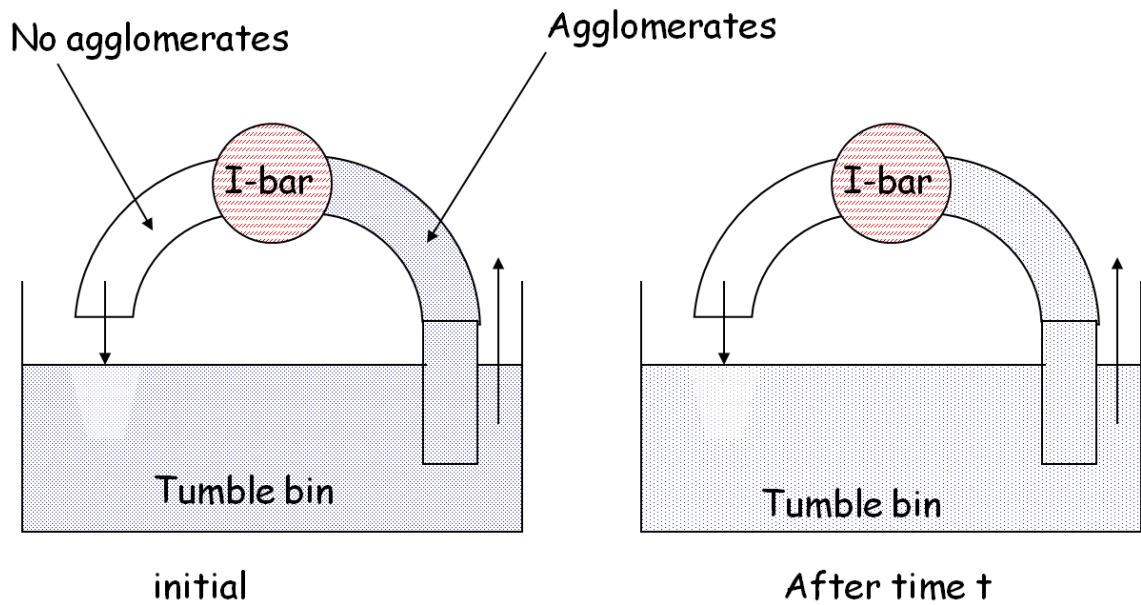


Figure 5. Explanation of the ideal mixing model used to describe the agglomerate survival kinetics of powder blending incorporating an intensifier bar.

### Conclusion

Quantitative X ray micro CT has been used to monitor the survival of agglomerates in a pharmaceutical dry powder blending process. Results support the proposed ideal mixing model of powder blending with an intensifier bar. These data provide a calibration for a specific powder operating in a specific blender at two different I-bar speeds. This work provides a basis for determining minimum required blend times for low-dose products and products with agglomerated drug substance or excipients.