Monitoring Fluid-Bed Granulation and Milling Processes In-Line with Real-Time Imaging

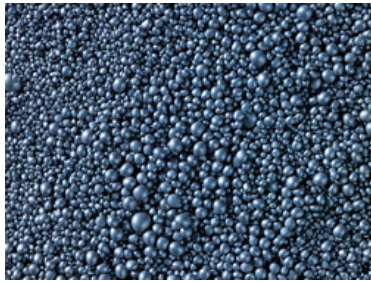Sunny/Digital Vision/Getty Images

Granulation methods are used in the pharmaceutical sector to enlarge and densify small powder particles into larger ones, typically to improve powder flow so that the material can be processed effectively and efficiently into solid dosage forms. In addition, granulation methods are important for "locking in" the API within the formulation, thereby reducing the risk of segregation. Granulated material is attained by direct size enlargement of primary particles or size reduction from dry compacted material (1).

Granule properties play a pivotal role in the final performance of the tablet; for example, granule size can affect the flowability and hence the average tablet weight and weight variation. The effect of granule size and size distribution on final blend properties and tablet characteristics is dependent on formulation ingredients, their concentration, and the type of granulating equipment and processing conditions employed. Granulation and sizing of granulation are therefore critical unit operations in the manufacture of oral solid dosage forms (2). Granulation methods can be divided into two types—wet methods, which use some form of liquid to bind particles together, and dry methods, which do not use liquid (1).

The objectives of this study were to assess the ability to measure particle size distributions under static (offline) and dynamic (on-line) conditions for milled and fluidized particles as well as to determine the following:

- A correlation with known particle size ranges for certified ceramic spheroids for at-line benchtop analysis
- Acquisition of high resolution images during a dynamic manufacturing environment
- The tracking of a fluidized bed process within a fluid-bed granulator and the ability to monitor the wetting, agglomeration, and drying phases of granulation
- A correlation between mesh size reductions and particle size distribution for polyvinylpyrrolidone (PVP) during cone milling.
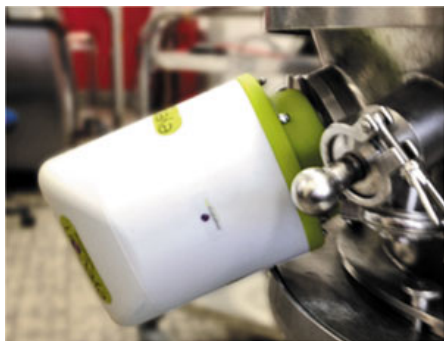
Figure 1: Image of Eyecon particle characterizer on a Glatt fluidized-bed granulator.

Materials and methods

For the off-line analysis, aluminium oxide (Al2O3) ceramic microspheres (Brace GMBH) of size ranges 212–250 μm, 500–560 μm and 900–1120 μm were tested to determine the precision of the instrument. For in-line evaluation within a fluidized-bed chamber, a placebo of microcrystalline cellulose (Avicel) and lactose was granulated. Four granulation experiments were carried out in a laboratory scale fluid-bed granulator (Glatt, model GPCG15). The formulation comprised of 33.33% Avicel 101 (BASF), 66.66% lactose 200 (Meggle). The spray solution comprised of water and 5.5% PVP 90 (supplier BASF) with an addition rate of 220 g/min using a Watson Marlow 505S peristaltic pump. Measurements were taken in real-time and the
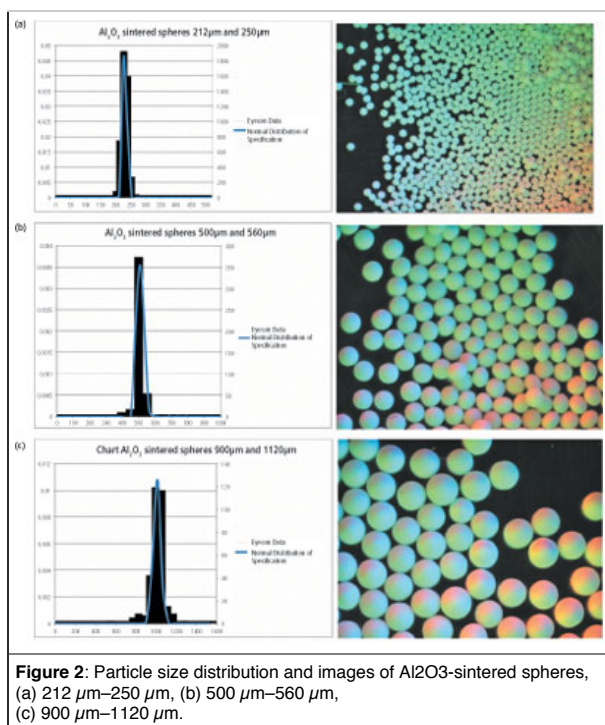
granulate growth per batch was evaluated. For the in-line evaluation of the rotary milling process, granulate that was processed by twin-screw granulation and fluid-bed drying was measured during rotary milling. During this study, granules of PVP (Kollidon 30, supplier BASF) were milled through mesh sizes of 2000, 1575, 1397, and 991 μm.

The imaging technology (the Eyecon particle characterizer) employed in this study is based on high-speed machine vision. It enables the capture of both size and shape of particles between 50 and 3000 microns. A continuous image sequence of the particles is captured using illumination pulses with a length of one microsecond for freezing the movement of particles which are moving at a speed up to several meters per second. The illumination is arranged according to the principle of photometric stereo for capturing the 3-D features of the particles in addition to a regular 2-D image. The particle size is calculated from the images using the 2-D and 3-D information, applying novel image analysis methods and direct geometrical measurement. As the approach is based on direct measurement instead of indirect, such as laser diffraction, there is no need for material based calibration. In addition, the method is non-contact and can be applied, for example, behind a view glass on a granulator without physical modification of the process equipment. Direct imaging technologies may be considered more accurate methods of measurement compared with laser and sieve analysis techniques because of the two dimensional method of measurement. These advantages of non-product contact and more accurate size estimation for in-line measurement are considered beneficial to the pharmaceutical development and manufacturing sector where reduction of cross contamination risks and accuracy of measurement are paramount. **Figure 1** provides an example of an integrated technology on a Glatt fluidized bed granulator.

Results and discussion
Summary of data from benchtop, fluidized bed and milling platforms
Experiment 1: Benchtop evaluation. Figures 2a, b, and c show the size distributions from Al2O3-sintered spheres plotted against their certified size ranges. The red line indicates a normal distribution of the sample based on defined lower and upper range specifications to 3σ. Representative images for each distribution are also presented. During experiment 1, the at-line benchtop analysis using certified Al2O3-sintered spheres of known size distributions indicates a significant level of accuracy of the imaging technology. **Figures 2a, b, and c** indicate that a minimum of 91% of spheres were calculated as being within the pre-defined supplier certified specifications. The number of Al2O3-sintered spheres measured were 4572 (212 μm-250 μm), 440 (500 μm-560 μm), and 314 (900 μm-1120 μm). Because of the tight certified distribution range for these samples, it was deemed that a low sample population was acceptable. A larger data set may be required if greater variability is present within the sample set, for example, when evaluating granulates or milled materials.


Figure 2: Particle size distribution and images of Al2O3-sintered spheres, (a) 212 μm–250 μm, (b) 500 μm–560 μm, (c) 900 μm–1120 μm.

Experiment 2: Fluidized bed evaluation. Figures 3a, b, and c show the D10 and D90 (i.e., the diameters at which 10% and 90% of the samples mass is comprised of smaller particles and mean particle distributions during fluid-bed granulation trials. All fluid-bed granulation trials were circa 40 minutes in duration. Graphs illustrating the D10, D90, and mean indicate the wetting, agglomeration, and drying phases that are typical of a fluid-bed granulation process. Other D values (D25, D50, and D75) were also tracked and similar profiles were identified. During the process, the technology successfully captured images, measured granulate size, and tracked a typical fluid-bed granulation process. The granulate size for all four batches reflected the typical granulate growth profile for a fluid-bed granulation process, including the wetting, agglomeration, and drying phases. The granulation growth trajectory (3) and end points (as illustrated in **Figure 3a**) could be monitored with this data. The variability between batches 1 and 4 versus 2 and 3 is most likely linked to variability in humidity levels during the trials as the dew point was not a controlled parameter and all other parameters remained fixed. These changes were confirmed through off line sieve analysis.

It can be seen from the particle size data illustrated in **Figures 3a-3c** that the dried granulate is of a smaller size compared to wet granulates earlier in the agglomeration process. This observation is to be expected when considering the removal of moisture and granule-granule attrition during the fluidized bed drying phase. All of the information presented in **Figures 3a-3c** could be used to develop, model, and control

fluid-bed granulation processes.
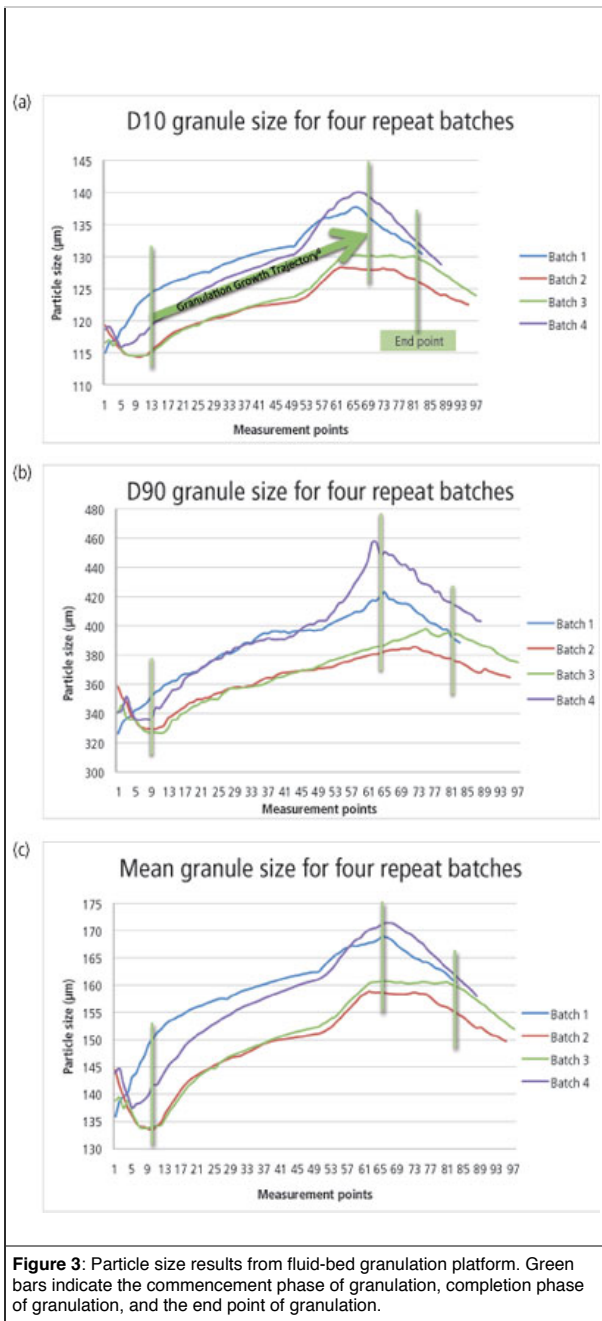
Figure 3: Particle size results from fluid-bed granulation platform. Green bars indicate the commencement phase of granulation, completion phase of granulation, and the end point of granulation.

Experiment 3: Rotary cone milling evaluation. Figures 4a, b, c, and d show the results achieved with the imaging technology during a rotary cone milling evaluation. The technology was capable of detecting the reduction in particle size of the milled material as the mesh size was reduced from 2000 μm to 991 μm as measured with D90 values. A positive correlation (weighted R^2 = 0.8696) was calculated.

The reduction in particle size was also evident in the images that were captured during each milling run. A sample of images are included in **Figures 4a-4d**. There is a visible reduction of larger particles as the mesh size was reduced.
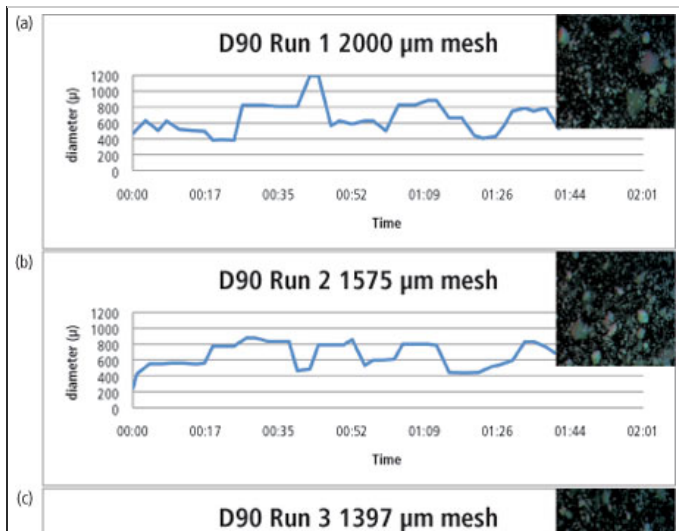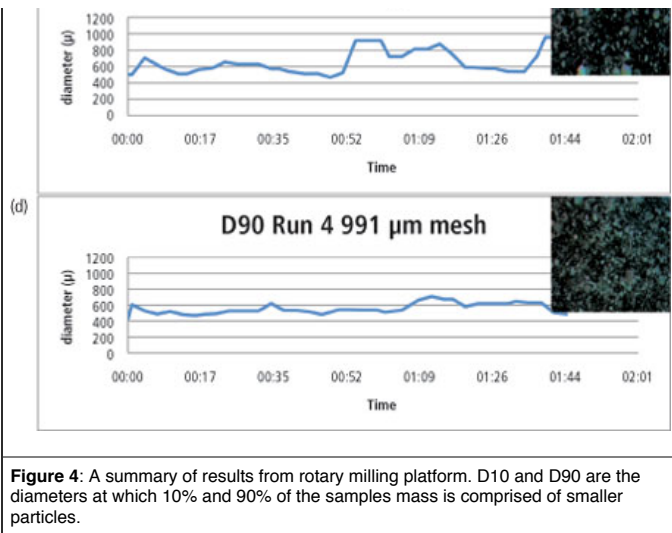
Figure 4: A summary of results from rotary milling platform. D10 and D90 are the diameters at which 10% and 90% of the samples mass is comprised of smaller particles.

It can be seen in **Figure 5** that the level of particle size variability reduces with the reduction in mesh sizes. Run 1 with a mesh size of 2000 μm mesh generated a D90 particle size range from 385 μm to 1196 μm (standard deviation = 199 μm). Run 4 with a mesh size of 991 μm generated a D90 particle size range from 427 μm to 707 μm (standard deviation = 69 μm).

The sample size was considerable with over 46,000 particles measured during each run, which was between 90 and 120 seconds in duration. The number of particles analyzed will vary depending on the speed of material flow, the volume of material transferred to the interface window for analysis, and the particle size range being analyzed. The density, hardness, and moisture content of particles were also considered during the development of the integration device to ensure a repeatable and representative sample for analysis.
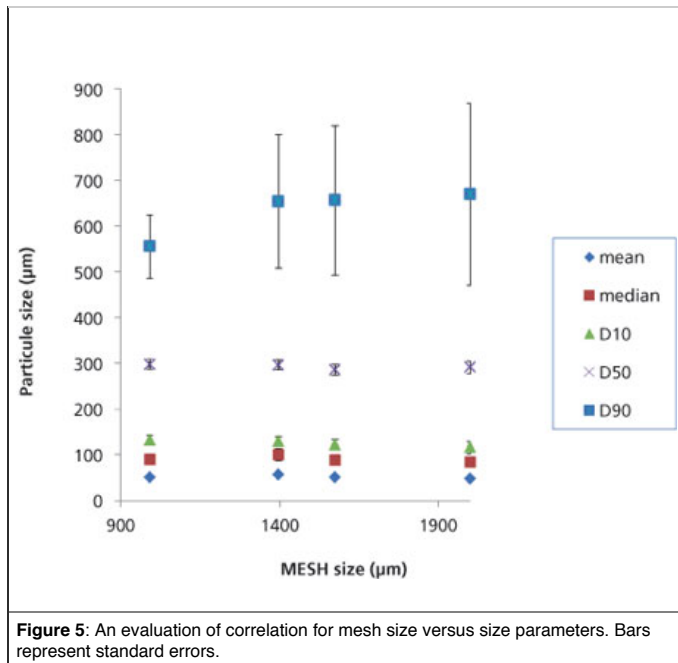
Figure 5: An evaluation of correlation for mesh size versus size parameters. Bars represent standard errors.

Conclusion

The imaging technology (the Eyecon particle characterizer) successfully captured images and subsequently calculated particle size distributions for the sample materials in a rapid and accurate manner. As expected, there will be a degree of modification required as part of integration on new equipment types to ensure a representative and consistent sample presentation--which is critical to enabling accurate sample measurement. It can be concluded that the Eyecon particle characterizer can be successfully integrated within typical pharmaceutical fluid-bed granulators and milling environments in addition to accurately measuring samples in an at-line benchtop set-up.

References

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