



## **PARTICLE SHAPE FACTORS AND THEIR USE IN IMAGE ANALYSIS PART II: PRACTICAL APPLICATIONS**

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### **ABSTRACT**

The first installment of this two-part discussion concluded by stating a single linear measurement (i.e., circular equivalent diameter) may not be adequate to describe a typical non-spherical particle with some degree of surface roughness. There are various definitions and several standardized shape factors available that can provide additional descriptors to a particle population of interest. These valuable shape descriptors can be measured using image analysis. There are numerous examples of how the shape of the particle may influence its behavior, or at least, correlate to a response of interest. Because of this importance, shape factors may be necessary to consider in validated characterization methods. In Part II, case studies are given that illustrate the importance of shape factors and how they may be used to solve various problems.

### **INTRODUCTION**

Shape plays an important role in fine particles in many ways. For instance, the correlation between specific surface area and pharmaceutical dissolution is well documented and governed by Fick's first law of diffusion (1-3). Aside from a decrease in particle size and an increase in particle porosity, the other major way of increasing the specific surface area of a fine particle is by increasing the surface roughness. Thus, given two hypothetical situations where there are two active pharmaceutical ingredient (API) particles of the same mean diameter, one might see an increase of dissolution and bioavailability in the API particle with the most surface roughness.

Another example of the use of particle shape is in milling, ablation, and particle destruction. It is often important to know the mechanism by which a particle is reduced in size. For instance, when milling, a particle may fracture along large crystal faces, forming two particles, each with a lower aspect ratio. Another possibility may be for small pieces to break off the particle, eventually forming a bimodal or skewed population of fine particles and larger, rounded particles.

Similarly, particle shape may be used to determine the mechanism of particle growth. Small particles of a given shape and size may coalesce or ripen into a larger particle of a similar shape. The particles may fuse into pairs of particles that are peanut-shaped or form spherulites. Small particles may also aggregate into large open clusters, the shape and roughness of which may correlate to several properties of the particle (4).

Shape factors may be used to differentiate between species. An example of this may be a particle size analysis of material taken from a fiberglass filter. Because the particles of interest and the loose fibrous filter material are often of very different shapes, the data collected on the filter material may sometimes be separated from the data representative of the particles of interest, solely by particle shape factors. With modern image analysis systems, this can be done and separate distributions and statistics can be calculated for each material type independently. Similarly, this approach has also been used to analyze API particles that have been formulated with several solid excipients. In many cases, the API and excipients may be separated based on shape factors and particle size.

The particle shape may also be correlated to rheological properties of a suspension. It is not difficult to envision how the shape of a particle, especially one that is rather rough and non-spherical, might have a very different packing fraction than a particle that is smooth and spherical. Several derived and empirical equations exist, which relate packing fraction to viscosity (5-7).



Finally, the particle shape may also be correlated to or play a role in powder flowability, permeability, compressibility, bulk and tap density, sedimentation rate, angle of repose, and many other measurements that are common to fine particle characterization (8-14).

## SHAPE FACTORS AND COMPLIANCE

The need for shape determination is stated in the *United States Pharmacopoeia* <776> Optical Microscopy, *British Pharmacopoeia* Appendix XVII O. Optical Microscopy, *Pharmacopoeia Europe* method 2.9.37, and in the Japanese Pharmacopoeia 3.04 Particle Size Determination. They all state, "For spherical particles, size is defined by the diameter. For irregular particles, a variety of definitions of particle size exists. In general, for irregularly shaped particles, characterization of particle size must also include information on the type of diameter measured as well as information on particle shape" (15-18).

One interpretation of this statement is that for particles which are non-spherical (or irregularly shaped), the use of image analysis to determine particle size and shape information may be warranted, especially when multiple lots of the same material exhibit different behaviors. Image analysis data may also be warranted when the particle size of a non-spherical (or irregularly shaped) particle as observed under a microscope does not agree with more routine data such as those obtained through laser diffraction.

There are multiple examples when laser diffraction does not agree with microscopy in the public literature, a fact that may be expanded upon in a separate discussion (19-21).

## CASE STUDIES AND DISCUSSION

### Case Study One

A common sample type is one in which particles have been captured on a fiber filter then rinsed off prior to analysis. This type of analysis is often problematic because of the stray fibrous material, which is usually present in the prepared sample. The stray fibrous material is quite difficult to deal with, especially when attempting to use laser diffraction, an instrument based on the Coulter principle, or a light obscuration or photozone instrument. One possible solution is to use image analysis and shape factors to differentiate between the particles of interest and the unwanted filter fibers.

Case study one was conducted using a Malvern Morphologi G3S and involves an environmental sample that has been gathered by rinsing the particles off a fiberglass filter. Quite often, the particles of interest are somewhat round; while the stray filter fibers are acicular. By making use of the shape factors, it is relatively routine to eliminate the stray fibers from the analysis. Figure 1 demonstrates the difference observed in the aspect ratio distributions before and after the stray filter fibers were removed from the analysis. As expected, removal of the acicular, low aspect ratio, filter fibers, caused a shift in the mean to more round, higher aspect ratio particles. In addition, the aspect ratio distribution was narrowed considerably.

The effect of removing the unwanted filter fibers from the analysis is also demonstrated by the circular equivalent (CE) diameter as shown in Figure 2. After the filter fibers were removed, the mean CE diameter shifted lower. Furthermore, there was a drastic reduction in the population above five microns, which can be attributed to the filter fibers.

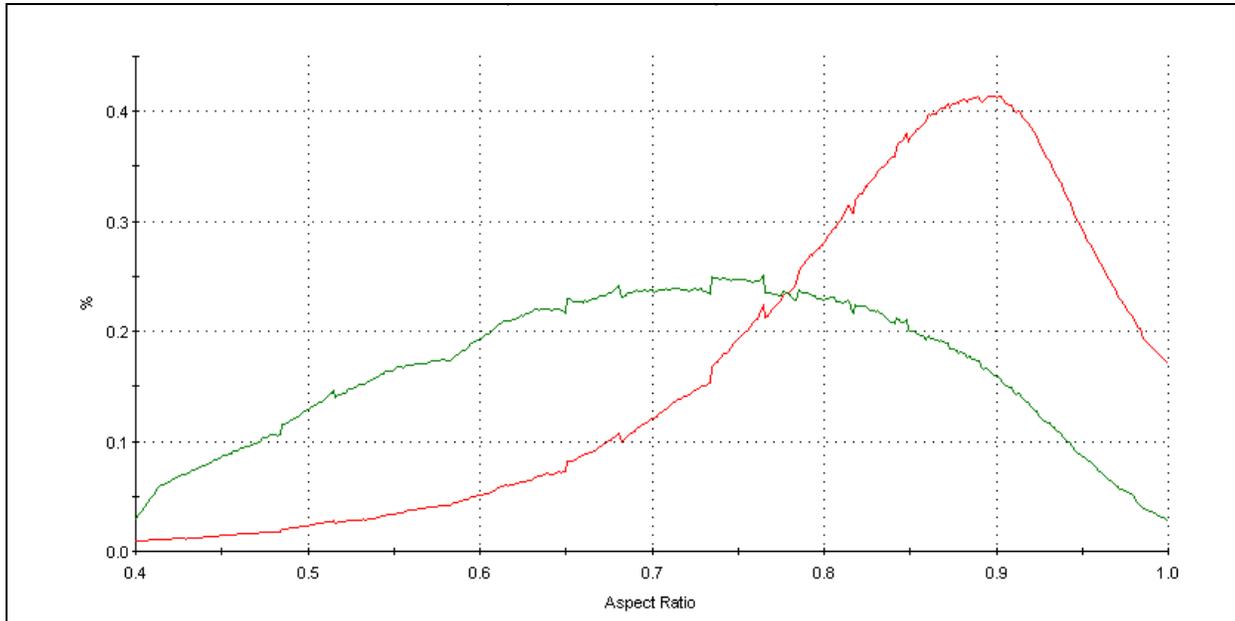


Figure 1. Case study one. Aspect ratio with filter fibers (green) and after the filter fibers were removed (red).

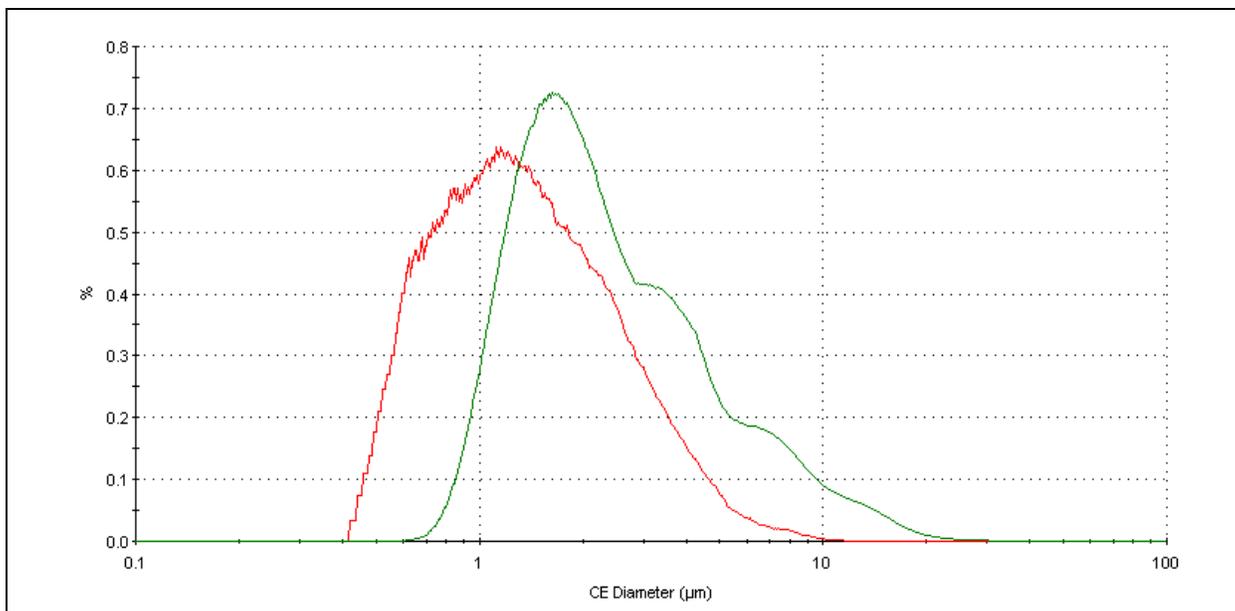


Figure 2. Case study one. Number weighted CE diameter with filter fibers (green) and after the filter fibers were removed (red).

Figures 3 and 4 show representative particle images of the particles of interest after the filter fibers were removed (Figure 3) and the removed filter fibers (Figure 4). The number below each particle or fiber is a unique particle ID number assigned by the instrument software during each analysis.

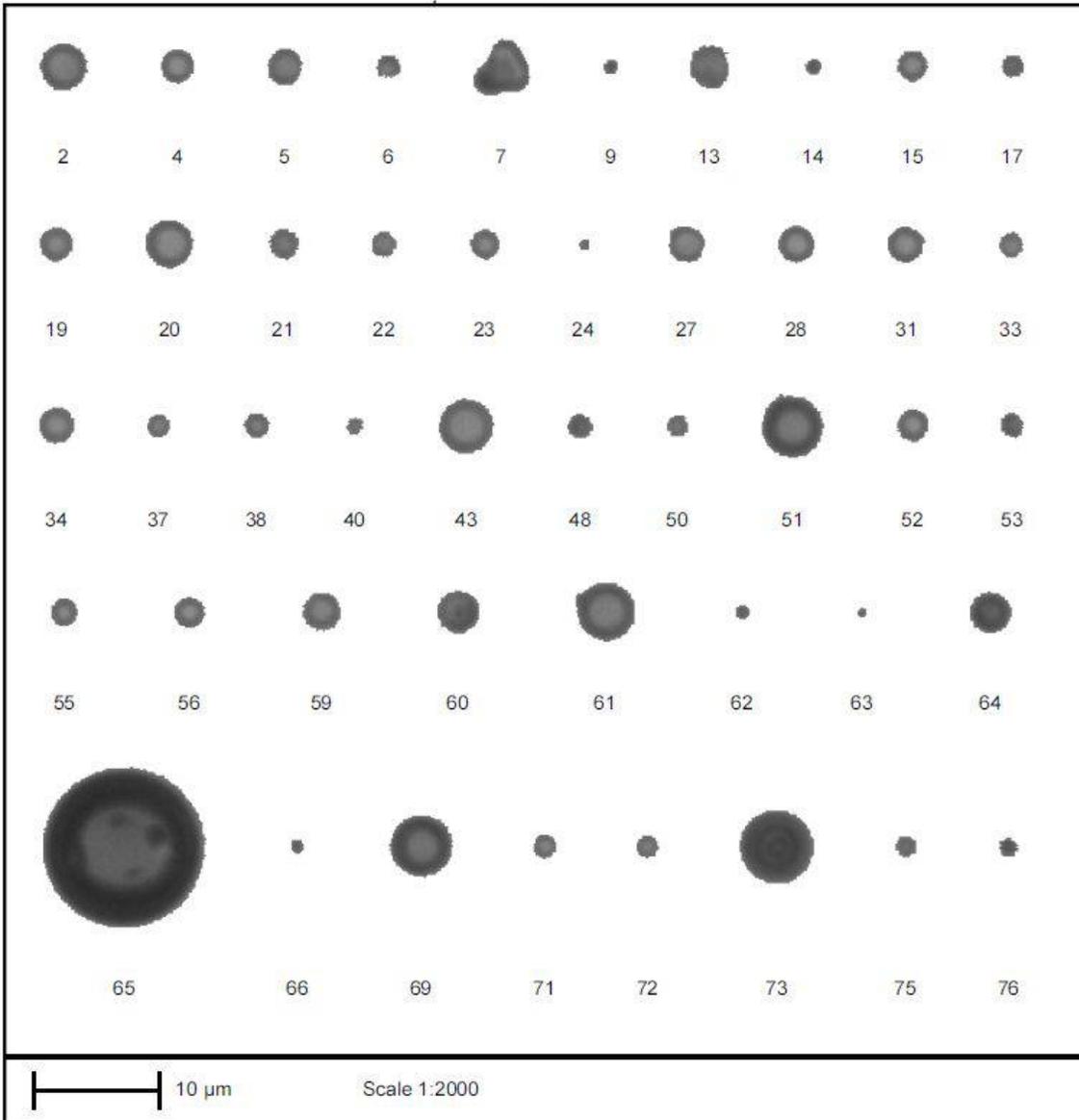
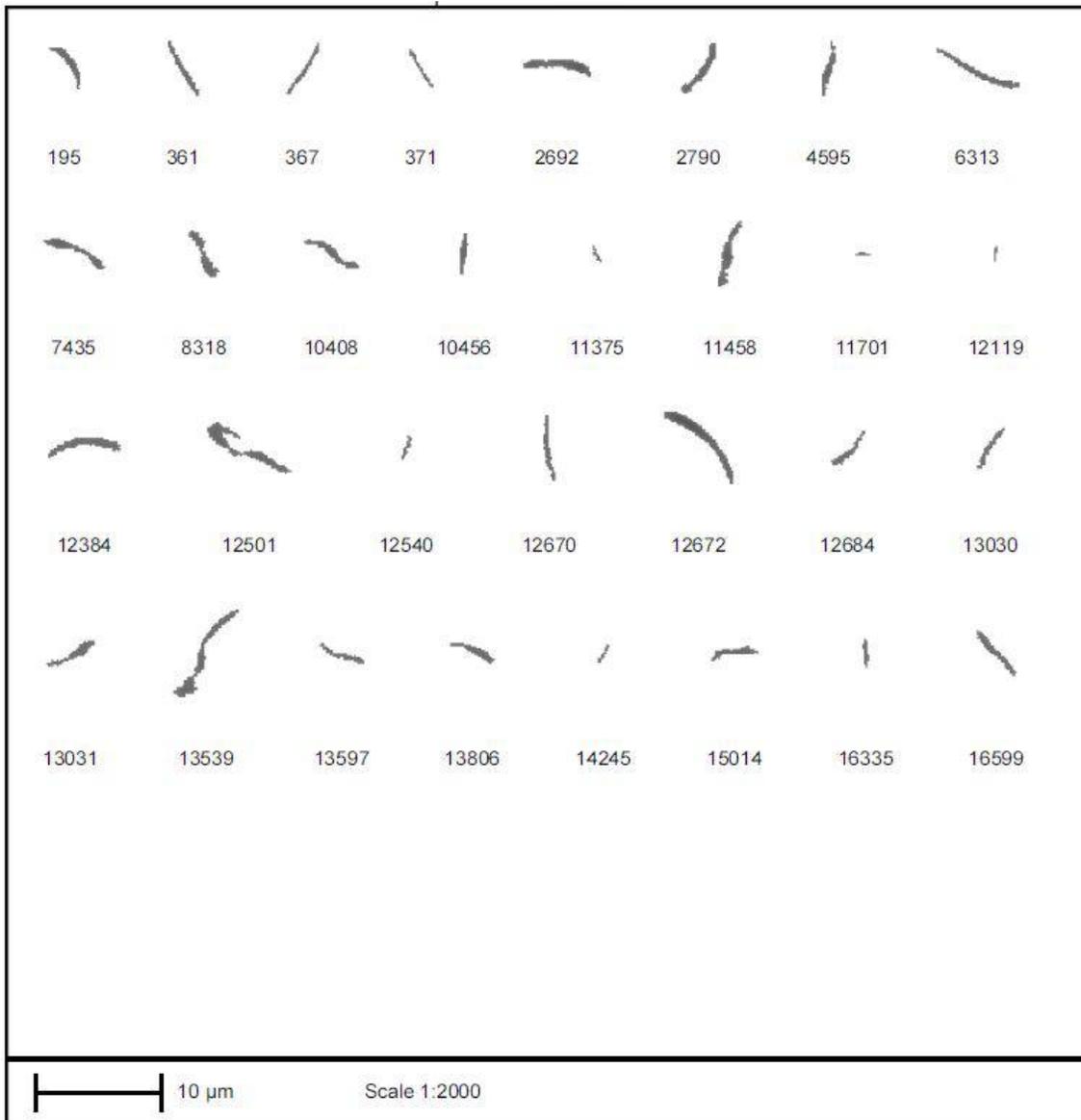


Figure 3. Case study one. Particles of interest after the filter fibers had been removed.



**Figure 4. Case study one. Filter fibers removed from the analysis.**

### Case Study Two

A different use of shape factors is to gain insight into the mechanism by which particles are fractured or otherwise reduced in size. The question asked at the onset of this analysis was whether the particles were being fractured along a crystal face or if they were being reduced in size by chipping away at the edges and corners.

One common mechanism for particle size reduction, in this case a crystal, is to split cleanly along a crystal face, forming two particles as shown in Figures 5 to 7.

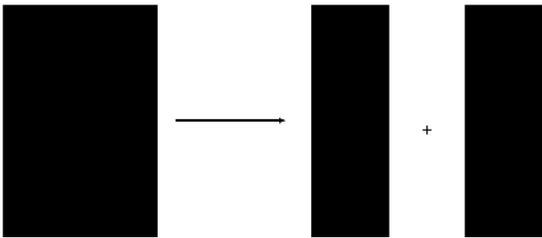


Figure 5. Hypothetical fracture of a crystal along its major axis.

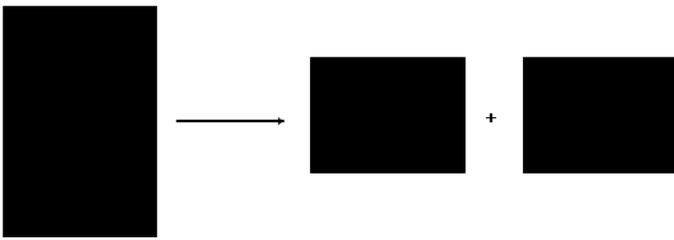


Figure 6. Hypothetical fracture of a crystal along its minor axis.

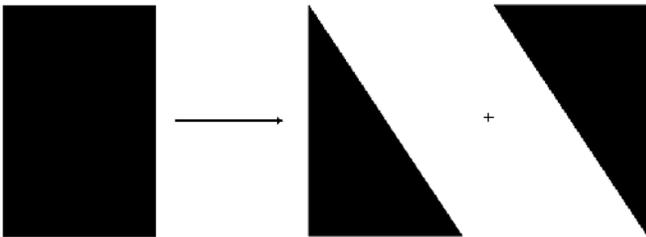


Figure 7. Hypothetical fracture of a crystal along its diagonal axis.

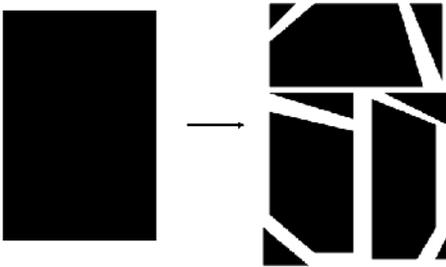
The Table gives the relative CE diameters, aspect ratios, circularities, convexities, and solidities for the unmilled particle and the three crystal cleavages as shown in Figures 5 to 7. The data shown are calculated using geometric principles and assuming all the particles are perfectly smooth and regular. It is for this reason all the convexity and solidity values are one. The units of length are arbitrary, but are relative to each other.

**TABLE: CE diameter and shape factors as calculated using geometric principles.**

Example	CE diameter	Aspect Ratio	Circularity	Convexity	Solidity
Unmilled	$2\sqrt{\frac{6}{\pi}} = 2.76$	$\frac{2}{3} = 0.67$	$\sqrt{\frac{4\pi 6}{10^2}} = 0.87$	1	1
1	$2\sqrt{\frac{3}{\pi}} = 1.95$	$\frac{1}{3} = 0.33$	$\sqrt{\frac{4\pi 3}{8^2}} = 0.77$	1	1
2	$2\sqrt{\frac{3}{\pi}} = 1.95$	$\frac{1.5}{2} = 0.75$	$\sqrt{\frac{4\pi 3}{7^2}} = 0.88$	1	1
3	$2\sqrt{\frac{3}{\pi}} = 1.95$	$\frac{2}{3} = 0.67$	$\sqrt{\frac{4\pi 3}{(5 + \sqrt{13})^2}} = 0.71$	1	1

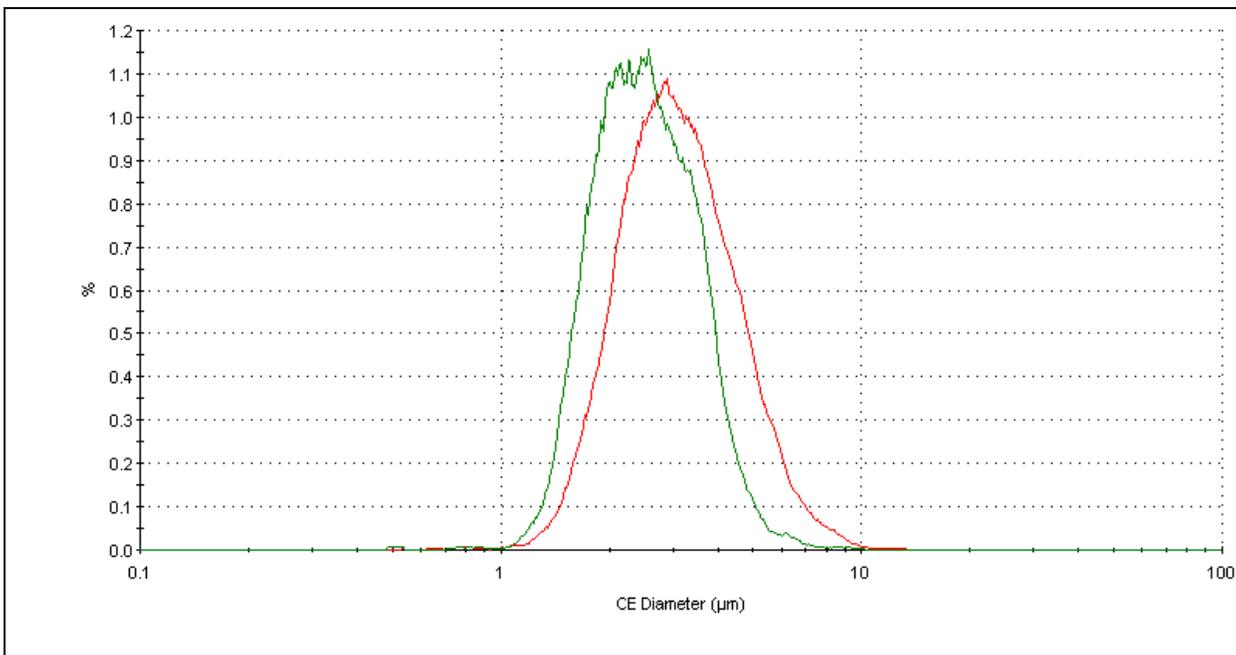


Another alternative mechanism of particle size reduction is related to attrition, whereby irregular pieces of the original particle are broken off as shown in Figure 8. This, in theory, will yield a broad particle size distribution with a lower mean size after enough milling cycles. However, it is difficult to predict the effect on the aspect ratios, convexity, circularity, and solidity values due to the resulting random particle sizes and shapes.



**Figure 8. Hypothetical random attrition of a crystal.**

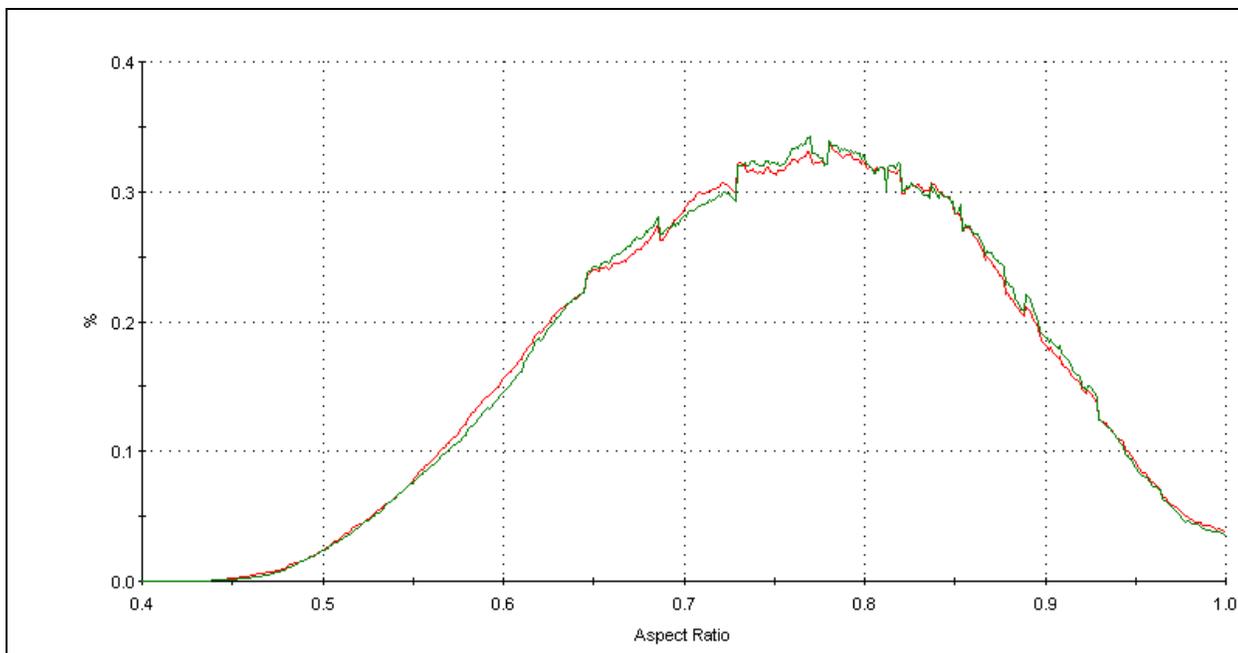
Case study two was conducted using a Malvern Morphologi G3S. Figure 9 shows a particular API before a particle size reduction step (red) and after (green). As one would expect, the particle size or CE diameter was reduced, in this case from a mean of about 3.3  $\mu\text{m}$  to a mean of about 2.6  $\mu\text{m}$ .



**Figure 9. Case study two. Number weighted CE diameter of a pharmaceutical active ingredient before a particle size reduction step (red) and after (green).**

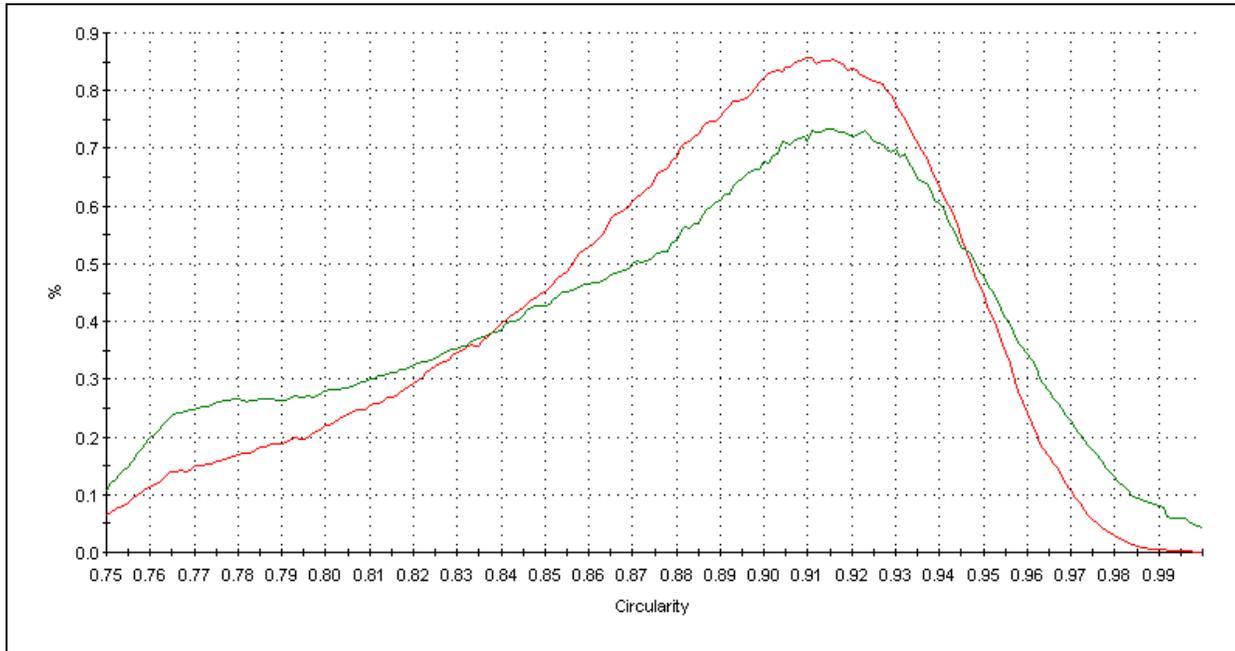


As shown by the aspect ratio data (Figure 10), the particles before and after the particle size reduction step have virtually identical aspect ratios.



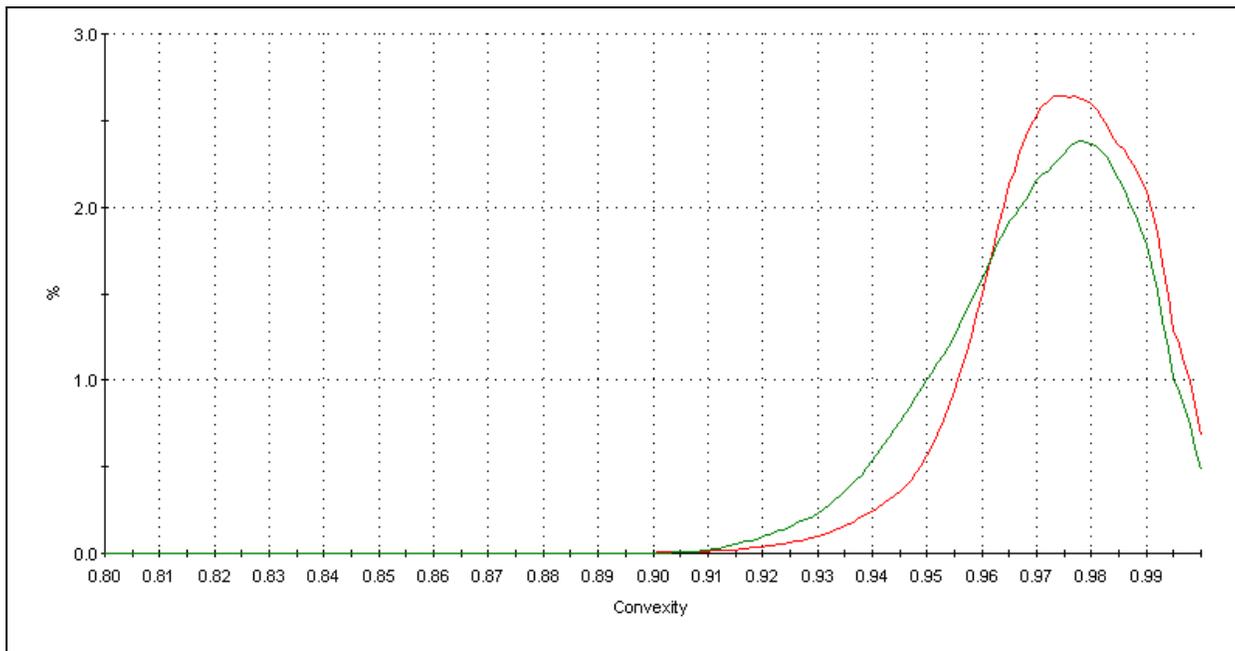
**Figure 10. Case study two. Aspect ratios of a pharmaceutical active ingredient before a particle size reduction step (red) and after (green).**

As indicated by the circularity data (Figure 11), the particles exhibited a slight decrease in circularity upon particle size reduction, which suggests the resulting particles were less round or less smooth.



**Figure 11. Case study two. Circularity of a pharmaceutical active ingredient before a particle size reduction step (red) and after (green).**

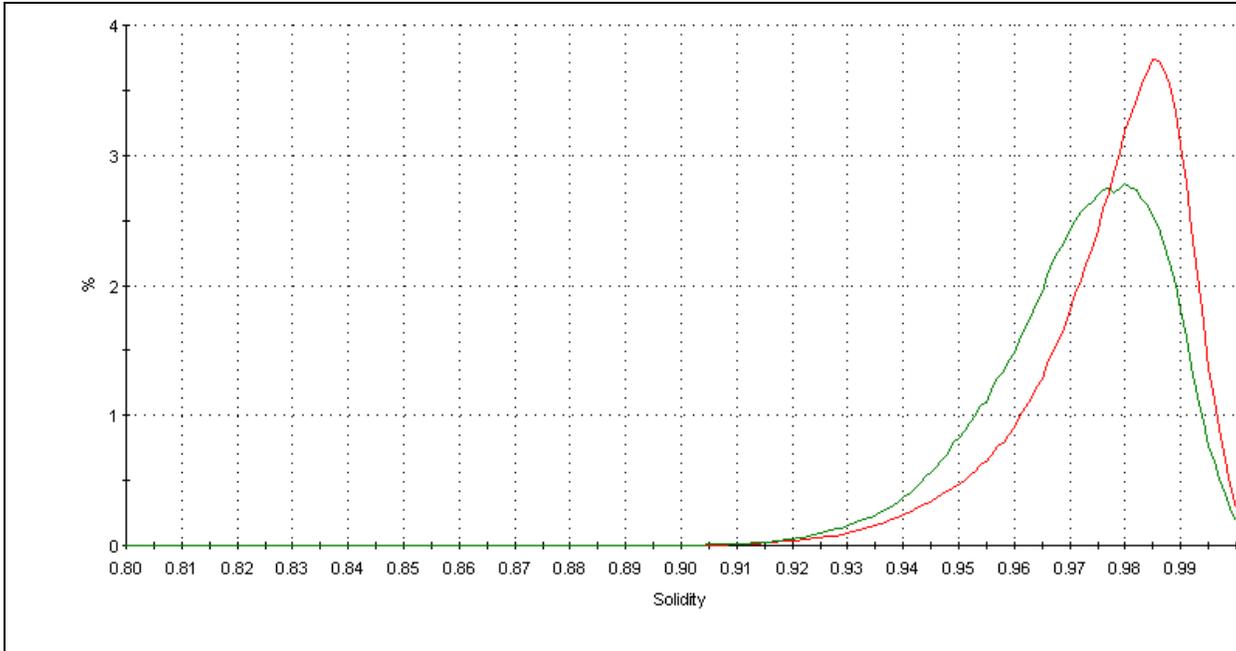
The increase in convexity (Figure 12) over the narrow range from about 0.91 to 0.96 suggests the resulting particles were less smooth than the particles before being reduced in size.



**Figure 12. Case study two. Convexity of a pharmaceutical active ingredient before a particle size reduction step (red) and after (green).**



Likewise, the slight shift observed in solidity (Figure 13) also suggests the resulting particles were less smooth than the particles before being reduced in size.



**Figure 13. Case study two. Solidity of a pharmaceutical active ingredient before a particle size reduction step (red) and after (green).**

The conclusion of this study was a small portion of the active pharmaceutical ingredient had most likely been fractured along its diagonal axis as shown in Figure 7. Figures 14 and 15 are representative images of the particles before the particle size reduction step (Figure 14) and after (Figure 15).



**Figure 14. Case study two. Image of a typical particle before a particle size reduction step.**



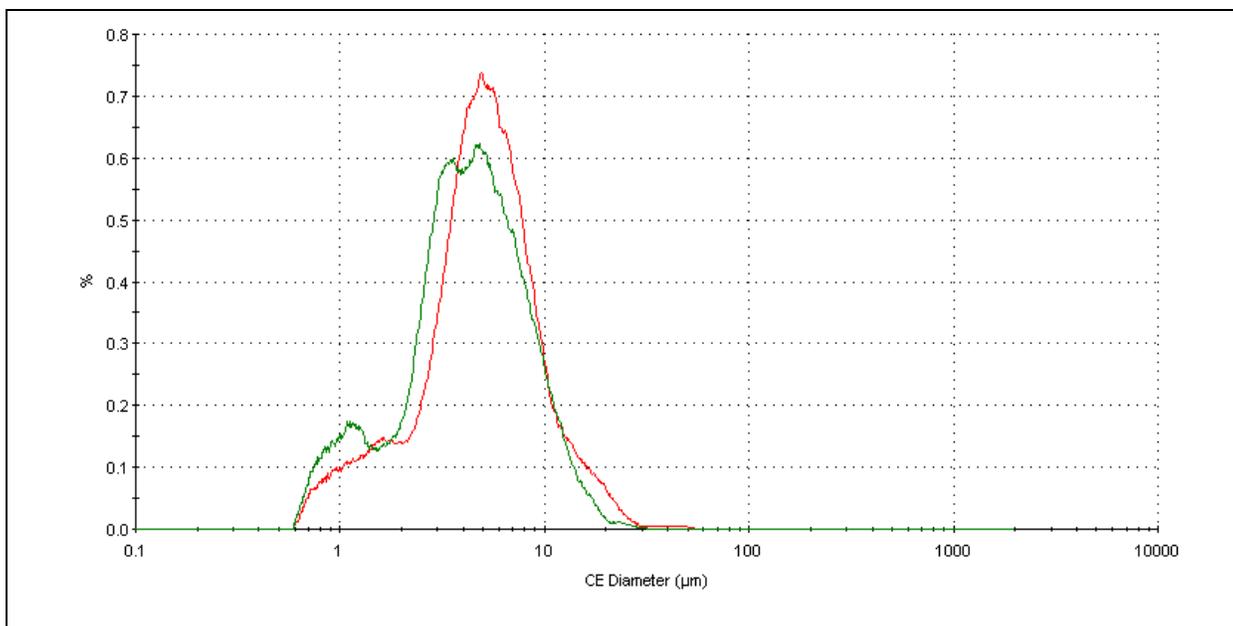
**Figure 15. Case study two. Image of a typical particle after a particle size reduction step.**



### Case Study Three

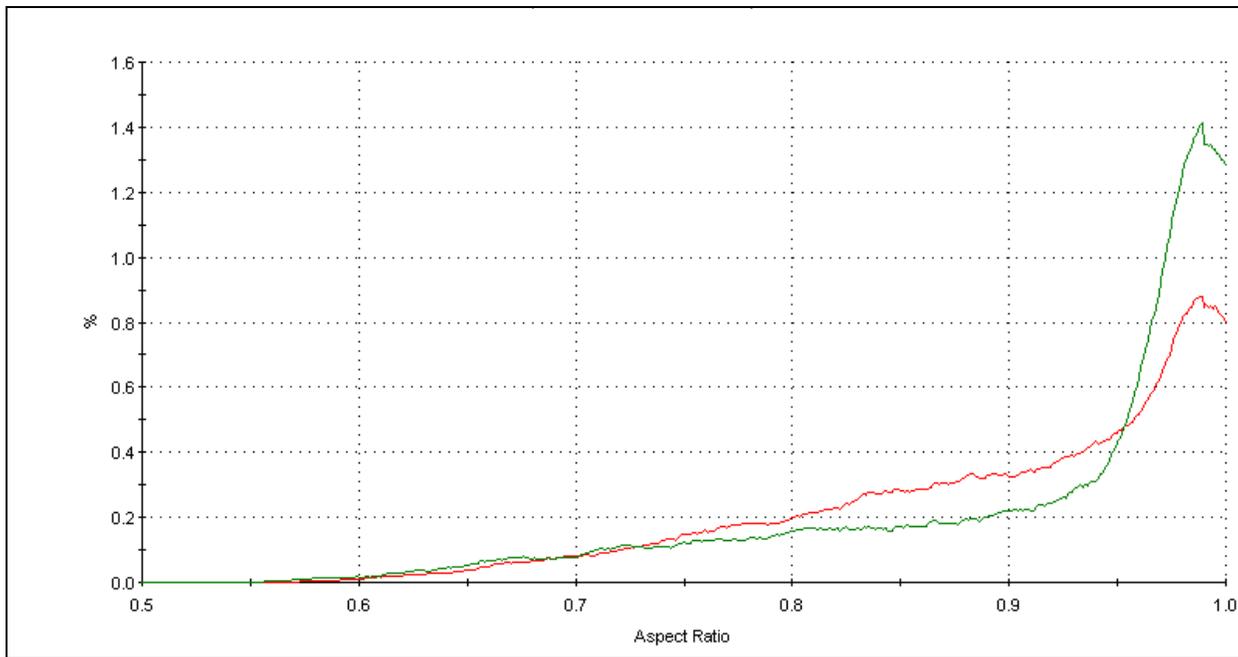
Case study three involves two lots of a particular sample and was conducted using a Malvern Morphologi G3S. The specification for the incoming raw material was based solely on particle size distribution (i.e., equivalent spherical diameter). As shown in Figure 16, the mean CE diameter and the distribution shape are quite similar for both lots. However, one of the lots (shown in green), which was an older retain sample, behaved quite differently than the newer incoming lot (shown in red). The client indicated the new lot did not flow very easily, forming rat-holes in the hopper. In addition, the new lot did not form a homogeneous formulation upon mixing.

Figures 17 to 20 show the aspect ratio, circularity, convexity, and solidity results, respectively. It is obvious given these data sets the particle size distribution of the two lots may be very similar, but the shapes of the particles in the two lots vary drastically.



**Figure 16. Case study three. Number weighted CE diameters of the retain lot (green) and incoming lot (red).**

Figure 17 gives the respective aspect ratio plots. As shown, both lots have practically no observed particles with an aspect ratio below 0.6, and both lots have a peak aspect ratio near 0.98. However, it appears the peak is lower for the new lot, but has a significantly higher amount of particles in the aspect ratio range from about 0.8 to 0.95 than the old lot. This suggests the old lot was comprised of primarily round or very symmetric particles. The shape of the particles was confirmed to be quite spherical. By comparison, though a significant portion of the particles of the new lot was also spherical, there were also a significant number of slightly elliptical particles.



**Figure 17. Case study three. Aspect ratios of the retain lot (green) and incoming lot (red).**

These results are supported by the circularity, convexity, and solidity data. In all three cases, the old lot of material has a relatively sharp, narrow distribution near the maximum of each measurement. By circularity (Figure 18), this suggests the majority of the particles were round in shape as well as quite smooth. The smoothness of the particles of the old lot is supported by the convexity data (Figure 19). Likewise, the solidity results also suggest the particles were very uniform and quite smooth (Figure 20).

By comparison, the new lot of material has relatively broad distributions with modes that are less than the corresponding modes of the old lot. By circularity (Figure 18), this suggests the particles were less round in shape or less smooth. The decrease in smoothness of the particles of the new lot is supported by the convexity data (Figure 19). Likewise, the solidity results also suggest the particles were less uniform and smooth (Figure 20).

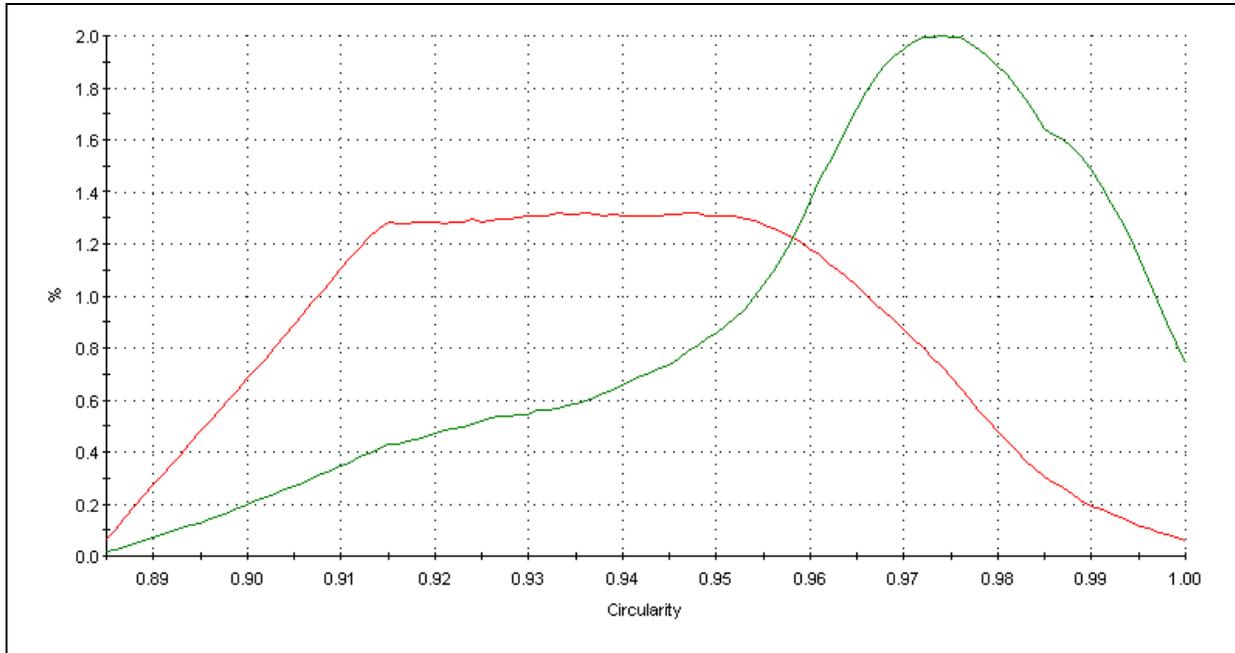


Figure 18. Case study three. Circularities of the retain lot (green) and incoming lot (red).

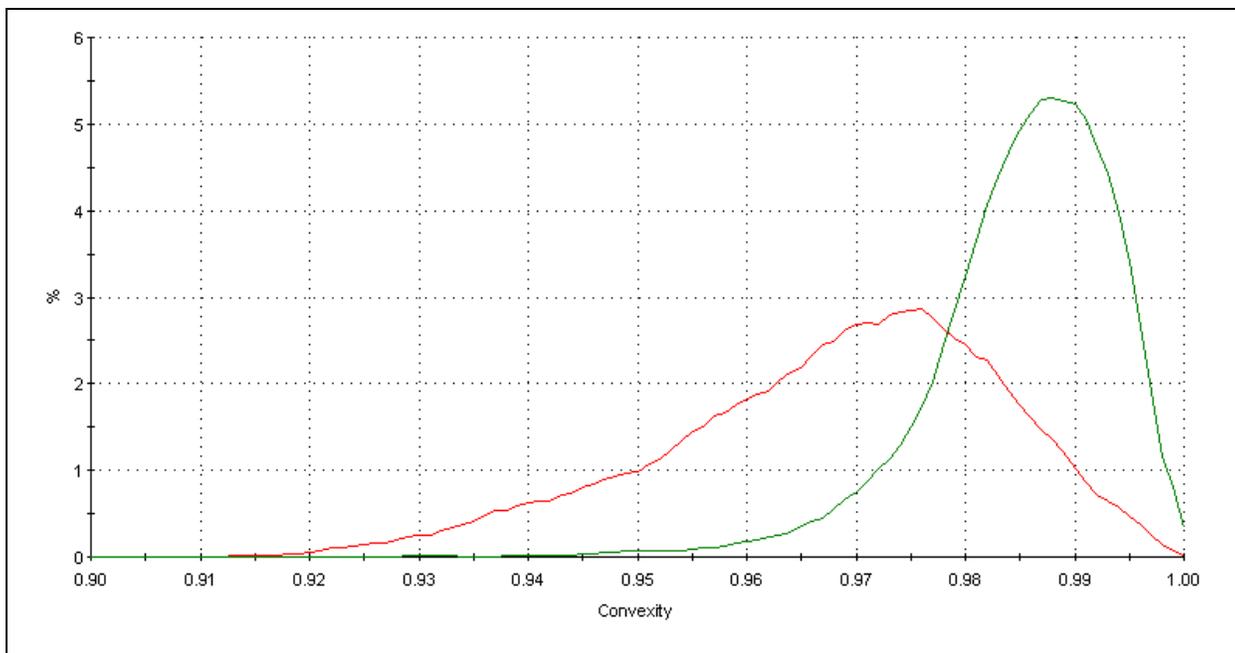
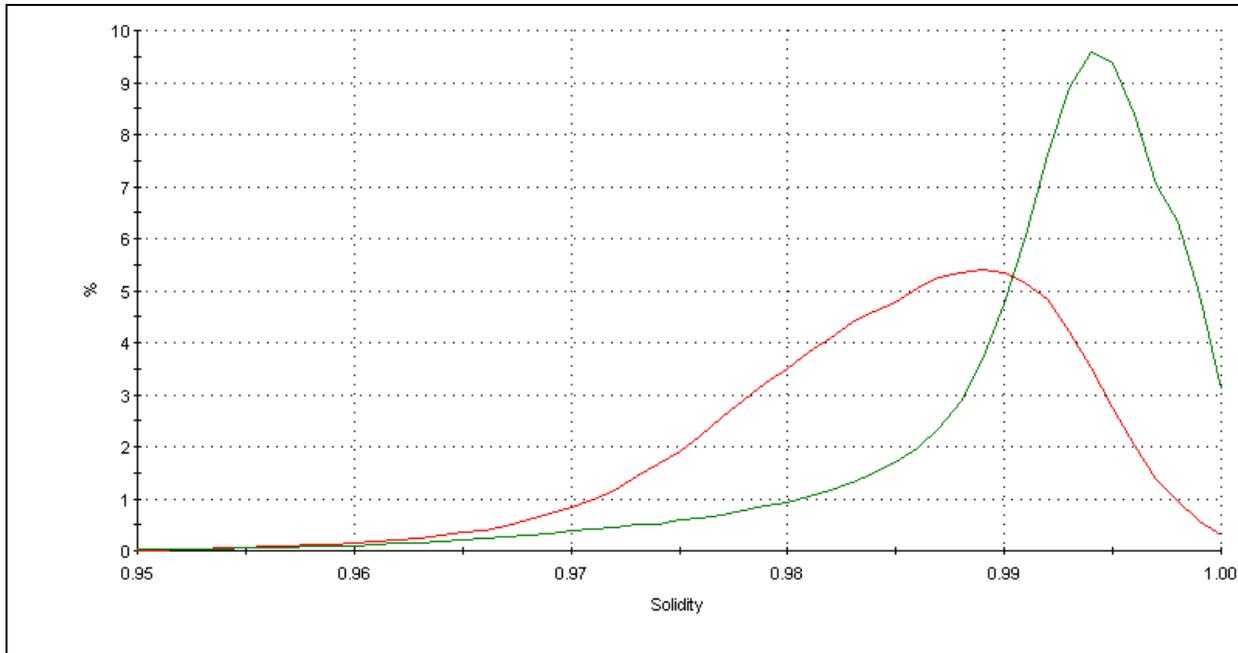
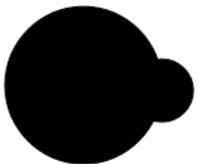


Figure 19. Case study three. Convexities of the retain lot (green) and incoming lot (red).



**Figure 20. Case study three. Solidities of the retain lot (green) and incoming lot (red).**

The conclusion of this study was though both lots of material were nearly spherical, the older retain lot of material was more circular than the incoming lot of material. Furthermore, the incoming lot of material had a larger population of particles with a shape similar to that found in Figure 21.



**Figure 21. Shape of a minor population of particles observed in the incoming lot of material.**

## CONCLUSIONS

Through use of particle shape factors, which can be measured by image analysis, conclusions may often be drawn about particles that would not be possible with a single linear measurement (i.e., circular equivalent diameter). As shown in the first case study, the shape factors could be used as filters to distinguish between particles of interest and unwanted filter fibers. In the second case study, conclusions could be drawn about the effects and mechanism of a particle size reduction step on an active pharmaceutical ingredient. Finally, in the third case study, two lots of material with nearly identical particle size distributions were easily distinguishable through use of shape factors. The shape factors could then be used to explain differences observed in powder flow ability.



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