The Impact of Dissolution on Particle Size and Particle Shape of Multi-Component Drug Delivery Systems

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Purpose

The particle size and particle shape of multi-component controlled release drugs must be considered during their dissolution. Though the size and shape of the particles are well known during formulation and manufacture, oftentimes, little is known about the changes in size, shape, and morphology during dissolution. Particles that start as spheres or granules will eventually take new shapes as they break down. Particle shape analysis is used to show that the multiple components of the drug are similar in size but have distinct shapes as well as to demonstrate that particle shapes change as they dissolve.

Background

Particle size and shape are critical quality attributes of materials used in the production of many pharmaceuticals. The evolution of particle sizes and shapes as they dissolve over time is not completely understood for many released drugs as well as those in development. Oftentimes there are multiple active ingredients present. These multifunctional components resulting in varying particle shapes present challenges to traditional particle size distribution devices. Additionally, the particle sizes and particle shapes of these components may have an impact on physicochemical properties, bioavailability and other pharmacokinetic phenomena. Applying many of the analytical tools available for size and shape analysis is on the rise and is being considered for many new drug formulations currently under development. New regulatory initiatives are forcing researchers to identify and employ new test methods that will provide a better understanding of material properties that can impact functionality.

Though many of the materials used in the formulation and production of drug materials are screened for particle size, very few are tested for particle shape. There are many automated systems available for the measurement of particle shape and their use is on the rise.

Particle size measurement alone is not always effective in determining subtle differences in particle size and shape. Differences such as particle smoothness or aspect ratio may not significantly impact the equivalent circular area (ECA) that is reported by traditional particle size analysis systems. These subtle differences can be lost in the transformation to ECA.

Methods

Particle Size of a tableted drug material as a controlled release delivery mechanism was determined using the Saturn Digisizer manufactured by Micromeritics Instrument Corporation, Norcross, Ga. Particle Shape was determined using the Particle Insight manufactured by Particulate Systems, Norcross, Ga. The Saturn Digisizer uses static light scattering to measure particle size. The Particle Insight utilizes the dynamic image analysis technique to measure particle size and particle shape. Dynamic image analysis provides additional utility in that it does not assume that all particles are spheres as do many commonly used particle size distribution analysis systems such as light scattering. In this study, we reported particle size using both techniques as well as various shape parameters that include circularity, smoothness, and aspect ratio. In each case, the tablets were allowed to dissolve in an aqueous solution where measurements were taken at 10 minute intervals.

Results and Discussion

There are hundreds of shape parameters that are used to describe or represent particle shape. For this discussion we have included smoothness, aspect ratio, and equivalent circular area (ECA).

In most cases, the data that scientists use to determine the particle size distribution of their materials assumes that all particles are spheres. Figure 1 shows some of the particles present during the dissolution of a common OTC pain reliever.

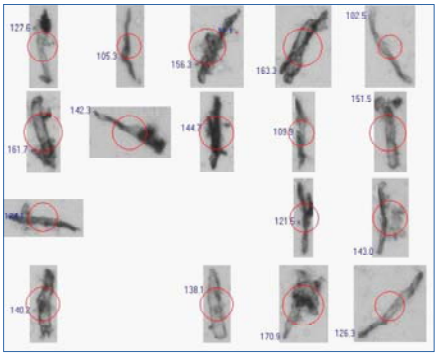

Figure 1. Dynamic image analysis data showing particle shape. The equivalent circular area is illustrated in red.

Figure 2 shows the change in surface smoothness of the same OTC pain reliever as the particles dissolve over time. When suspended in the analysis liquid, the drug granules break down and the various components of the drug formulation emerge.

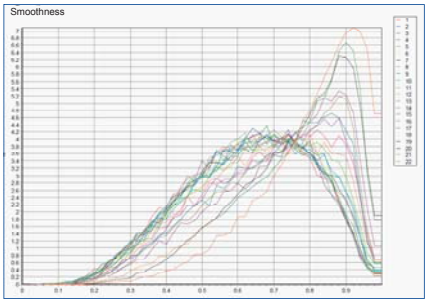

Figure 2. Dynamic image analysis shows the particles are becoming smoother over time

Figure 3 further illustrates the shape change that the particles undergo during dissolution. The bounding rectangle aspect ratio allows for a mechanism to monitor the population of rod like particles and their evolution over time

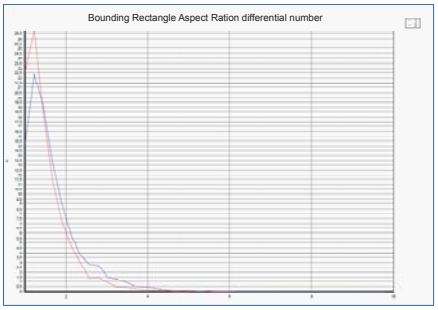

Figure 3. Test 2 (red) shows a larger population of high aspect ratio particles 10 minutes after dissolution commences.

In comparison the same material was analyzed using a static light scattering instrument. Figure 4 shows that though shape has changed, the equivalent circular area does not significantly change over time.

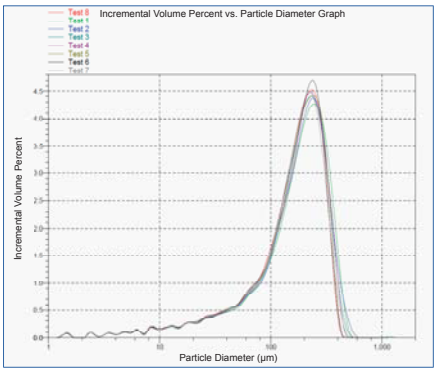

Figure 4. Static light scattering data that shows little change in particle size over time.

Conclusion

Particles come in a variety of shapes and sizes. It is generally understood that modifications or changes in size and shape impact functionality. The data that was collected shows the impact of dissolution on the shape and size of the drug components.

Particle shape analysis provides additional information about particles that is missed with traditional systems for the measurement of particle size. Additionally, particle shape measurement systems provide a means for collecting images of particles for verification of calculated results.

The use of particle size and image analysis paints a clearer picture of the true nature of particles providing users with a deeper understanding of their material.

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