analytical techniques

Computed tomography: Applications for evaluating tablets and capsules

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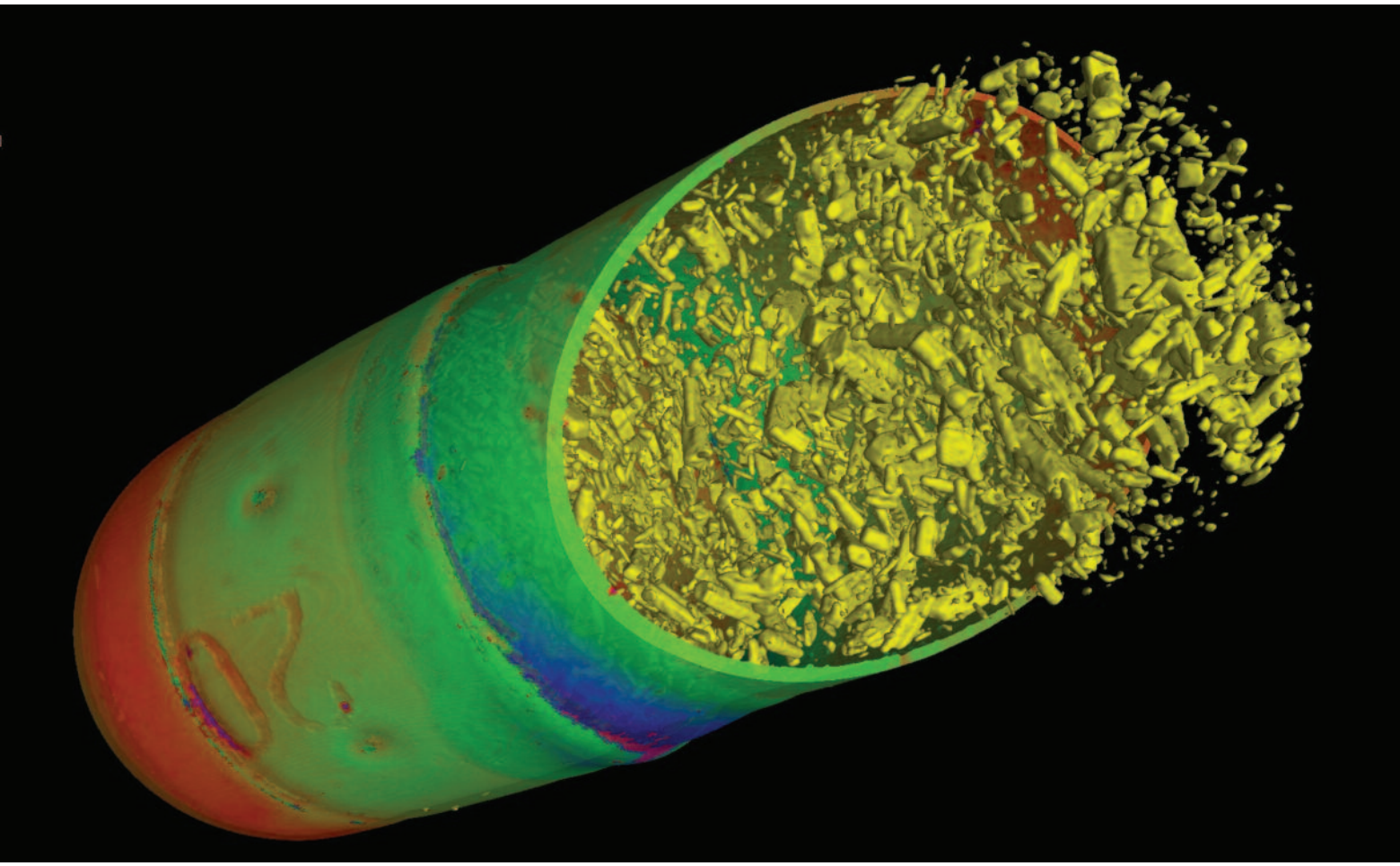


Computerized axial tomography (CAT), also known as CT, has been used in clinics and hospitals for decades and has become a life-saving diagnostic tool. The technology is also responsible for significant advances in industrial and scientific applications, offering image resolutions hundreds of times higher than what is used in the medical fields. This article outlines the benefits of using CT to study tablets and capsules.

CT in motion

Links to videos of 3D CT scans:
1. Coated pharmaceutical tablet: http://bit.ly/PharmTabNSI
2. Pharmaceutical tablet: http://bit.ly/PharmTab2NSI
3. Multilayer softgel bead: http://bit.ly/ProbioNSI

In pharmaceutical applications, CT can help fast-track new product and process development and assess the characteristics of existing products. Tablets and capsules, for example, can be CT-scanned using area detectors and micro-focus x-ray tubes to provide extremely high-resolution and high-contrast sensitivity of the dosage form's features and materials. In fact, it's common to scan an entire tablet or capsule at voxel (three-dimensional (3D) pixel) resolutions of 3 to 15 microns. Even sub-micron voxel resolutions are attainable if the study requires detail in the nanometer range. These 3D views provide unequaled volumetric detail, and in some products you can see the location of individual particles of the active pharmaceutical ingredient (API).

Figure 1

During CT scanning, some photons penetrate the product and reach the imaging detector, carrying with them detailed information.

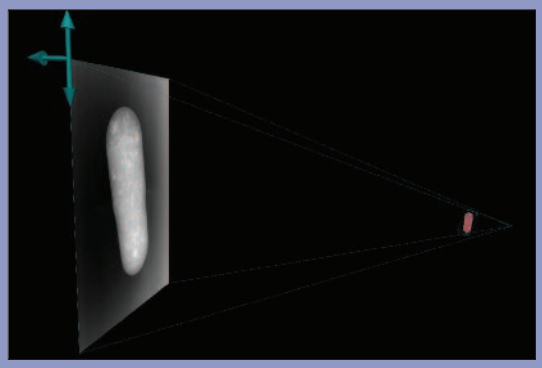
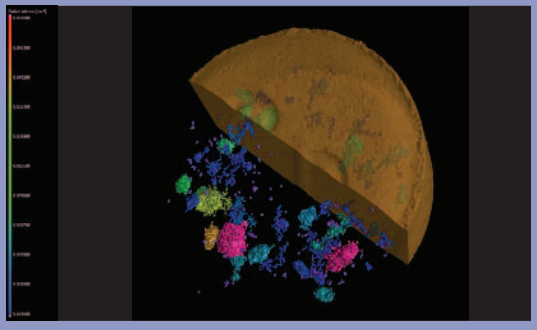


Figure 2

CT enables you to visually evaluate specific areas or materials within tablets and capsules.



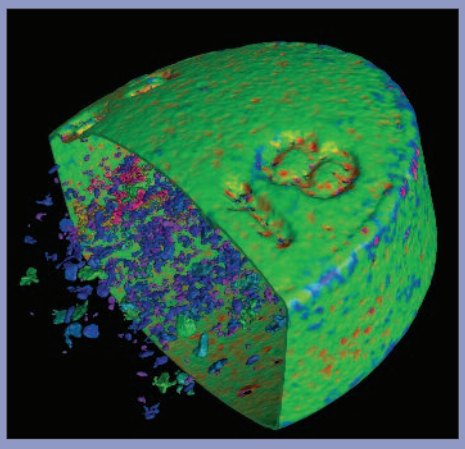
How CT works

In general terms, a CT system comprises an x-ray tube, a detector, a material handling apparatus, a shielding chamber, a work station for image acquisition, and a work station for image reconstruction and data analysis. CT is a nondestructive evaluation method that doesn't heat the specimen/product. In operation, it generates x-ray photons that either travel through the product or are attenuated by it. The photons that penetrate the product enter the imaging detector, carrying with them detailed information (Figure 1). The degree of photon attenuation depends on the amount of energy applied and the thickness or density of the material that the photons pass through. When scanning a tablet, for example, the system rotates it 360 degrees, which typically generates hundreds to thousands of images acquired at an equal number of different angles. Next, an algorithm reconstructs a 3D volumetric representation of the product, which you can adjust to optimize 3D visualization or slice into a number of planes. Other tools enable you to conduct an array of analyses of both single and global voxel data.

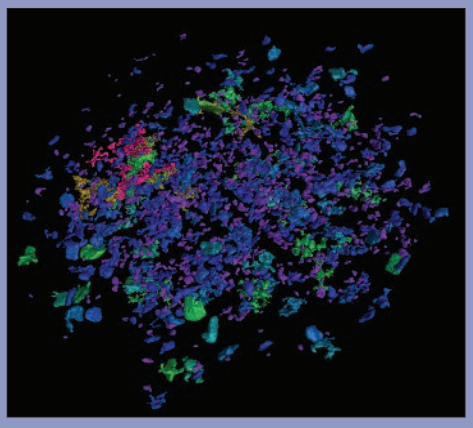
It's possible, for example, to bring to the fore materials and features based on material density, creating a polygonal mesh surface. That surface, in turn, can be used to visually evaluate specific areas or materials within the product. You can also use it to generate highly accurate metrology data, CAD files, 3D printing files, CAD comparisons, finite element analyses, and other data sets (Figure 2).

Figure 3

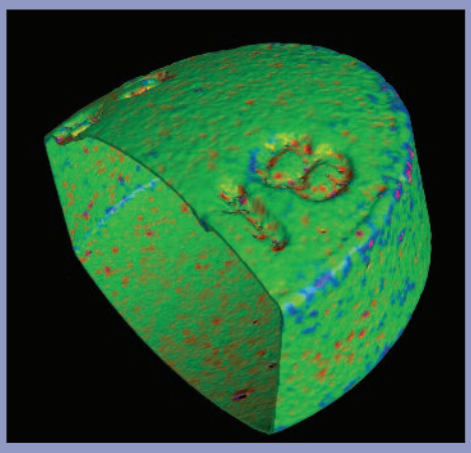
Volumetric analysis of materials: assessment of coating thickness and core uniformity



a. Tablet core and coating



b. Core only



c. Coating only

Tablet and capsule applications

CT capabilities comprise volumetric analysis of individual materials; analysis of particle size, shape, and volume; analysis of API distribution; and assessment of coating thickness and uniformity (Figure 3). These CT-viewable product characteristics carry with them information that can assist you in developing new products and processes, verifying quality, protecting intellectual property, and testing performance.

Coating thickness and spatial uniformity. CT enables you to measure the thickness and the uniformity of coatings applied to tablets and capsules, and because it can segment those measurements from the substrate, you can analyze the coating independent of the product's internal structure. Software tools also allow you to specify minimum and maximum thickness criteria and automatically report both in a spreadsheet format. Furthermore, the data can be displayed in 3D, with the thicknesses spatially color-coded within the product image (Figure 4). It's even possible to evaluate products with more than one coating layer, enabling you to see thickness anomalies, gaps between layers, and inclusions and voids within or between the layers (Figure 5).

Product development. Developing a new drug product—and often a new process to go with it—may require theoretical modeling, followed by manufacturing some samples. You then test those samples to see how they jibe with the models. If you use traditional equipment, many of the samples will be destroyed. CT, however, can reduce and sometimes eliminate the need for destructive testing, and the data you obtain can be used to fine-tune the manufacturing process. That's possible because just one CT scan of a tablet can produce the equivalent of thousands of the cross-sections that would be obtained using destructive means. These virtual slices through multiple planes within the product's CT volume enable you to identify and define process variability faster. That, in turn, enables you to refine the model or the process itself to obtain the critical quality attributes the product requires. CT processes specimens so quickly that some types of data are available in minutes or even seconds.

Variability in composition and density. Depending on how a tablet granulation is prepared, how it performs on the tablet press, and other factors, particles of the API(s) and excipients may segregate due to differences in density, size, shape, or other characteristics. That becomes a problem when how uniformly the API is distributed within the tablet corresponds to its efficacy. It may even be a critical quality attribute—particularly in multiparticulate, modified-release, and multilayer tablets. With CT, you can visualize the distribution of the ingredients in the final dosage form and use the information to adjust the formulation and/or process. Evaluating how well a granulation process prevents powder segregation is one example. By spatially mapping the API or the excipient, CT can reveal how changing different variables affects the final product (Figure 6).

Impurities and foreign material. Even with tight controls, there is always the potential for impurities or foreign materials to taint the product. If that happens and the foreign material varies in density, shape, or size from that of the baseline formulation, CT can often detect it (Figure 7). CT can even characterize the foreign material if a database of material standards is accessible.

Intellectual property. Thousands of patents address the physical makeup of tablets and capsules in terms of coatings, excipients, shape, and manufacturing processes. With CT, you can add precision to patent applications that define the physical form of a product. Additionally, CT provides exceedingly fine detail that helps you compare products during intellectual property investigations.

Figure 4

Spatial color coding of capsule wall thickness

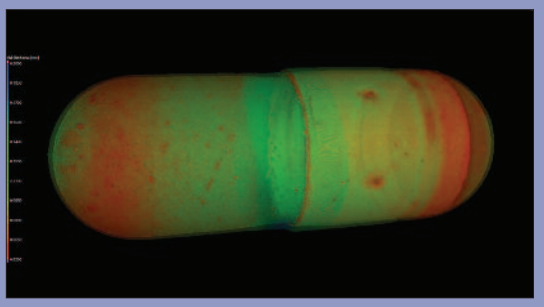


Figure 5

CT scans of coated tablets can measure wall thickness and reveal thickness anomalies, gaps between multiple layers, and inclusions and voids.

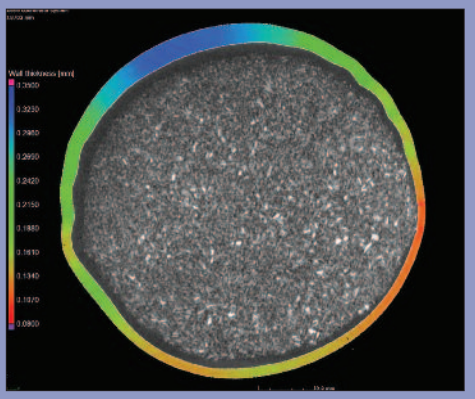
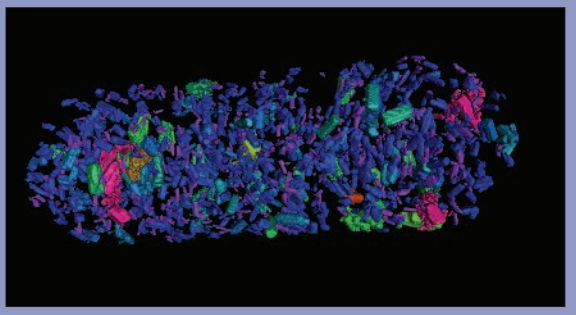


Figure 6

Spatial mapping of a capsule product's constituents



Performance correlation. When we "pop a pill" we obviously expect it to perform as intended. In some cases, it relieves a painful symptom, and other times it keeps us alive. Whatever the case, we expect that tablet or capsule to work the same every time, within the same time frame, and at the same potency. In fact, some people's careers are dedicated to ensuring the uniform, consistent function of drug products. CT can help meet that goal—in tandem with existing techniques—by providing a more complete reference point for performance-correlation studies. The CT-derived data can then be used to establish more comprehensive product-screening standards.

FIGURE 7

CT scans can detect foreign materials.

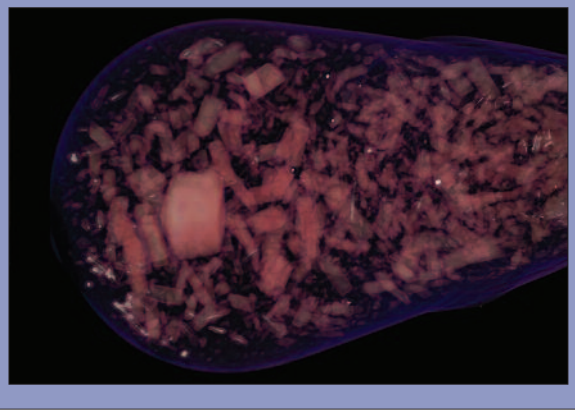
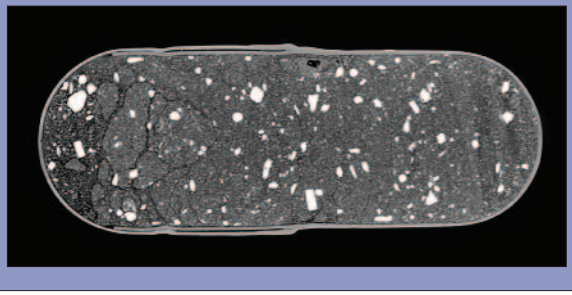


FIGURE 8

CT can detect anomalies and voids and determine their size, absolute volume, and percentage of total product volume.



Additive manufacturing and other new processes. With advances in manufacturing technology come new methods of manufacturing existing products and the ability to create products and formulations that were previously impossible. A good example is additive manufacturing, also known as 3D printing, which has improved the manufacturability and performance of many industrial products. Last August, in fact, the FDA approved Spritam, a 3D-printed orally disintegrating tablet, which indicates that some limits or barriers to formulation are falling away [1]. Perhaps the next advance will enable formulators to strategically place the API within a tablet or capsule, opening up more opportunity for hybrid products that combine APIs in ways never thought possible. Many of these new product configurations could be evaluated and verified using CT. Additionally, CT could help us quickly understand the limitations and variability of these new processes and accelerate process development.

Product shelf life. Even under normal environmental conditions, the density of coatings can change over time, and even subtle changes may affect the drug product's performance. These changes, at least in some materials, can be detected using high-contrast CT techniques, which can help you establish correlations between coating density, drug product performance, and product expiration dates.

Porosity and voids. Some materials, processes, and formulations are prone to the development of high porosity or voids. CT can easily detect these anomalies and provide data about their size, absolute volume, and percentage of total product volume (Figure 8).

In-motion imaging. Four-dimensional imaging—essentially 3D imaging over time—captures true 3D information of an event. Much recent research has focused on CT scanning a product while stresses are introduced in order to reveal how the product or its components react and move. Other work involved putting products in contact with different substances or having substances flow through or around the product. One obvious application of 4D imaging for tablets and capsules is to simulate their behavior in digestive solutions to better understand the dissolution process, from the product's surface to its center. Yet another example: Applying stresses representative of those that the product would undergo during manufacturing or handling processes. By generating multiple, back-to-back CT data sets that capture the product variations under these stresses, you can see how the product's material structure changes over time. From that, you can glean information about how cracks, chips, granular compression, and general surface changes develop and propagate under various stress conditions.

At-line application. While there are many applications for doing laboratory work with CT, the size and speed of the equipment makes it well suited for at-line or even in-line use. That would enable you to conduct tests of batch samples at regular intervals and to evaluate how process changes affected the samples. Using automatic reconstruction and analysis algorithms, CT could deliver quick results to help monitor high-volume operations.

FDA support. Section 3 of the FDA's "Strategic Plan for Regulatory Science," is titled "Support New Approaches to Improve Product Manufacturing and Quality" [2]. It makes clear that the Agency wants manufacturers to investigate and develop new and improved analytical technologies to support or replace existing methods of evaluating product quality. While the document doesn't name CT, it clearly fits into the FDA's strategy. *T&C*

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Additional reading

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