

# Imaging techniques for dry powder inhaler capsules

## An overview of established and emerging capsule imaging techniques

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Dry powder inhalers (DPIs) that employ drug-loaded, two-piece capsules for pulmonary drug delivery have been in use for more than 45 years.<sup>1</sup> During this period, the desire of pharmaceutical companies to improve product function and patient outcomes has resulted in significant changes to the capsules used in DPIs.<sup>2</sup> The first type of capsule used for this purpose was primarily composed of gelatin but more recently, hydroxypropyl methylcellulose (HPMC), or hypromellose as referred to in pharmacopeiae, has emerged as an alternative with a number of potential advantages. HPMC capsules have a lower water content than gelatin capsules, which may be preferable when using water-unstable drug formulations.<sup>3</sup> The elevated water content in gelatin capsules, compared to HPMC capsules, is essential because gelatin capsules require water as a plasticizer. Therefore, at low relative humidity, the mechanical properties of HPMC capsules are relatively unaffected compared to gelatin capsules, which become brittle in these conditions.<sup>4</sup>

Capsules for inhalation are typically filled with a dry powder drug formulation, loaded into a DPI and then punctured using a set of steel pins (typically two or eight pins) to enable powder emission and aerosolization during patient inspiration. The nature of this capsule-puncturing event and its relationship to powder emptying has been well characterized.<sup>5-8</sup> Recent advances in imaging technology may now provide us with further insight into those properties that influence capsule puncturing, as well as new opportunities to extend quality control of the manufactured capsule product.

This article will describe some established and emerging imaging systems that can be utilized to picture two-piece capsules and will highlight potential benefits and limitations of each. These techniques could be employed to image a variety of capsule shell materials. However, exceptions (such as transparency limitations when using optical coherence tomography) are noted. Capsule fill material would not be observed with most of these imaging techniques and the majority of referenced studies were conducted on empty capsules. An exception is computed tomography scanning, which can visualize both shell and fill material.

## Inspection and photography

The first attempts at measuring the dimensions of gelatin DPI capsule punctures was performed using low magnification devices, such as a 10x eyepiece with a graticule marked on the lens.<sup>5</sup> The graticule had a series of circles of increasing sizes. The analyst had to estimate which of the marked holes was the closest in area to the capsule puncture. This method only gave an approximate value and large sample sizes were required to provide reasonable conclusions. This was a time-consuming manual process but it did enable both the size and shape of puncture holes to be characterized and allowed observation of whether the “flaps” of shell material that are formed during the puncture event remained attached to the capsule.

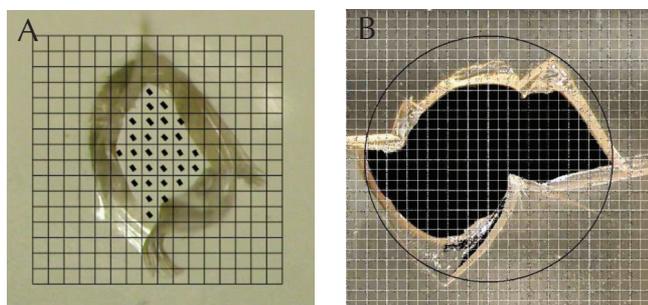
A binocular light microscope with a standard camera was then used to capture images of the capsule puncture sites. The size of punctures was measured using a metal ruler. A scoring system was designed that ranked the uniformity of the puncture hole, i.e., 1 = circular opening and 10 = large, irregular hole, as well as condition of the puncture flap, i.e., 1 = attached, regular shape, no pieces missing and 10 = flap parts of wall missing. The capsules in these tests were all preconditioned by storage in desiccators over saturated salt solutions at relative humidities that would produce capsules with a moisture content below their moisture specification, in the lower half of the moisture specification or at the upper half of the specification. This simple system enabled a comparison of gross puncture performance between different types of capsules and the effect of capsule moisture content on puncturing.

## Optical light microscopy

Attaching a digital camera to a light microscope was a significant breakthrough in gelatin capsule imaging, as it allowed digital images to be displayed on a

**Figure 1**

Images of capsule punctures and the manual method used to calculate the area of the puncture; (A) image of a puncture hole overlaid with a measurement grid to estimate the hole's area; (B) image with grid overlay and a circle drawn to enclose the opening. The ratio of the area of the opening compared to the area of the circle can be used as a measure of circularity.



computer screen and accurate measurements to be made by overlaying them with a grid.<sup>5</sup> Puncture areas could be measured by counting the grid compartments inside the opening and puncture circularity could be derived through comparing the puncture area against the area of a circle drawn around the puncture area; the higher the percentage, the more circular the hole (Figure 1). The digital light microscopy system provided efficiency savings over previous methods due to greater throughput and improved data storage.

The next major development was to post-process images using software such as ImageJ, an open source program developed by the United States National Institutes of Health, designed to characterize multidimensional images.<sup>9</sup> Figure 2 provides examples of the ways an imaging software tool can be used to characterize basic features of capsule punctures. A measurement scale is set using a part of the image of known dimensions, e.g., the diameter of the capsule part being examined. The puncture hole can then be highlighted and its area calculated. In addition, if there is an internal flap present, the area of visible opening can also be measured. ImageJ is therefore able to provide accurate measurements related to the size and shape of two-dimensional digital images of capsule punctures. Contemporary light microscopes and image processing software therefore provide simple, rapid and low cost analyses of DPI capsules. The technology is available in most academic and pharmaceutical industry laboratories and provides a method to examine the gross features of DPI capsule punctures, up to 1,000x magnification.

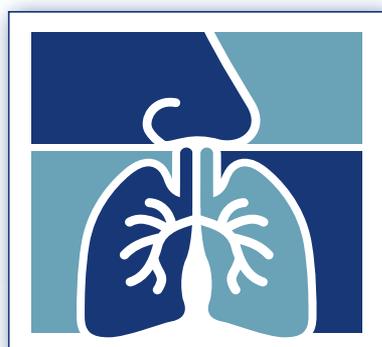
### Scanning electron microscopy (SEM)

Scanning electron microscopy, commonly referred to as SEM, facilitates detailed examination of objects at magnifications that are up to 1,000x greater than optical microscopes (Figure 3). [\(Click to see Figure 3.\)](#) While SEM is not a standard imaging modality for the pharmaceutical industry, the enhanced magnifica-

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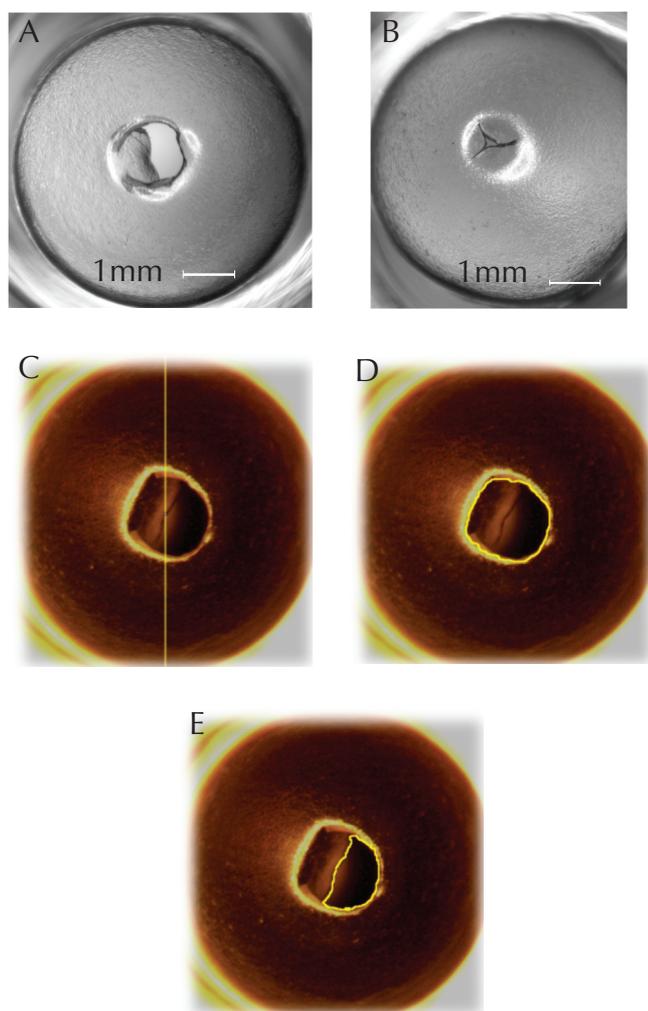
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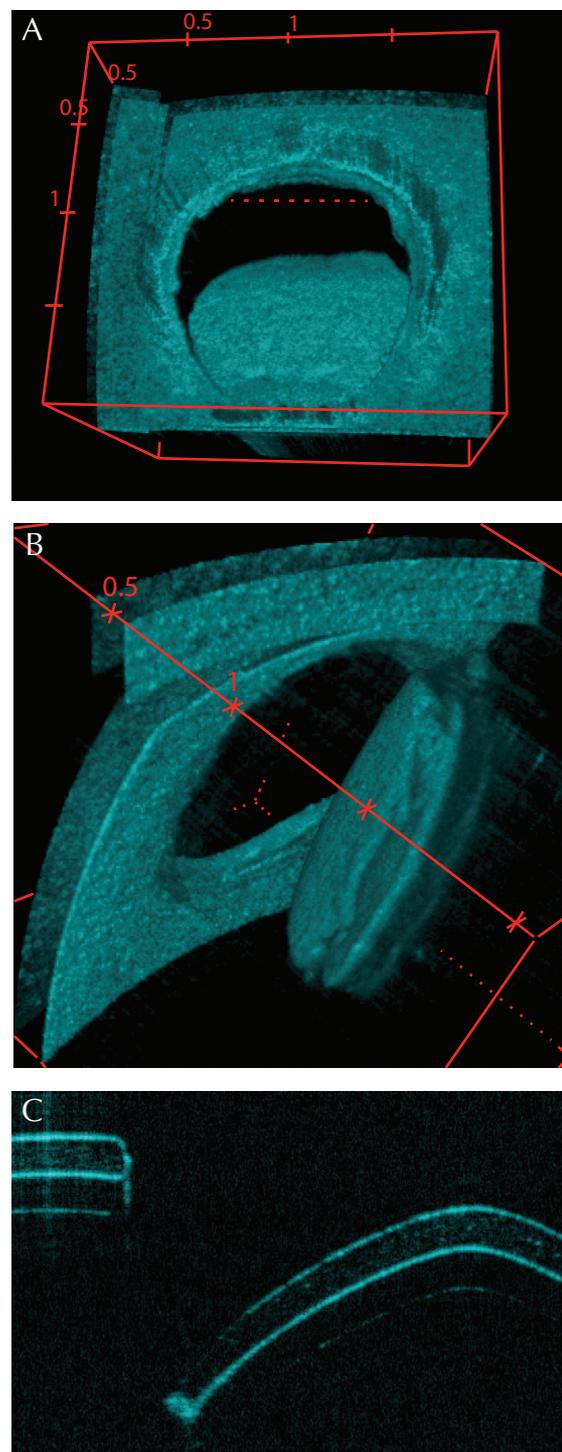
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**Figure 2**

Optical microscope images of capsule punctures (A and B; scale bar = 1 mm). Parameters that can be calculated using appropriate software include measurement line for capsule cap diameter (C), two-dimensional area of a puncture hole (D), two-dimensional area of clear void, not obscured by the flap (E).

**Figure 4**

OCT images of a two-piece HPMC capsule punctured by a Plastiapie RS01 monodose dry powder inhaler. OCT scans are taken in the x, y and z planes. Images A, B and C illustrate some of the orientations that can be used to characterize a punctured capsule.



tion and resolution of SEM enables characterization of fine surface morphology in the nanometer scale.<sup>10</sup> SEM has been used in laboratory studies to provide useful insight into the ultrastructure of both intact and punctured capsules,<sup>11</sup> as well as capsule fragments,<sup>12</sup> from both HPMC- and gelatin-based capsule products.

The technique focuses a fine beam of electrons on to the object surface and uses the resulting signals, predominantly secondary electrons, to construct an image. Successful SEM imaging requires (i) the object surface to be a good electrical and thermal conductor, and (ii) limited volatile components to permit high vacuum conditions. Two-piece capsules are therefore pre-treated with a nanometer-thick coating of an electrically conducting metallic film such as gold, prior to analysis. Sample preparation for SEM is a standard laboratory technique, however it is associated with a number of acknowledged limi-

tations, including the creation of artifacts such as the concealment of surface coatings and features by the metallic coating.

Technical advances in recent years have led to the development of environmental scanning electron microscopy (ESEM).<sup>13</sup> This variation of SEM permits observation of hydrated and non-conductive materials without sample preparation and therefore

the technique has established itself as a key analytical tool for biological specimens and polymers. More recently, ESEM has been used to visualize capsule materials without any prior sample preparation<sup>11</sup> and therefore, while this imaging technique is not as accessible as optical microscopy, laboratory studies are now able to characterize capsule fine structural detail without the influence of artifacts.

### Optical coherence tomography (OCT)

Although SEM can provide high magnification images with nanometer resolution, the data that is captured provides a two-dimensional representation of a three-dimensional (3D) object. Optical coherence tomography (OCT) is a medical imaging technology that has been used extensively to capture data from biological tissues such as the eye and the skin.<sup>14, 15</sup> OCT uses near-infrared light to obtain sub-surface data and therefore can be used to provide 3D visualizations. In recent years, OCT has emerged in laboratory studies as a potential non-destructive method to image the shell of a two-piece capsule<sup>11</sup> and has been able to provide live imaging of the object, including transverse sections of the capsule shell and ImageJ-rendered 3D reconstructions of puncturing events in both gelatin and HPMC capsules (Figure 4).

One of the major advantages of this technology is that it requires no sample preparation and, unlike computed tomography (described below), it does

not use ionizing radiation. It therefore provides rapid and safe analysis and does not damage the sample. OCT has been likened to an optical form of ultrasound, however a major difference from ultrasound is the lower penetrative capabilities of optical light. Data is typically collected up to a depth of a few millimeters and while this enables capture of detailed information about the capsule shell, it does not permit visualization of capsule contents. Additionally, OCT can only be used on translucent samples and therefore some pigments in capsule formulations e.g., titanium dioxide, prevent its use.

### Computed tomography (CT)

Computed tomography (CT) uses multiple X-rays to produce a series of images that can be constructed to provide a non-invasive, 3D representation of the object. CT scanning is established in the medical field as a critical diagnostic tool to provide detailed 3D images of biological tissues. In recent years, CT has been utilized in a growing range of industries, including the pharmaceutical industry, where the technique provides a powerful tool for the assessment of solid pharmaceutical formulations as well as the accompanying packaging.<sup>15</sup> CT scanning can extract sub-surface measurements in the micron range and, unlike OCT, is not constrained by the depth of penetration. Therefore, it can be used to capture 3D images of an entire two-piece capsule at multiple orientations (Figure 5), thereby providing

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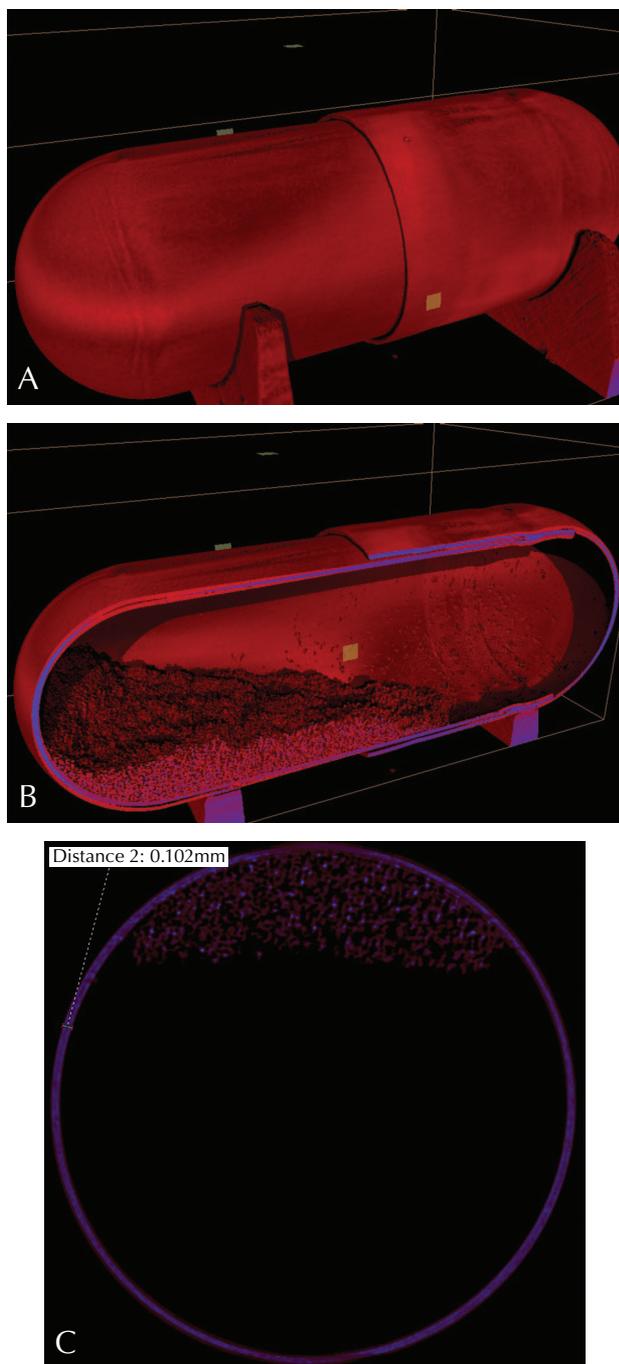
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- The AOS (Axial Oscillating Sphere) add-on device as a novel tool to improve powder dispersion
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## Figure 5

CT scans of a Quali-V-I capsule (Qualicaps, Whitsett, NC, US) containing 20 mg of Pharmatose (lactose monohydrate, DFE Pharma). Images illustrate views of the intact capsule from the exterior (A), interior (B) and in transverse section (C).



information, in a non-destructive manner, about capsule shell thickness, uniformity and integrity and also the capsule contents.<sup>16</sup>

At present, the technology is costly and, unlike OCT, relies on the use of potentially harmful x-radiation to analyze samples. There are a number of practical constraints to ensure the x-radiation is contained during sample analysis, but this has restricted sample sizes and analytical speed. However, leading technologists in this area are now developing high-speed, and potentially high-throughput, imaging systems that are

capable of capturing images in seconds rather than minutes.<sup>17</sup> High-resolution, 3D images (potentially in the sub-micron range) and the non-destructive nature of this technique enable the user to evaluate capsule formulations in a way that has not been previously possible. Therefore, although CT is currently used in laboratory research and development (Figure 5), there is significant potential in both product development and quality assurance in the industrial setting.

## Concluding thoughts

The development of new imaging technologies, combined with advances in some of the more established techniques, has facilitated better characterization of capsules. In recent years, technologies such as ESEM, OCT and CT have extended their utility from biological samples to pharmaceutical products. Enhanced imaging techniques have enabled research and development teams to better understand the behavior of capsules following puncture by a DPI as well as interaction of capsule material with powdered contents. While to date the majority of these imaging modalities have been applied exclusively in the laboratory setting, they have potential applications in the pharmaceutical industry where their use could improve characterization of capsule products and enhance quality assurance. It is therefore important that those involved in development and quality assurance of DPI capsule-based products keep abreast of these advancements because it is not difficult to picture a future where capsules will be viewed differently.

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