When it comes to imaging at high magnifications, the traditional optical microscope has given way to a number of alternative technologies. The Scanning Electron Microscope (SEM) has been used for approximately 50 years and, compared with its optical ancestors, offers high resolution images with large depth of field. But advancement in image resolution of the SEM (~2nm in practice) has stagnated in recent years, mostly due to electron diffraction and the physics of the beam/sample interaction.

The transmission electron microscope (TEM) avoids these problems, but requires a very sophisticated sample preparation procedure. In the special case of where it is permissible to be in contact with the sample, there are a number of scanning probe techniques that can be used such as Atomic Force Microscopy (AFM), Scanning Tunnelling Microscopy (STM) and Near-Field Scanning Optical Microscopy (NSOM). While offering excellent resolution, these images require some manipulation before the human eye can intuitively interpret them.

One could reasonably argue that the last dramatic breakthrough in the world of imaging happened in the early 1980s with the discovery of the scanning tunnelling microscope by Gerd Binnig and Heinrich Rohrer, for which they won the 1986 Nobel Prize in Physics. More recently, the development of the Helium Ion Microscope by ALIS Corporation offers the promise of a new and unique imaging technique as an alternative to existing microscopes.

THE HELIUM ION MICROSCOPE

The ALIS helium ion source provides intense ion currents from a volume no larger than a single atom. The ion source consists of a sharp needle that is maintained under high vacuum and cryogenic temperatures. A high voltage is applied to the needle to produce an extremely intense beam of helium ions that can be used to probe and image materials at the atomic level.
electric field at its apex. The field is sufficiently strong that any nearby helium gas atom will have an appreciable probability of having an electron tunnel out. The resulting positive ion will then be accelerated away from the needle. When the needle is appropriately shaped (see Figure 2), the ionisation process happens in the vicinity of a single atom at the apex of the needle, and the resulting ion beam appears to be emanating from a region that is less than one Angstrom in size. Consequently, the resulting ion beam has a remarkable brightness of $4 \times 10^9$ A/cm$^2$sr. The high brightness is a necessary condition for focusing the beam to a small probe size (1).

The helium ion beam is then steered down a column that includes a series of focusing, alignment and scanning elements. The resulting beam can be brought to a focused probe size of just 0.75 nm. Much like a SEM, the beam is rastered across the sample, pixel by pixel. The number of detected secondary electrons is used to determine the grey level of each particular pixel. Since the number of detected secondary electrons varies with material composition and shape, the images provide excellent topographic and compositional information. Some examples of the images that can be obtained with a helium ion microscope are shown in Figures 3 and 4. Figure 3 is an image of a white blood cell that shows both topographic and material details, and Figure 4 shows a high magnification image of a carbon nanotube.

Some of the advantages of the helium ion microscope arise from the properties of helium. Helium atoms are much more massive than electrons, so their deBroglie wavelength is short enough that the focused probe is not strongly affected by diffraction effects. In contrast, most traditional SEMs are limited by the diffraction effects arising from the electron’s wave-like properties. As the helium ion beam penetrates into the sample, there is little scattering, so the images do not suffer from the sub-surface blurring effects that are common in SEM images (2). Therefore, the helium ion microscope can provide images with higher resolution and more surface specific information.

In addition to images created through secondary electron detection, the incident helium ion beam offers other opportunities for imaging and analysis. A small fraction of the helium atoms will be scattered by heavier nuclei and ricochet out of the sample. The probability of this occurring depends critically upon the atomic number of the scattering nucleus. So images based on the abundance of scattered helium ions provide a strong elemental contrast which can be used to distinguish different materials. The image in Figure 5 (see page 30) demonstrates the strong contrast between the chrome and quartz of a photomask. Another advantage of this imaging mode is the strong immunity to charging artifacts, since the scattered helium atoms are not appreciably deflected by these electric fields.

**HIGH RESOLUTION IMAGING**

Scanning Electron Microscopes are commonly used in the pharmaceutical industry for imaging drugs and for doing chemical analysis using Energy Dispersive X-Ray Spectroscopy (3). Environmental SEMs (ESEMs) are typically the instrument of choice for imaging as they can mitigate the charging effects that are often encountered when imaging non-conductive samples in a SEM. In the ESEM, a small amount of gas, typically water vapour, is injected into the vacuum chamber in close proximity to the sample in order to help dissipate charge. The water vapour can and does react with the sample. This can be beneficial if one wants to study the effect that water has on a particular sample (4). However, if one doesn’t want the sample to interact with a gas such as water, imaging non-conductive samples can pose a problem with the SEM.

The Helium Ion Microscope does not suffer from the charging issues commonly encountered with the SEM. The imaging beam is positively charged helium ions; these can induce a positive charge on the sample, but this charge can be effectively neutralised using an electron floodgun. In the multiplexed imaging mode, the electron floodgun can be turned on and off rapidly during image acquisition to effectively neutralise any charge induced...
by the helium ion beam. This image acquisition technique has been used by focused ion beam tools in the semiconductor industry for more than twenty years. Figure 6 shows an image of the cephalosporin antibiotic cefuroxime (Ceftin, GlaxoSmithKline) acquired using multiplexed imaging on the Orion helium ion microscope. There is no evidence of charging in the image.

MATERIAL ANALYSIS

It is often desirable to analyse a sample to ascertain some information about its chemical composition. This can be accomplished with a SEM using Energy Dispersive X-Ray Spectroscopy (EDS). With this technique, an electron beam of sufficient energy to generate X-rays is focused on the sample being analysed. The X-rays that are induced by the electron beam are collected and analysed to determine the elemental composition of the sample. This technique has two shortcomings. Insulating samples can charge up and deflect the beam from its intended location, giving false or misleading information. Also, the interaction volume in the sample from which the X-rays are emitted can be relatively large, limiting the spatial resolution of this technique.

Since helium is so much heavier than an electron, low and medium energy helium ions don’t produce appreciable X-rays. Fortunately, even in the absence of X-rays, helium ions can still be used to provide elemental identification. The helium ions scatter off of heavier nuclei, and their scatter angle and energy can be used to determine the mass of the scattering atom. The same method can also provide structural arrangement of the surface atoms. Although this option is not presently available in the commercial helium ion microscope, the physics is highly developed and well understood. The same principle of analysis is used with the established techniques of Medium Energy Ion Scattering (MEIS), Low Energy Ion Scattering (LEIS) and Rutherford Back-Scattering (RBS) (5). But unlike these techniques, which use ion beams measured in mm, the helium ion beam can provide information at the nanometer length scale.

CONCLUSION

The Orion Helium Ion Microscope represents a breakthrough in the field of microscopy and the first commercial shipments of the instrument have now taken place. Much investigation remains to be done to find those applications for which this technology is best suited. Several attributes of the technology – such as high resolution, strong material contrast, immunity to charging and the ability to perform material analysis at the nanometer scale – make it an intriguing option for the imaging needs of the pharmaceutical industry.

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