Published on *MDDI Magazine* (http://www.mddionline.com)

The Microsphere of Influence

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Created *01/04/2011 - 12:56*

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Published: January 2011
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The Microsphere of Influence

A variety of microspheres are useful in validating and testing medical devices.

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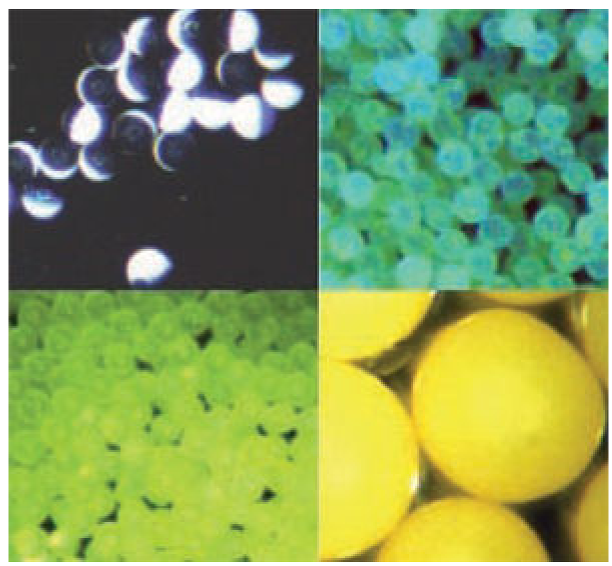
Microspheres are round microparticles that typically range from 1 to 1000 µm in diameter. In the pharmaceutical and cosmetics industry, microspheres are well known for their ability to deliver active materials. This process usually involves the microencapsulation of a drug or an active cosmetic ingredient to protect it from the deteriorating effects of the environment or for optimal release and performance in the final product. Active ingredients are released by dissolution of the capsule walls, mechanical rupture (rubbing, pressure, or impact), melting, or digestion processes. Solid microspheres are widely used as fillers and spacers in a variety of industries.



Microspheres come in many different grades and sizes, and are usually solid particles that are composed of polymers, glass, and ceramics. ***All images courtesy of COSPHERIC LLC***

Microspheres used to manufacture and test medical devices are typically solid particles that are made from robust and stable raw materials such as polymers, glass, and in some cases, ceramics. Different types and grades of microspheres are available and selected based on specific application requirements.

They are often used as tracers and challenge particles in medical devices. In these situations, it is beneficial to use larger microspheres with sphere diameters greater than 50 µm that are vividly colored (red, blue, black, yellow, or green), since they provide contrast with the background material and visibility to the naked eye in daylight. Colored microspheres are typically used in the testing of filtration media and systems, vial and container cleaning evaluations, flow tracing and fluid mechanics, centrifugation and sedimentation processes, pharmaceutical manufacturing, and contamination control.

Fluorescent microspheres are recommended for applications that require the use of particles that emit distinctive colors when illuminated by UV light and offer additional sensitivity for observation through the use of microscopes, lasers, and other analytical methods. Examples include microcirculation and biological research, imaging, and flow cytometry. Fluorescent microspheres can be excited and detected by a wide range of methods and are useful as experimental particles for acoustical and optical analytical systems.

Other types of microspheres that are relevant to medical devices are optically opaque and radiopaque, as well as charged and magnetic microspheres. Opaque microspheres are desirable for maximum contrast in optical and electron beams. Charged and magnetic particles are capable of being manipulated with electromagnetic fields.

Monodisperse microspheres are used for calibrating microscopes, light-scattering equipment, and other particle measuring devices. They are ideal for spacer applications in which uniform bond thickness is a necessity. Particle-size standard spheres can be used to develop and test new analytical instruments for particle size materials characterization.

Microspheres are particles that are often supplied as dry powder or in a solution. Superior sphericity and roundness offer omni-directional spreadability and easy cleanup. Microspheres can be directly observed on the surface or in the media being tested. In addition, due to their controlled particle size, they can be filtered out, collected, and recycled at the end of the testing process.

Fluorescent Microspheres

Fluorescence occurs when a molecule absorbs energy in the form of light and immediately releases this energy again in the form of light. The excitation wavelength is the characteristic wavelength that a molecule absorbs, and the emission wavelength is the characteristic wavelength that a molecule emits.

Fluorescent microspheres emit bright and distinctive colors when illuminated by light of shorter wavelengths than the emission wavelength. The intense color emission improves their contrast and visibility relative to background materials. In addition to the benefits of conventional high-quality microspheres, such as sphericity, smoothness, and spreadability, fluorescent spheres offer extra sensitivity and detectability for analytical methods. Fluorescent microspheres can be detected with an epifluorescence microscope, confocal microscope, fluorometer, fluorescence spectrophotometer, or fluorescence-activated cell sorter. They can also be detected using a mineral or UV light.

Fluorescent microspheres are available in a variety of excitation and emission wavelengths. These wavelength variations enable complex technical experiments in which colored microspheres represent different experimental variables or conditions and can be separated on the basis of either their excitation or emission spectra. For example, using fluorescent microspheres in different sphere diameters provides an additional controlled variable that lets scientists and engineers track the initial location of the microspheres.

Yellow polyethylene microspheres, measuring 355 to 425 µm (magnification 40x) can stand out against background materials.

A unique property of fluorescent spheres is their ability to appear translucent and practically invisible under ordinary light and emit intense visible color when energized. This effect enables blind tests and controlled experiments in which the microspheres are invisible to the operator until the procedure has been conducted, eliminating any operator bias and uncertainty in the validity of experiment. This unique feature of fluorescent microspheres has numerous applications in the development and testing of medical devices (e.g., simulating the spread of contamination and viruses, vial and container cleaning evaluations, and process troubleshooting and control).

Most fluorescent microspheres are hard-dyed (internally dyed) polymer beads that use proprietary processes to incorporate the fluorescent colorant throughout the polymer matrix. This method produces bright fluorescent colors, minimizes photobleaching, and prevents colorants from leaching into surrounding media. The spectral properties of the fluorochromes are dependent on their concentration and physical environment. The exact excitation and emission maxima may vary depending on the size and composition of the microspheres. There are several different types of fluorescent polymer microspheres on the market that are produced from a variety of raw materials, making them suitable for a variety of applications.

The specific gravity of fluorescent microspheres can be adjusted to match the specific gravity of water or other desired media. Particles that are heavier than the media in which they are dispersed will settle to the bottom of the container over time. Particles that are lighter than the media will float to the top and accumulate on the surface. Matching the specific gravity of the microspheres to that of the base solution creates a stable suspension of particles, which ensures uniform distribution and prevents their settling out or collecting at the top of the container. This matching is achieved by selecting a base polymer close to the desired density and using proprietary additives that are incorporated into the polymer matrix during the manufacturing process. This process matches the specific gravity of the microspheres to water or other desired media and results in neutrally buoyant particles and an optimal suspension of particles in solution.

Fluorescent microspheres are often used in fluorescence microscopy and photography, as well as biomedical technology research and biomedical diagnostics. They are often used for water- and airflow testing and bead-based diagnostic applications. Unique applications of fluorescent spheres are continuously being discovered.

Colored Microspheres

Microspheres used as tracers and challenge particles in medical devices do not necessarily have to be fluorescent. As previously stated, brightly colored microspheres can provide contrast with the background material and visibility to the naked eye in daylight.

Solid polyethylene microspheres are smooth, highly spherical particles that are nonsoluble in water and most solvents. They can be manufactured in any color and withstand temperatures of up to 100°C. These spheres can be manufactured with specific gravities from 0.96 to 1.3 g/cc. Solid polyethylene microspheres incorporate pigments and additives inside the polymer matrix to achieve colorful particles that are visualized on the surface of a material or in a solution.

The advantage of using solid, colored microspheres instead of pigments or dyes is that microspheres are much more robust and controlled particles, and easy to handle and clean up. Pigment particles are very small, difficult to disperse, and can be hazardous. Typically, pigments of particle sizes smaller than 1 μm are used to increase tint strength. However, powders of pigment particles in the submicron size range are difficult to work with because they tend to clump together, and as a result, do not disperse properly in a solution. In addition, powders less than 5 μm in size are considered respirable by the Occupational Safety and Health Administration because they are small enough to penetrate the nose, upper respiratory system, and the lungs, which is a health hazard for workers regularly exposed to the dust. Because microspheres are usually 5 μm or larger, they are easier to handle and do not create respiratory hazards.

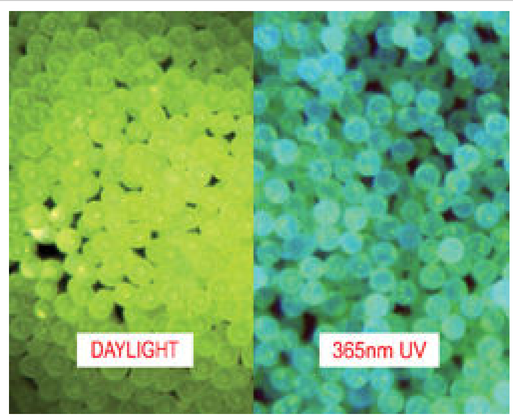
Microspheres are often supplied as a free-flowing dry powder to ensure a simple formulation, controlled application, and easy cleanup. Colored microspheres can be visualized with the naked eye, measured and filtered out, wiped off, or recycled at the end of the process. For example, if rinse water is being examined, microspheres can be collected on filter membranes for visual or microscopic inspection.

Opaque Microspheres

Generally, when light strikes an interface between two substances, some of the light is reflected, absorbed, and scattered, and the remainder is transmitted. An opaque substance transmits little if any light and therefore reflects, scatters, or absorbs most of it. The opacity of the microspheres can be quantified in many ways, including viewing the spheres under a microscope with a backlight or measuring the reflectance of the monolayer spheres on white and black backgrounds.

Opaque microspheres do not allow light to pass through, which means that a monolayer of opaque spheres will not transmit light, resulting in maximum hiding of material and color underneath. Opaque microspheres are desirable for maximum contrast in optical and electron beams. They are also beneficial for applications in which uniform color and hiding power of the color beneath is desired. Polymer microspheres can be designed as transparent and invisible to the eye, partially translucent, or opaque, which provides maximum hiding power.

In general, high levels of opacity become more difficult to achieve in microscopic particles because opacity is proportional to the material thickness. Due to the chemistry of glass, it is difficult to create opaque glass spheres. Most colored glass microspheres are made by attaching dyes to the surface of the particle and do not achieve significant opacity. Ceramic microspheres can be opaque but microspheres in a batch usually do not have the same level of opacity (some are more opaque than others). The manufacturing process for the polyethylene microspheres enables the incorporation of colorants and opacifiers inside the solid sphere, which ensures that spheres are produced with identical color and opacity.



Fluorescent polyethylene microspheres change color under UV light.

Optical opacity, as described above, is defined as the degree to which something reduces the passage of light. It should not be confused with radiopacity, which is the phenomenon of not permitting the passage of electromagnetic radiation, otherwise known as opacity, to x-rays or other forms of radiation. Some medical device development applications require radiopaque microspheres, which can be achieved by incorporating magnetic and metallic elements into the microsphere structure. This process allows the microspheres to be easily detectable by x-ray and demonstrates superior contrast and reflectivity in optical, ultrasonic, and electron beam detection methods.

Monodisperse Microspheres

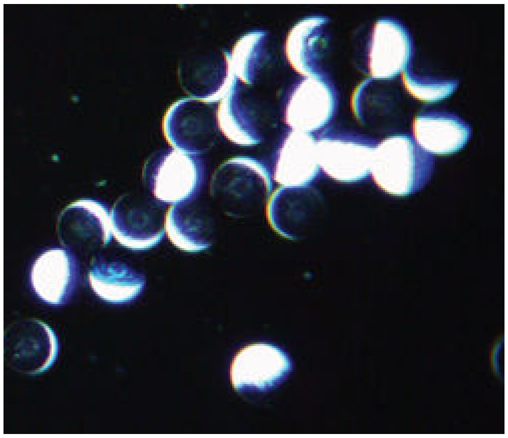
As previously mentioned, monodisperse microspheres have applications in microscopes, light-scattering equipment, and other particle measuring devices. Certified particle-size standard microspheres are traceable to the standard meter through the National Institute of Standards and Technology (NIST). This feature lets laboratories demonstrate the traceability of their analytical methods as required by ISO 9000, ISO 10012, ANSI/NCSL Z540, GMP/GLP, and other standards and regulations. Particle-size standard spheres can be used to develop and test new analytical instruments for particle size characterization of materials. It is very difficult to visualize 3-D objects with analytical instruments. Because the instruments can typically focus on only one surface, 3-D objects often produce images of distorted shapes. Using spheres, which have the same dimensions when viewed from all angles, instead of irregularly shaped particles, minimizes these effects.

Charged, Magnetic, and Metallic Microspheres

To create positive or negative charges, proprietary additives are embedded into each microsphere during the manufacturing process. This charge is permanent; it does not dissipate over time and cannot be grounded. The whole microsphere is charged and will respond to electric fields. Dark-colored or black microspheres can be made magnetic or static-dissipative, and a black magnetic coating on a portion of the microsphere can be used to create functionalized hemispheres. For example, magnetic half-shells can be manipulated to rotate microspheres with an electromagnetic field.

One particularly interesting and unique feature of magnetic half-shell microspheres is their ability to orient themselves in response to electromagnetic fields and show a visual response to the observer. This response is achieved by making spheres both bipolar and bichromal, with the dipole precisely aligned with two differently colored hemispheres. Due to the dipole, the sphere will rotate in an electromagnetic field to align the more positive hemisphere to the negatively charged stimuli and vice-versa. As the spheres align themselves, the viewer will observe the color of one hemisphere, while the other hemisphere will be hidden from view to provide a strong visible indication of the presence of the field. In an alternating electromagnetic field, these microspheres can spin at hundreds of times per second.

This superior functionality is achieved with a proprietary and patented process that allows extremely precise coating on one hemisphere without affecting the other. Each coating is custom formulated for color, charge, and solvent resistance, and magnetic, electric and surface properties per a customer’s needs. Hemispherical coatings of less than 1 μm with tolerances as low as 0.25 μm have been routinely demonstrated. Color combinations are virtually unlimited —white, black, silver, blue, green, red, yellow, brown, and purple, as well as transparent microspheres, have been made. Sphericity exceeding 90% and custom particle size ranges are available.



Functionalized bichromal microspheres (magnetic half shells).

The spheres were originally developed for very high-tolerance electronic paper reflective digital displays in which functionalized microspheres were used to create an image that appears to the viewer. To achieve high resolution in display applications, it is critical that every single sphere responds to the electromagnetic field in the same way and at the same time and that it aligns precisely with the other spheres. It is also critical that there are no color gradients in the display.

The orientation of bichromal microspheres for application in medical devices requires further exploration but is a promising area of future development. This technology could potentially be used as a visible marker of the presence of an electromagnetic field in a medical device, as well as for tracer or carrier particles manipulated with an electromagnetic field.

For skin-based medical devices, charged microspheres can be used to design products that are attracted to or repelled from the skin. Human skin has a highly positive electrostatic charge. Because like charges repel and opposite charges attract, the charge of the product can be manipulated to be more attracted to the skin if the product is designed to remain on the skin for a long time. It can also be manipulated to be less attracted to the skin if the product only needs to remain for a short time, making the product easy for the user to remove.

Conclusion

High-quality polymer microspheres are commercially available in a wide variety of colors and with controlled fluorescence, opacity, specific gravity, particle size distribution, and electrostatic charge, presenting endless possibilities for use in developing and testing medical devices. To select the right microsphere for the job, one must rely on detailed knowledge of the application and on the technical judgment of those working on the project, and employ a simple trial-and-error approach.

Yelena Lipovetskaya is cofounder of Cospheric LLC (Santa Barbara, CA).