Microspheres Play Role In Medical, Sensor, Energy, Space Technologies

■ Symposium highlights their potential as laser fusion targets, blood substitutes, sensors, and antistatic coatings

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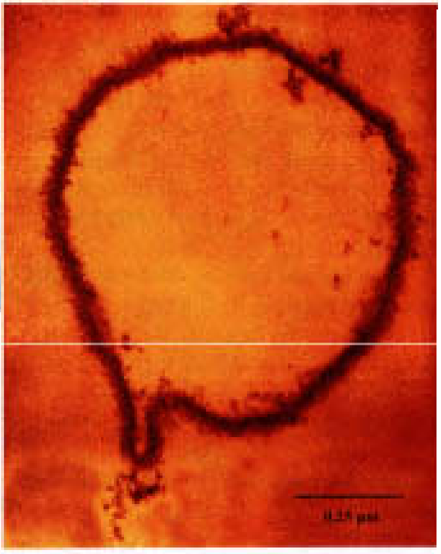
David L. Wilcox Sr. squeezed the trigger of the toy gun in his hand, shooting iridescent soap bubbles toward his colleagues seated before him in the hotel meeting room. Wilcox, an adjunct professor of materials science and engineering at the University of Illinois, Urbana-Champaign, was conveying how our fascination with bubbles-and spherical shapes in general-is rooted in childhood.


C&EN staff photo



Suslick (above left) and Wong may have created a promising blood substitute, hemoglobin microbubbles; a thin slice of one microbubble is seen in a transmission electron micrograph (right) produced at the University of Illinois Center for Electron Microscopy by Lu Ann Miller, Wong and Suslick.

It was a playful, albeit appropriate, way to launch into a symposium on the science and technology of spheres and microspheres, held earlier this month at the Materials Research Society meeting in Boston.

The scientists at this gathering, though, were interested in spherical objects much smaller than a soap bubble-and made of much more robust material. Here's a sampling of the materials and applications that attracted their attention:

- Hemoglobin microbubbles that might one day be utilized as a blood substitute.
- Porous glass microspheres, doped with dye, that form the heart of a versatile new fiber-optic sensor system.
- Hollow plastic microspheres that are used in nuclear fusion experiments to hold the fuel before it is blasted by powerful laser beams.
- And indium oxide microspheres that, when blended into a polymer matrix, could provide a superior antistatic coating for spacecraft.

As Wilcox noted in his introductory talk, fabrication technology for microspheres-both solid and hollow--are critical for a broad range of applications that have been or are being developed-including bearings, catalyst supports, abrasives, ballpoint pen tips, composites, thermal insulation, electrical circuit boards, shock-absorbing armor plate, metering, drug release, and gas or chemical storage, to name just a few.

A good chunk of the symposium, which was organized by Wilcox and his colleagues, dealt with various methods used to make microspheres.

One of the more unusual methods involves high-intensity ultrasound. Kenneth S. Suslick, a professor of chemistry and of materials science and engineering at the University of Illinois, Urbana-Champaign, previously showed that ultrasound can convert serum albumin into hollow proteinaceous microspheres. These microspheres are formed by chemically cross-linking cysteine residues of the protein around a micrometer-sized gas bubble or liquid droplet. The cross-linking is effected by superoxide (HO_2), which is sonochemically generated from oxygen and water when bubbles energetically form and collapse in the irradiated liquid.

In Boston, Suslick and graduate student Mike Wong described for the first time how they have extended this work to make functional, gas-filled microbubbles of hemoglobin. These spherical particles are about 2.5 pm in diameter-half the size of a red blood cell. And they have a 35-nm-thick shell (about six protein molecules thick). Wong and Suslick calculate that a microbubble 3 pm in diameter would contain about 1 million hemoglobin molecules.

According to Suslick and Wong, these hemoglobin microspheres have many of the characteristics sought in a blood substitute. The ideal blood substitute must fully bind oxygen in the lungs and efficiently unload it in the tissues. It should respond to naturally occurring molecules in the body (such as. organic phosphates) that regulate its oxygen-binding properties in vivo in response to metabolic needs. A usable blood substitute should have adequate oxygen-carrying capacity. It must not trigger an allergic response or damage the kidneys or other organs. And it must be stable under storage conditions. In tests so far, the hemoglobin microbubbles appear to meet these criteria "surprisingly well," the Illinois chemists report.

The research, which is funded by the National Science Foundation and the National Institutes of Health, has led to a series of surprising discoveries, Suslick says. The biggest surprise involves the so-called cooperativity of oxygen binding. Hemoglobin is a tetrameric protein containing four O_2-binding heme groups. Scientists have known for a long time that the binding of O_2 to hemoglobin enhances the binding of additional O_2 to the same hemoglobin molecule. Wong and Suslick found that the degree of this cooperativity between O_2-binding sites is significantly enhanced in the microbubbles over that observed in native (non-cross-linked) hemoglobin.

The increase in cooperativity apparently is due to cross-linking between hemoglobin tetramers within the proteinaceous shell of the microbubble, Suslick explains. Experimental data indicate that cross-linking allows some 20 heme sites to interact-that is, to sense the conformation of nearby sites. This interaction changes the conformation of the protein so that the heme binding sites become fully occupied with O_2 at high oxygen pressure (in the lungs) and liberate all of the oxygen at low pressure (in tissues needing oxygen).

Wong and Suslick have performed calculations showing that hemoglobin microbubbles can carry more oxygen than whole blood or the fluorocarbon emulsion Fluosol-DA 20% (a blood substitute commercially approved for a surgical procedure). Each milliliter of whole blood can carry 0.2 mL of O_2. Fluosol-DA is not as good, carrying only 0.05 mL of O_2 per mL of fluid. When hemoglobin microbubbles are filled with pure O_2, their gas-carrying capacity is 0.32 mL per mL–50% greater than whole blood. In addition, the microbubbles show minimal degradation (less than 25%) after storage for 6 months at 4 "C. Considering that whole blood has to be discarded after six weeks, Suslick thinks that's pretty good.

Nevertheless, he notes that "we're at a very early stage" in the testing of these hemoglobin microbubbles. In vivo studies, for example, will be needed to assess the microbubbles' longevity in the bloodstream and to check for possible toxic or immunogenic effects. Even if the microbubbles pass all these tests with flying colors, it will be years before they are approved for human use.

Ceramic microbubbles also can be used to transport gases (not to mention liquids and solids), but they have a lot of other potential applications as well. Materials scientist Edward J. A. Pope, for instance, is interested in using porous glass microspheres as the "nose" for new sensing systems. He dopes these microspheres with an optically active organic compound (a dye) whose spectral signature changes in the presence of a specific analyte. The microsphere is glued to the tip of an optical fiber that conducts light from a spectrophotometer into the microsphere and then back to the instrument. The presence of certain chemical species causes the dye's absorption or emission spectrum to shift, and this change can be spectrophotometrically detected.

Pope is president of Matech, a four-person materials technology company in Westlake Village, Calif., near Los Angeles. In his laboratory there, he makes silica (SiO_2) microspheres by stirring together two immiscible liquids-tetraethoxysilane and hydrochloric acid solution-near room temperature. By adjusting the stirring speed, he can control the average diameter of the microspheres formed, from a few micrometers to a few millimeters. When organic dyes (or other dopants, such as metal salts) are added to the acid solution, they are incorporated into the porous microspheres.

Pope has used this variant of the well-known sol-gel process to make microspheres that luminesce in different colors. These glowing microspheres serve as the pixel elements in a new type of flat-panel color display that he has developed as a prototype. He hopes to develop this flat-panel technology further.

In Boston, though, Pope focused on use of doped microspheres as part of fiber-optic microsensors. The optical fiber allows the microsphere sensor to be deployed to remote locations that may be difficult or impossible to reach by other means. For example, Pope says, fibers can be used for medical biopsies of the human body. They can also be sent down wells and mine shafts or to the bottom of lakes and rivers for environmental monitoring.

Pope has demonstrated that fiber-optic microsphere sensors could be used for such mundane tasks as measuring pH, temperature, and the organic solvent content of aqueous solutions. He is more enthusiastic, though, about two other potential applications: detecting heavy metals in the environment and detecting antibodies or antigens in biomedical diagnostics.

All this work is very preliminary, Pope stresses, and many key issues, such as dye leaching, long-term stability, and sensitivity, will need to be addressed. But he sees a bright future for such microsphere-based sensors.

The future also looks bright for experiments using a very different type of microsphere to try to harness nuclear fusion for producing electrical energy. Researchers at Lawrence Livermore National Laboratory in California make hollow plastic microspheres and load them with gaseous deuterium, a fusion fuel.

During the fusion experiments, energy from high-powered laser beams is absorbed by the surface of the plastic shell. "As the outside of the shell (called the ablator) burns off, the reaction force accelerates the rest of the shell inward, compressing and heating the deuterium inside," explains physical chemist Robert C. Cook, who heads the group developing capsule materials for Livermore's laser fusion program. If high enough densities and temperatures are produced in the center of the capsule, deuterium nuclei fuse to give tritium, helium, and other particles, releasing an enormous amount of energy. "The fuel's inward motion is all that keeps it together long enough for all this to occur," Cook says. Hence the name for this process: inertial confinement fusion (ICF).

"Although the laser system that provides the energy is as large as a football field, the [microsphere] target containing the fuel is only about 0.5 mm in diameter," Cook points out. The target consists of three layers. The inner layer, which compresses the fuel, is a polystyrene shell about 3 pm thick. Next comes a layer of poly(vinyl alcohol), also about 3 µm thick, that retards diffusion of deuterium out of the capsule. The outer layer (the ablator) is about 50 pm thick and consists of a highly cross-linked polymer made from 2-butene.

The three-layer capsules are constructed in three steps. In the first, a polystyrene solution is dripped down a heated tower 15 feet high. The solvent evaporates as the droplets fall, leaving a hollow polymer shell. The poly(vinyl alcohol) layer is added in a second "drop-tower" operation. The ablator layer is laid down by a plasma-assisted polymerization coating technique similar to those used in the semiconductor industry.

The resulting microspheres have extremely smooth surfaces--surface roughness is about 0.004% of the sphere's diameter. By comparison, ball bearings this size typically are about six times rougher-their surface roughness is about 0.025% of their diameter.

This exceptional smoothness (and symmetry) is necessary "to help overcome one of ICF's most difficult problems-the capsule's strong tendency to implode asymmetrically," Cook says. Any perturbations in the ablator surface tend to get bigger as the capsule is compressed. When this happens, relatively cool material becomes mixed with the hot, compressed fuel, spoiling the compression.

ICF targets made of organic materials have been in use only since the mid-1980s, Cook notes. Before then, the targets were made of glass. Cook's group makes thousands of polymer microcapsules each year, but only the best 150 or so are used in fusion experiments.

Scientists are now planning the construction of the National Ignition Facility (NIF), which is expected to begin operating early in the next century. Its more powerful ICF lasers will be able to generate at least as much fusion energy as is consumed in compressing the fuel capsule.

NIF's more powerful lasers call for a new type of target capsule--one that will be at least 2 mm in diameter and hold liquid or solid hydrogenic fuels at cryogenic temperatures. To support the frigid fuel, the capsule's inner walls may need to be fabricated from a low-density organic foam. Several groups around the world, including Lawrence Livermore's, are developing materials technologies to meet these needs.

Microspheres also may have a role to play in space. Chemist Donna M. Speckman of Aerospace Corp. in El Segundo, Calif., is trying to develop an improved antistatic coating to protect satellites and other spacecraft. Charge buildup on surfaces causes electrostatic discharges, which can damage microelectronics and sensors on spacecraft. Currently, the problem is handled typically by depositing a thin, electrically conductive film of indium tin oxide (ITO) over a thermal coating that prevents the craft from heating up too much. The IT0 film, however, is prone to crack, peel, and lose its conductivity in the hostile environment of low Earth orbit.

Speckman's idea is to combine the requisite antistatic and thermal protective properties in a single, flexible, stable film. She hopes to achieve this by dispersing conductive indium oxide (In2O3) microspheres in a polymer matrix. Successful dispersion into the polymer requires that the oxide particles be of micrometer size or smaller and that they not agglomerate. Indium oxide particles produced by conventional methods such as ball-milling tend to clump, making them unsuitable for this use.

At the Boston meeting, Speckman reported that she has produced spherical In_2O_3 particles 0.5 to 2 pm in size that should meet spacecraft requirements. The particles are formed by spraying a solution of the precursor, indium acetate, in a heated chamber to form the oxide. The resulting particles do not clump, and their mechanical properties seem promising, she says. Scaleup and polymer-loading experiments still need to be done.

The progress reported by Speckman, Cook, Pope, and Suslick is just a sampling of what scientists are achieving with spherical materials. A lot of relevant research probably never made it to the one-and-a-half-day symposium because the research can be hard to find, says co-organizer Wilcox. In other words, microsphere researchers aren't a tightly knit group.

Cook, for example, admits that besides their use as laser targets in fusion research, he "had no idea what else microspheres were used for. So it was educational [to see that] they have applications in lots of different areas."

"Hopefully, we've [begun] to get some people talking to one another and sharing ideas," says Wilcox. "I think we'll hear a lot more about microspheres in the future."