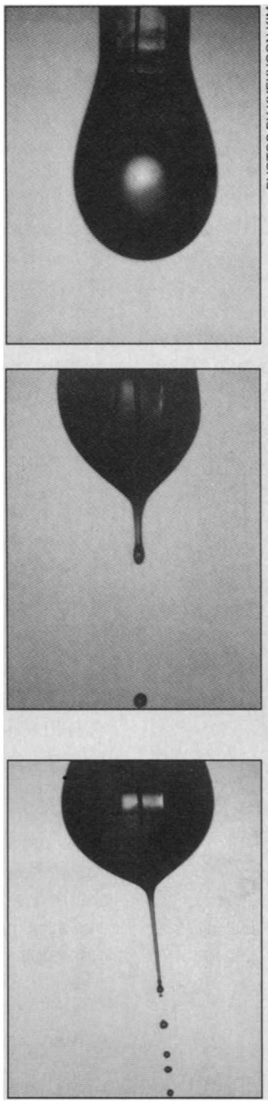
Small Spheres Lead to Big Ideas

New construction methods allow unprecedented control over microscopic bubble-making. Scientists hope to turn the tiny spheres into everything from artificial blood to laser fusion targets

Nature packs a lot into a sphere, and now scientists are trying to do the same. Spheres have the highest ratio of volume to surface area of any possible geometric form, and their lack of edges or corners makes them exceptionally strong containers. That's why engineers have used air-filled microscopic glass spheres as bulking materials in everything from paints to auto bodies for decades; recently materials scientists have begun making spherical drug delivery vehicles out of fatty molecules and polymers (*Science*, 15 July 1994, p. 316). Now the sphere-makers are mastering a variety of new construction techniques that will give them greater control than ever before over sphere size, materials, and surface smoothness—properties that could well extend their usefulness into entirely new areas.

At the University of Illinois, Urbana-Champaign, for example, chemist Ken Suslick and his graduate student Mike Wong are developing a potential blood substitute by using high-frequency sound to weld oxygen-carrying hemoglobin proteins together into microspheres two microns in diameter (roughly one quarter the size of a red blood cell, where hemoglobin normally resides). Hemoglobin binds oxygen to the sphere surface, and oxygen is also trapped within the hollow sphere core. Tests show that these bubbles carry 50% more oxygen per container volume than do even natural hemoglobin-packed red blood cells.



PHOTOS BY KYEKYOON KIM

Blown to bits. Injected electrons, repelled from one another, force this fluid droplet to explode into spheres only 10 nanometers in size.

"Quite fascinating and exciting" is how materials scientist Morris Berg of the University of Illinois describes the work. The results have also caught the attention of artificial-blood experts. One, Robert Winslow at the University of California, San Diego, says the research "sounds very interesting" because this type of performance outstrips that of hemoglobin-based blood substitutes currently in clinical trials. At the same time, he cautions that all blood substitutes need to jump "some pretty humongous hurdles" to make it to the clinic.

Still, the ability to make minuscule spheres out of functioning proteins is itself no mean feat. And the technique is but one of several deft sphere fabrication methods that were on display at a recent meeting of the Materials Research Society in Boston.* Many of the techniques were developed in relative isolation by researchers and were making their debut in the research community. The meeting "introduced us to each other's work for the first time," says University of Illinois ceramicist Kyekyoon "Kevin" Kim. Of course, researchers cautioned, many of these methods have yet to make it off the lab bench and into real-world tests, where grand expectations are often cut down to size.

Welding with sound

Suslick's hemoglobin microspheres are one class of newly constructed bubbles that researchers hope can make this real-world transition. Researchers have tried to make blood substitutes out of hemoglobin molecules before, but when they used the naked protein, the hemoglobin was quickly broken down by protein-dissolving enzymes in the circulatory system and was also toxic to the kidneys. By welding together roughly 1 million hemoglobin molecules, however, Suslick and Wong believe they have made spheroids large enough to avoid enzymatic degradation, yet small enough to weave their way through the body's capillaries.

Suslick and Wong begin by blasting ultrasound waves at a water-based solution containing hemoglobin. The agitation produced by these high-frequency waves creates tiny air bubbles in the solution. Hemoglobin molecules are drawn to the surface of these bubbles, because the molecules contain a hydrophobic component that is repelled by water. To escape aquatic contact, they arrange themselves around the air bubbles with that part of the molecule facing in.

While this is happening, other bubbles in the solution collapse, due to a process known as cavitation. The pressure created by these imploding bubbles generates bursts of heat "intense enough to rip apart water molecules" into their constituent atoms, says Suslick. Reactions between these constituents create a reactive compound called superoxide (HO_2); the superoxide molecules react with amino acids called cysteines on neighboring hemoglobin molecules, forging them in a "spot weld," says Wong. The welding continues until more than 1 million hemoglobin molecules have linked up in a solid hemoglobin microsphere.

The spheres retain hemoglobin's ability to pick up oxygen under high-pressure conditions—in the lungs, for example—and discharge it under lower pressure, as in other body tissues. The hollow core takes in and diffuses additional oxygen. And as well as being able to deliver more oxygen than natural blood, Suslick notes that the hemoglobin microspheres have the advantage of a longer shelf life. While whole human blood must be thrown out after only a few weeks of storage, tests have shown that microspheres remain 80% effective after 6 months. Nevertheless, despite what Suslick calls these "exceptionally promising" early results, the fate of the hemoglobin microspheres must await the outcome of animal and human trials, the first of which are just now under way at the University of Illinois.

Drop drying

Using a variation of the ultrasound technique, but adding a baking step to the process, Donna Speckman told the Boston meeting that she and her colleagues at the Aerospace Corporation in El Segundo, California, are making electronically conductive ceramic microspheres for use in antistatic coatings on satellites and other spacecraft. Bombardment by charged particles, such as protons, can lead to a dangerous

*Materials Research Society fall meeting, Boston, 28 November to 2 December, 1994.

buildup of electrical potential on a spacecraft surface, which can discharge like a bolt of lightning and blow out the craft's electronics. Anti-static films prevent this charge buildup by allowing static charges to flow to a ground, where they are dissipated. But present coatings—made of stiff indium-tin-oxide thin films—tend to crack, which can lead to failure.

Speckman and her colleagues believe an electrically conductive flexible plastic coating may do better. The researchers initially added electronically conductive microparticles of indium-oxide to a plastic resin. But the irregularly shaped indium-oxide particles "ball up and stick together," says Speckman, making them useless for conductive plastic films. So the group turned to microspheres, because they "just roll off one another like little ball bearings," says Speckman.

The researchers begin making their spheres by dissolving indium-acetate in water. They then place an ultrasonic transducer inside the liquid container, which vibrates, creating a fine mist of droplets. The droplets are sucked away and dropped down a tube that runs through a furnace at 650 degrees Celsius. As the drops slowly fall through the heated tube, water evaporates from the drop surface and acetate residues burn away, leaving a hollow, hard ceramic sphere of indium-oxide. While the California researchers have yet to embed the spheres in a plastic resin, Speckman says their hollow form should help them "float" and disperse evenly in the plastic, improving its conductivity.

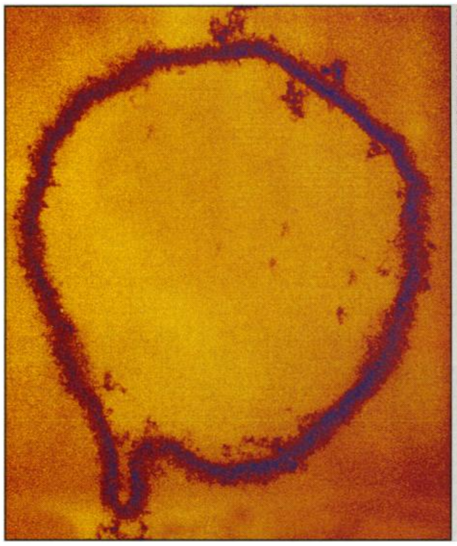
Gary Messing, a professor of ceramic science at Pennsylvania State University who has been exploring a related technique, says the drop-drying method gives researchers better control over the makeup of their spheres because "you can make microspheres out of anything you can put into solution." Messing has made microspheres out of alumina and barium-oxide, and expects to be able to construct them from ceramics, metals, polymers, and alloys. Those in turn may find commercial applications in everything from microwave filters on cellular phones to new electronic materials.

Smoothing the way

Another application that depends on making hollow spheres—as well as on making them exceptionally smooth—has what may be the grandest aspiration of all: to serve as fuel containers in laser fusion experiments. Robert Cook and his colleagues at Lawrence Livermore National Laboratory in California have been making ultrasmooth plastic microspheres to help recreate the thermonuclear processes of the sun, bringing atoms of hydrogen so close together that they fuse, liberating excess energy in the process.

To achieve this, researchers must be able to compress their fuel—in this case a form of hydrogen gas known as deuterium—with the same force, at the same instant, from all sides, says Cook. And that requires a series of powerful lasers around the target to trigger the compression, as well as deuterium-loaded spheres smooth enough to ensure that the contents implode evenly, because any instabilities will grow rapidly, preventing fusion. Early laser fusion efforts used hollow glass microspheres for their laser target practice and had limited success. But when calculations showed that carbon-based spheres compress the fuel more efficiently, the researchers turned to carbon-based plastic.

The spheres made by Cook and his colleagues consist of three incredibly smooth layers, whose tiny hills and valleys have a depth that represents only 0.0004% of the sphere's 500-micron diameter. The deuterium is inserted after the final layer is complete. To create the first, innermost layer, the researchers start with a solution of polystyrene in a solvent. As in Speckman's "drop tower" technique, they make tiny droplets, which are dropped down a heated 15-foot tower. As the droplets fall, solvent at the surface evaporates, leaving a polystyrene skin. Additional solvent is trapped inside, where it can no longer evaporate, and so the microsphere heats up until the solvent boils. This pushes the plastic walls out like an inflating balloon until the walls grow thin enough to allow the solvent to escape as a gas. And, like a blown-up balloon, the plastic spheres also become ultrasmooth—inside and out.



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Air bubble. This microscopic sphere—shown in cross section—is made from oxygen-carrying hemoglobin molecules and could be the basis for a blood substitute.

The spheres are then dunked into a solution containing poly(vinyl alcohol), or PVA, and sent down another drop tower. But unlike the first trip, the purpose of this second is to dry the PVA into a hard coating around the polystyrene, says Cook. The coating acts a sealant to prevent the deuterium fuel from leaking out. Then an outer plastic shell is added. This shell is burned off during the fusion experiment, creating the symmetric "kick" that compresses the fuel inside. And finally, the spheres are placed in a deuterium-filled, high-pressure chamber for several days; the pressure forces the deuterium through the three layers into the core of the sphere.

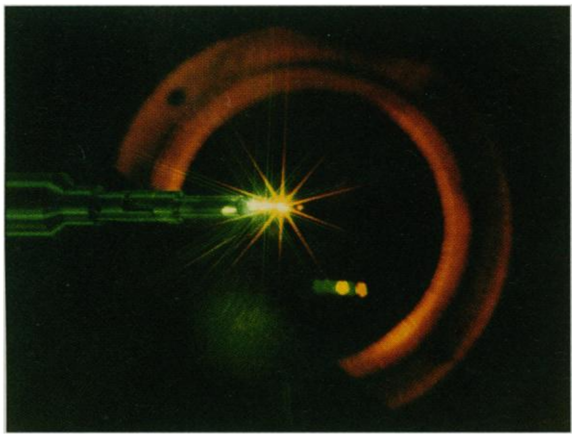
The ultimate goal of the Livermore group—and of other laser fusion groups—is to generate more energy through fusion than is consumed in driving the 100-kilojoule lasers. But thus far "inertial confinement fusion," or ICF, techniques using microspheres have yet to generate more than a few percent of the energy used by the lasers. In hopes of reaching the break-even point, researchers must use lasers with more power, compressing the targets still further. While this will add to the input energy costs, calculations show that this should be offset by additional fusion produced in the process, says Cook.

That is, it will be offset if Cook can quadruple the size of the spheres, making room for additional fuel. Several groups around the world, including Livermore's, are working toward this goal. Their hope is to test them at the planned National Ignition Facility, although funding for the facility remains up in the air (*Science*, 3 December 1993, p. 1504).

Blowing tiny bubbles

While Cook's group is trying to make bigger spheres, others are trying to shrink them to the vanishing point. One technique presented at the meeting—fragmenting tiny fluid droplets by loading them with extra electrons—is producing spheres of comparatively Lilliputian dimensions, down to 10 nanometers in size, less than 0.01% of the thickness of a human hair. What's more, adds Illinois's Kim, who developed the technique, this method "can make [these nanospheres] with any chemical composition." Kim and colleagues have already used his new technique to make nanospheres from glass, iron oxide, tantalum oxide, and barium-titanium oxide. The technique seems to have leapfrogged ahead of applications, although such nanospheres could be used to control the behavior of materials down to the movement of individual electrons.

To make their ultrasmall glass spheres, the scientists start by mixing sphere-forming material—a blend of a silicate and ethyl alcohol, for instance—into a deionized water solution. The researchers force the liquid through a millimeterwide glass nozzle. That process yields relatively large droplets (two millimeters in diameter), as only at that size is the drop sufficiently heavy to overcome the capillary forces that hold the liquid to the nozzle.



LAWRENCE LIVERMORE NATIONAL LAB

Perfect target. A microsphere compresses deuterium when shot by a laser, triggering a fusion reaction. The smoothness of the sphere walls ensures that the reaction takes place.

To make the drops smaller, Kim and his colleagues blow them apart. They extend an exquisitely thin electrode through the nozzle so its tip sticks into the drops as they form. They then inject electrons into the liquid. The electrons' negative charges repel one another, breaking the drop apart; surface tension holds the new nanodroplets together. "It's like making the liquid heavier so smaller drops will form," says Kim. And as these small drops fall, the alcohol evaporates and they solidify.

Kim believes these nanospheres may be useful in constructing exotic semiconductor structures known as quantum dots that trap electrons and other charged particles, forcing them to emit light at very restricted wavelengths. Researchers at electronics companies worldwide are pursuing these exotic dots for use as tunable semiconductor lasers and light-emitting diodes. The most common method now used to make such dots is to etch them from a semiconductor surface, one by one, using an electron beam. But this technique is both slow and expensive, says Chris Palmstrom, a materials scientist at the University of Minnesota.

An alternative method tested by Kim places nanospheres on the surface of the semiconductor to act as a stencil. Instead of electron beams carving the dots, this technique uses chemicals that eat away the semiconductor surface but leave the nanospheres—and therefore the dot-sized areas of semiconductor underneath—unscathed. Such a method "would be a convenient way of making quantum dots," says Palmstrom. But the ability to arrange these dots into patterns suitable for electronic devices "has not yet been demonstrated," says Kim.

Even if this application, or some of the other proposed uses for the spheres, fails to pan out, it's clear that the new bridges formed between microsphere fabricators have already ignited imaginations. "We're just seeing the beginning of learning how to synthesize solid and hollow spheres," says David Wilcox, a materials engineer at the University of Illinois, Urbana-Champaign, who helped organize the Boston session. At the microsphere production company PQ Corporation in Valley Forge, Pennsylvania, for example, hollow-microsphere expert Jim Hagarman says he intends to adopt a version of the drop-drying technique in order to make microspheres with a variety of new components. And some of these tiny orbs could well have a large impact.

–Robert F. Service

SEISMOLOGY

Biggest Deep Quakes May Need Help

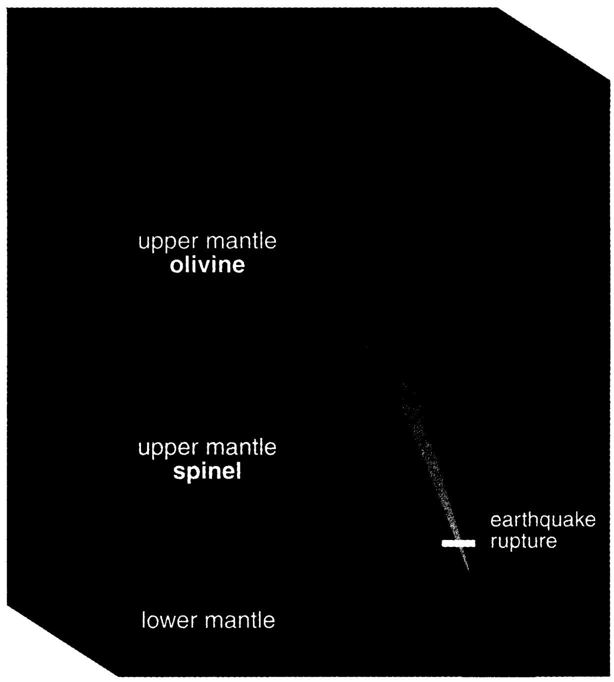
Earth's deepest earthquakes, buried more than 400 kilometers below the surface, can't match the threat to lives and property from temblors on the San Andreas. But these quakes, which take place in slabs of tectonic plate descending into the mantle, have always meant big trouble for theorists. The latest one—the biggest on record—has kept up that tradition.

Before the magnitude 8.3 quake struck 636 kilometers beneath Bolivia last June, seismologists thought they finally had a promising answer to a paradox posed by the deepest earthquakes: By rights, they shouldn't happen at all, because the enormous temperatures and pressures at such depths should allow rock to dissipate stress by flowing quietly rather than fracturing suddenly, as it does in earthquakes near the surface. By proposing that the fractures take place when rock abruptly changes to a denser crystal form, weakening the slab, the mechanism seemed to explain the paradoxical rupturing.

The Bolivian earthquake raises doubts about that seemingly neat solution to the paradox. "I think there's a basic geometrical problem" with the mechanism, says seismologist Paul Silver of the Carnegie Institution of Washington's Department of Terrestrial Magnetism, who voiced his doubts at last month's meeting of the American Geophysical Union in San Francisco. The problem is that the proposed mechanism, called transformational faulting, implies that the deepest quakes should be confined to a thin layer at the center of a descending slab—and the Bolivian quake was just too big to fit. To Silver, that discrepancy is "serious enough that we have to consider alternatives."

But not all his colleagues agree. Among them is Harry Green, a mineral physicist at the University of California, Riverside, who has provided much of the experimental evidence for transformational faulting. "The mechanism is not dead," he says. Still, many researchers suspect that it may need help, at least to explain really big quakes like the one under Bolivia.

Until the Bolivian earthquake, transformational faulting seemed to have everything going for it. The idea is that, at the pressures found below about 400 kilometers, the olivine that makes up much of a descending slab can transform suddenly into a form called spinel that is stable at high pressures. That sudden transformation occurs in proliferating "microcracks" that weaken the rock until a spinel-filled fracture forms. And because the new spinel has exceedingly fine crystals, it lubricates the fracture, enabling it to slip and generate an earthquake. The mechanism worked in laboratory experiments (*Science*, 26 April 1991, p. 510), and since then seismologists analyzing signals from deep quakes saw signs that



SOURCE: *SCIENTIFIC AMERICAN* ILLUSTRATION: C. FABER SMITH

Awkward fit. Last June's Bolivia earthquake, deep in a descending tectonic slab, was too big to fit in the narrow olivine wedge thought to be the slab's quake-prone region.