Colloidosomes: Selectively Permeable Capsules Composed of Colloidal Particles

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We present an approach to fabricate solid capsules with precise control of size, permeability, mechanical strength, and compatibility. The capsules are fabricated by the self-assembly of colloidal particles onto the interface of emulsion droplets. After the particles are locked together to form elastic shells, the emulsion droplets are transferred to a fresh continuous-phase fluid that is the same as that inside the droplets. The resultant structures, which we call "colloidosomes," are hollow, elastic shells whose permeability and elasticity can be precisely controlled. The generality and robustness of these structures and their potential for cellular immunoisolation are demonstrated by the use of a variety of solvents, particles, and contents.

Efficient encapsulation of active ingredients such as drugs, proteins, vitamins, flavors, gas bubbles, or even living cells is becoming increasingly important for a wide variety of applications and technologies, ranging from functional foods to drug delivery to biomedical applications (*1–8*). Increasingly sophisticated techniques are being developed to create physical structures that can meet the demanding requirements of these applications. A versatile technique should provide efficient encapsulation in structures whose size, permeability, mechanical strength, and compatibility can be easily controlled. Control of the size allows flexibility in applications and choice of encapsulated materials; control of the permeability allows selective and timed release; control of the mechanical strength allows the yield stress to be adjusted to withstand varying of mechanical loads and to enable release by defined shear rates; and control of compatibility allows encapsulation of fragile and sensitive ingredients, such as biomolecules and cells. Precise control of all these features would allow the strategic design of possible release mechanisms. Ideally, it should be feasible to construct these capsules from a wide variety of inorganic, organic, or polymeric materials to provide flexibility in their uses.

A variety of techniques has been developed to address specific encapsulation requirements: Coacervation, or controlled gelation, of polymers at the surface of water drops can be used to fabricate nano- or microporous capsules (*1–5, 9*); other fluid extrusion methods can also be used to create the polymer coating (*6, 7*). Coating immiscible templates by electrostatic deposition of alternating layers of charged polymers or particles can be used to fabricate nanoporous capsules (*10–18*). Microfabrication technology can be used to create submillimeter-sized silicon capsules with exquisitely precise nanometer-scale holes for selective permeability and slow release (*19*). However, despite the enormous progress in encapsulation technologies, these methods can be limited in their applicability, in the range of materials that can be used, in the uniformity of pore sizes, in the accessible permeabilities and elasticities, or in the ease of synthesis, filling efficiency, and yield.

We present a flexible approach to the preparation of hollow, elastic capsules, with sizes ranging from micrometers to millimeters and with easily adjusted and highly controllable permeability and elasticity. The capsule surfaces are composed of a close-packed layer of colloidal particles, linked together to form a solid shell; the interstices between the particles form an array of uniform pores, whose size is easily adjusted over the nanometer to micrometer scale to control the permeability. We call these capsules "colloidosomes" by analogy with liposomes, which are capsules composed of phospholipid bilayers.

Our fabrication process uses controlled self-assembly in three steps (Fig. 1). First, a suspension of the material to be encapsulated is emulsified in an immiscible fluid containing colloidal particles that adsorb on the surface of the emulsion droplets. Second, after the droplet surface is completely covered by particles, an elastic shell is formed by locking the particles together. The interstices between the particles form holes that define the colloidosomes' permeability. Third, if required, the capsules are transferred by centrifugation into a solvent that is typically the same as the internal phase. This eliminates the interface between the internal and external fluids and allows the interstitial holes to control the colloidosome permeability.

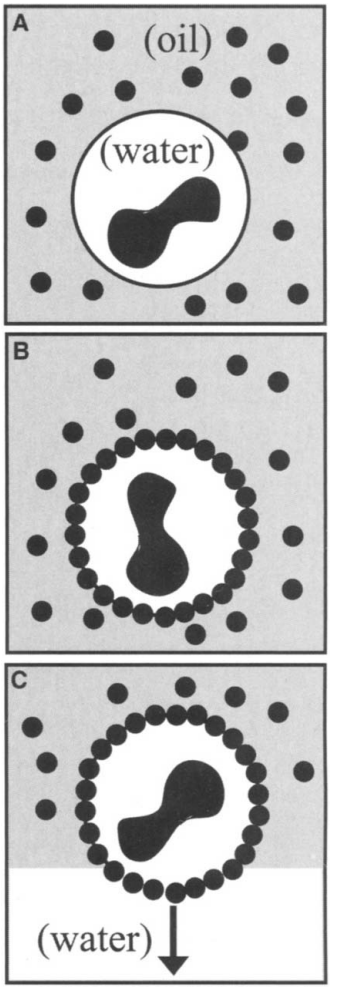

Fig. 1. Schematic illustration of the self-assembly process for colloidosomes. (**A**) Aqueous solution is added to oil containing colloidal particles. Aqueous droplets are formed by gentle continuous shearing for several seconds. (**B**) Particles adsorb onto the surface of the droplet to reduce the total surface energy. These particles are subsequently locked together by addition of polycations, by van der Waals forces, or by sintering the particles. (**C**) The structure is transferred to water by centrifugation. The same approach is used to encapsulate oil droplets with a shell of particles from an exterior water phase. Particles adsorbed because of the large oil-water surface energy, which is substantially larger than the difference between the particle-oil and particle-water surface energies; this differs substantially from previous reports, where colloidal particles were adsorbed electrostatically onto oil droplets, which required prior treatment of the droplet's surface (*16–18*).

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Coverage of the emulsified droplets by colloidal particles occurs by self-assembly. The particles spontaneously adsorb on the interface, provided that the surface energy between the two fluids, $\sigma_{i,e}$, exceeds the difference of the surface energies between the particle and the internal fluid, $\sigma_{p,i}$, and between the particle and the external fluid, $\sigma_{p,e}$. Thus, adsorption is energetically favored if $\sigma_{i,e} > |\sigma_{p,i} - \sigma_{p,e}|$ (*20*). A similar mechanism is used for Pickering emulsions, which are stabilized by surface adsorption of colloidal particles (*21*). Because $\sigma_{i,e}$ is relatively large, colloidal particles with sizes in the nanometer (*22*) to micrometer range and with a variety of compositions and surface functionalities readily adsorb. Pretreatment of the surface is not required; thus, this mechanism is more general than electrostatic adsorption, which depends on the delicate adjustment of surface charge (*16–18*). Once adsorbed, these particles never escape the interface, reflecting the existence of a deep, attractive well like that for particles at an air-water interface (*23*, *24*).

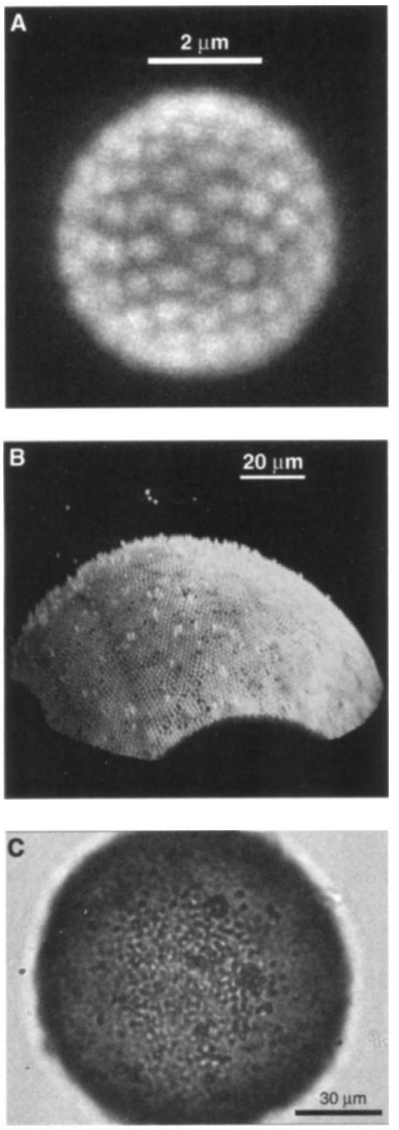

Fig. 2. (**A**) Projection of a three-dimensional confocal fluorescence microscope image of 0.7-μm-diameter PMMA colloidal particles adsorbed onto the surface of a water droplet in decalin. The local order is visible. (**B**) Confocal microscope image of a single-layer-thick film of PMMA particles, formed on a water droplet in decalin droplet as in (A). Chlorobenzene was added to the continuous phase (35/65 vol% chlorobenzene/decalin) to swell the particles; toluene was added (50 vol% toluene) to degrade the stabilizing layer and form a strong elastic shell held together by van der Waals forces. (**C**) A bright-field optical microscope image of an aqueous-phase colloidosome formed by polystyrene spheres. The colloidosome was formed by assembly of particles onto a water droplet with poly-L-lysine (1 mg/ml, 150 to 300 kD) in toluene/octanol containing PS particles. The coated droplets were washed in octanol, placed on top of an aqueous solution of nonionic surfactant (Tween 20; 10 mg/ml), and then centrifuged at 9300*g* to transfer them to water.

The packing of the particles at the interface can be adjusted by controlling their interactions (*25*). By retaining colloidal stability of the interfacial particles, full coverage is achieved. Ideally the packing of the colloidal particles on the surface would have perfect hexagonal symmetry. Topological constraints imposed by the curved surface, however, require a minimum of 12 five-fold disclinations, like the pentagons on a soccer ball (*26*, *27*). Polycrystalline, or glassy packing of the particles is also common; this does not qualitatively modify the properties of the colloidosomes. An example of a fully covered interface of a droplet is shown in Fig. 2A, which is a confocal microscope image of a water droplet in decahydronapthalene (decalin) containing poly(methyl methacrylate) (PMMA) colloidal particles with a poly(hydroxystearic acid) stabilizing layer (*28*, *29*). The particles have been dyed with rhodamine, allowing visualization with the confocal microscope. Particles become charged upon adsorption at the interface, possibly because of dissociation of charges on the hydrated surfaces (*25*). The resultant dipolar repulsion stabilizes the particles (*30*), allowing full coverage to be attained. By comparison, a section of a larger droplet, with many more adsorbed particles, is shown in Fig. 2B; this illustrates the complete coverage that can be attained, even for large surfaces. When the adsorbed particles are not electrostatically stabilized, a tenuous and highly porous particle packing is obtained, providing a more open yet still elastic structure (fig. S1).

The adsorption of colloidal particles onto the interface of emulsion droplets is a general and flexible self-assembly technique. Similarly fully packed surfaces were also formed on water droplets that were emulsified in a solution of 90% by volume (90 vol%) toluene and 10 vol% octanol containing carboxylate-modified polystyrene (PS) particles (*29*). Alternatively, to encapsulate hydrophobic material, oil droplets are emulsified in aqueous solutions containing particles (*29*). Several other examples of emulsion droplets fully coated with colloidal particles or filled with crystallizing colloidal particles (*31*) have been reported in the pioneering work of Velev and co-workers (*16–18*).

The second step in the fabrication of colloidosomes is the locking together of the adsorbed particles to form an elastic shell. This locking is essential to ensure that the capsules remain intact when they are transferred to a fresh fluid. Locking can be accomplished in several ways to achieve different final structures. To fabricate colloidosomes with precisely controlled permeability, we lightly sinter the particles. An example is shown in Fig. 3, which is a scanning electron microscope image of a colloidosome made from an oil droplet in an aqueous phase containing 0.9-μm-diameter PS particles. This sample was heated at 105°C for 5 min, somewhat above the glass transition of the PS, $T_g \approx 100$°C. Upon heating, the particles coalesced slightly, creating approximately 150-nm-diameter bridges, or "necks," between them. The resultant colloidosome, therefore, contains a precise array of uniform holes in an elastic shell. Increasing the sintering time leads to smaller pores: after 20 min, the particles coalesced completely and the holes were fully closed. The rupture stress of the colloidosomes

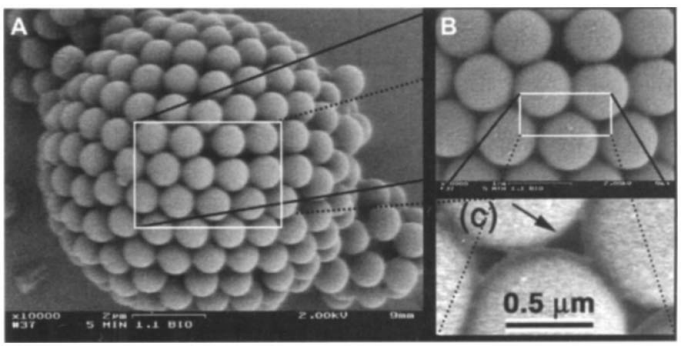

Fig. 3. (**A**) Scanning electron microscope image of a dried, 10-μm-diameter colloidosome composed of 0.9-μm-diameter polystyrene spheres, sintered at 105°C for 5 min. The colloidosome was formed with an oil droplet, containing 50 vol% vegetable oil and 50 vol% toluene. The water phase contained 50 vol% glycerol to increase its boiling temperature to allow the sintering. (**B** and **C**) Close-ups of (A) and (B), respectively. The arrow points to one of the 0.15-μm holes that define the permeability. To view these colloidosomes with the electron microscope, we washed them with ethanol and dried them in vacuum.

also increases substantially with longer sintering time, as confirmed by quantitative measurements using calibrated glass pipettes (*32*). By using particles with different T_g, the sintering temperature can be adjusted over a wide range; this might be advantageous for encapsulants incompatible with elevated temperatures.

Other methods can be used to lock the interfacial particles together. Coupling of the particles can be achieved by electrostatically binding a polyelectrolyte of the opposite charge to the particles. To illustrate this, we emulsified an aqueous solution of poly-L-lysine in a toluene-octanol mixture containing PS particles. The poly-L-lysine adsorbed to the particles at the interface, as confirmed with fluorescent labeling. The poly-L-lysine molecules bridge neighboring particles and lock them together, as confirmed by the observation that particles became immobilized at the interface. The adsorption of poly-L-lysine substantially enhanced the elastic properties of the colloidosomes, producing capsules that were flexible, deformable, and tough.

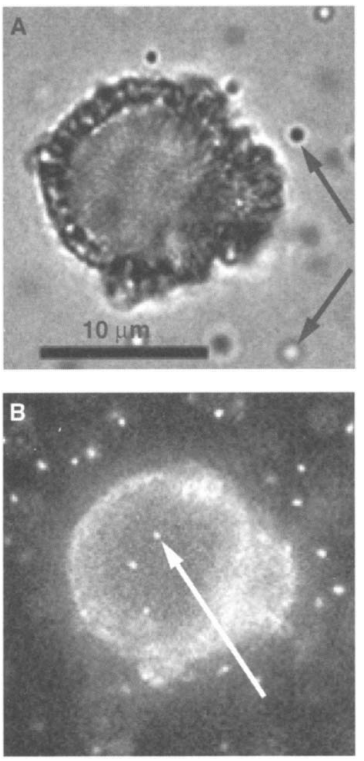

Fig. 4. Microscope images demonstrating selective permeability. Water-filled colloidosomes are composed of 1.3-μm-diameter polystyrene particles electrostatically locked together with poly-L-lysine. The exterior phase was exchanged with an aqueous suspension of 1.0-μm-diameter and 0.1-μm-diameter probe particles 8 hours before these images were taken. (**A**) Brightfield microscope image showing that the larger probe particles (arrows) are excluded from the interior. (Diffraction from the particles that form the shell is faintly visible. A smaller colloidosome is attached on the right side.) (**B**) Fluorescence image showing that smaller probe particles can permeate (arrow). Scale bar is as in (A).

Van der Waals forces provide another flexible means of locking the adsorbed particles together. As an illustration of this technique, we emulsified water in decalin and coated the droplets with PMMA particles. To induce the van der Waals interaction, we destroy their steric coating by adding toluene to the continuous phase. Similarly, PS particles adsorbed onto oil droplets suspended in water spontaneously formed rigid shells held together by van der Waals forces between particles.

The final step of the assembly process entails removing the fluid interface by exchanging the external fluid with one that is miscible with the fluid inside the colloidosome. This ensures that the pores in the elastic shell control the permeability by allowing exchange by diffusion across the colloidosome shell. This fluid exchange step is readily accomplished by transferring the capsules into the new fluid by gentle centrifugation, as shown schematically in Fig. 1C and as exemplified in Fig. 2C (*29*). The elasticity of the shell of interlocked colloidal particles is critical to allow the capsule to withstand the surface tension–induced stresses of crossing the interface. This final step is not necessary if the encapsulated fluid is immiscible with the desired continuous phase, as would be the case, for example, if a hydrophobic material were encapsulated in an aqueous medium.

The resultant colloidosome structures provide a rigid elastic shell that serves as a protective coating for the interior material. Because there is no interface, and thus no surface tension between the internal and external fluids, the permeability of the shell is controlled by the interstitial holes. It is this permeability that gives the colloidosomes the unique encapsulation capabilities and distinguish them from previously reported structures (*16–18*). Colloidosomes can be used to efficiently encapsulate and provide a rigid shell of controllable elasticity and permeability. Assuming the shell is a perfect hexagonal lattice of spheres of diameter d, the interstitial holes are roughly $0.15d$ in size. The particle size thus sets the basic pore size and, hence, the permeability. However, the permeability can be much more finely adjusted. For example, we show that sustained sintering can be used to further reduce the pore size in a controlled way. Alternatively, the permeability of the interstitial holes might be further reduced either by addition of a layer of much smaller colloidal particles or by addition of a film-forming polyelectrolyte or polymer, which could control permeability at the scale of small macromolecules. These additional layers would also help mitigate effects of any defects in the lattice of particles.

To demonstrate the selective permeability of the shell, we suspended colloidosomes in water containing fluorescently labeled PS probe spheres of various sizes, and we inspected them with an optical microscope to determine the number and sizes of particles within individual colloidosomes. An estimate of the time required for entry of the probe particles is $t = (1 + \pi s/(4\eta R))/(4\pi DRC)$, where D and C are the probe particle diffusion coefficient and concentration, R is the colloidosome radius, and η ($\approx$ 0.04) and s are the area fraction and radius of holes, which we approximate as circles (*33*). We waited more than $10t$, after which we found no further change in the distribution of probe particles. Colloidosomes prepared by coating water droplets with 1.3-μm-diameter particles locked together with poly-L-lysine were completely impermeable to 1-μm-diameter particles but allowed 0.1-μm-diameter particles to penetrate freely (Fig. 4). Colloidosomes prepared by coating oil droplets with 0.9-μm-diameter PS particles and sintering at 105°C for 5 min were impermeable to 0.5-μm-diameter probe particles but allowed 0.1-μm-diameter particles to penetrate freely. These results demonstrate that selective permeability of the colloidosomes can be readily achieved. Moreover, the measurements are consistent with the simple geometric model for the permeability.

An important feature of colloidosomes, which makes them promising as encapsulants, is the wide variety of potential mechanisms for release. Sustained release through the controlled pores is the most direct method, but other methods are also feasible. Because they are elastic shells, release may be triggered by rupture through shear stress. The elastic modulus, and hence the rupture stress, can be controlled by the method of preparation. To test this, we used a calibrated micropipette (*32*) to measure the rupture stress of colloidosomes. We obtained a value of 10^6 to 10^7 Pa for 60-μm-diameter capsules fabricated with lightly sintered PS particles. Measurements indicate that this value can be increased by well over a factor of 10 by sintering for longer times. It might also be increased by depositing multiple layers of colloidal particles or by additional coating with polyelectrolytes or other polymers. Colloidosomes locked together with the polyelectrolyte poly-L-lysine are even more deformable and can withstand strains of order 50% before rupturing (*32*). These methods provide a method to release the contents of the colloidosome through control of the rupture stress.

Still other release strategies are possible: There is substantial freedom to choose the core material of the colloidal particles because the fabrication process depends only on their surface properties. Thus, some particles could be made of a material that increases its volume, for example, upon increasing the pH, as in alkali-swellable microgel particles (*34*). Slight swelling would increase the pore sizes; greater swelling would introduce substantial surface stresses that would tear holes in the capsule and release the contents. Alternatively, the particles could be made of a material easily dissolved or swol-

len in situ, either chemically or photochemically, thereby releasing the contents.

Colloidosomes can address a wide variety of encapsulation needs in addition to nutrient and drug delivery. One important possibility is immunoisolation of living cells by encapsulation in colloidosomes; they would provide a rigid scaffold that supports the living cell while simultaneously protecting it from the immune system and allowing free diffusion of gases and nutrients (*1*, *3*, *35*). The required 25-nm pore diameter would be achieved using colloidal spheres of 170-nm diameter, well within the range of sizes of particles known to adsorb strongly onto droplets. Colloidosomes encapsulating cells could also have advantageous properties as bioreactors (*8*, *36*). Furthermore, a superstructure of colloidosomes may form templates for tissue growth by providing a protected environment that has a useful three-dimensional architecture and allows rapid permeation of small macromolecules. In preliminary experiments, we successfully encapsulated living fibroblast cells and maintained their viability for several hours using particle-coated water droplets in decalin oil. In many cases, the cells adhered to the solid surfaces, suggesting that colloidosomes can be fabricated as rigid porous superstructures to enhance the viability of the cells. Plant protoplast cells are known to survive and grow even after 25 days in contact with oxygen-perfused perfluorodecalin oil, suggesting that the exterior oil phase might not damage the cells during a brief exposure (*37*). The key to cell viability is the suitability of the colloidosomes surface; other methods of locking the particles together, such as avidin-biotin binding, may make the colloidosomes even more biocompatible.

Colloidosomes successfully meet many of the key requirements for encapsulation: Emulsification provides a simple means of producing capsules from a wide variety of fluids and with controlled sizes ranging from submicrometer to several millimeters (*38*, *39*). Furthermore, because the internal and external fluids remain completely separate until the final step, materials can be encapsulated efficiently with minimal loss. The choice of different colloidal particles allows for additional flexibility. We show that the permeability and rupture stress of the capsules can be controlled through the size of the coating particles and through postfabrication treatment by sintering or, alternatively, by further filling of the holes with smaller particles or polymers. A variety of release strategies may be feasible, either through control of their permeability for slow but sustained release, or through control of their rupture stress for shear-induced breakup. This flexibility will allow a wide range of potential applications to be explored.

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Supporting Online Material

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Materials and Methods

Figs. S1 and S2

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Detection and Monitoring of Ongoing Aseismic Slip in the Tokai Region, Central Japan

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Analysis of global positioning system data shows that the rate of crustal deformations in the Tokai region of Japan, a seismic gap area, changed over the past 18 months. Kalman filtering analysis shows aseismic slip on the plate boundary in the western Tokai region centered on Lake Hamana, adjacent to the anticipated Tokai earthquake source area. The cumulative moment magnitude reaches 6.7 in June 2002 with a relative slip increase northeast of Lake Haman from January 2002. An existence of aseismic slip in the western Tokai supports the hypothesis of a silent event as the cause of uplifting several days before the 1944 Tonankai earthquake.

The Tokai region is located along the Pacific coast of central Japan about 200 km to the southwest of Tokyo. The Suruga trough, a subduction plate boundary between the Eurasian plate and the Philippine Sea plate, runs just off the shore of this area (Fig. 1). In this tectonic setting, the Tokai area has experienced large offshore earthquakes with time intervals of around 150 years. Since the 1854 Tokai earthquake, Richter magnitude M = 8.4, the Tokai region has been loaded by the Philippine Sea plate and did not rupture at the time of the 1944 Tonankai earthquake (moment magnitude M_w = 8.1) (*1*–*3*). Continuous global p system (GPS) data since 1994 and historical geodetic survey data by the Geographical Survey Institute of Japan (GSI) for about 100 years indicate a steady strain

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