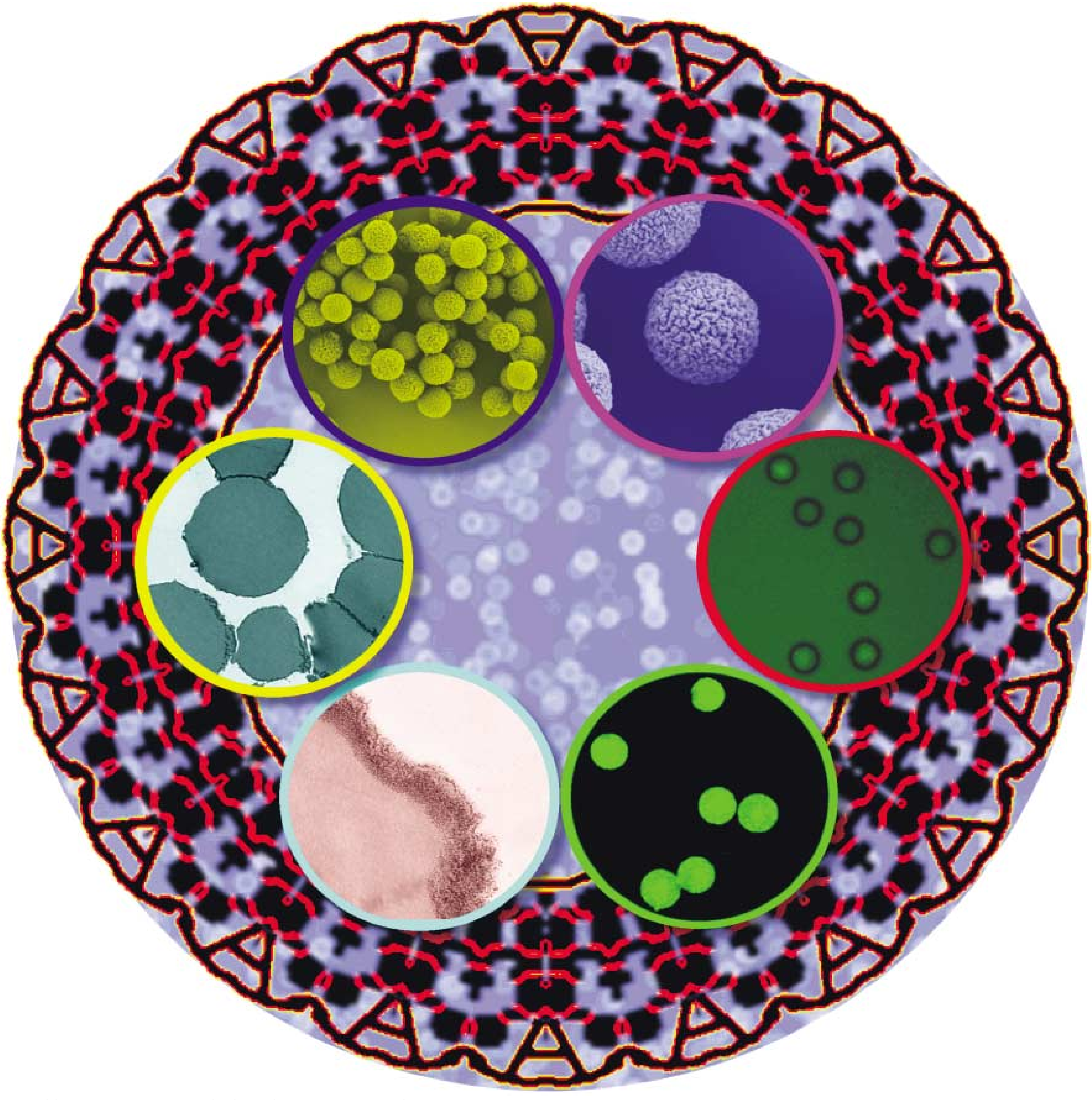
Zuschriften



Die Bildung von Kompositmikrokapseln aus anorganischen Nanopartikeln im Inneren von Polyelektrolytschalen beschreiben G. B. Sukhorukov et al. auf den folgenden Seiten. Die verkapselten Partikel verhindern ein Kollabieren der Struktur bei der Trocknung, Aufnahme- und Freisetzungseigenschaften der Schale werden durch pH-Wert-Änderung gesteuert.

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Inorganic/Organic Microcapsules

Smart Inorganic/Organic Nanocomposite Hollow Microcapsules**

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Polymeric capsules with shells made of polyelectrolyte multilayers[1] have recently attained widespread interest as novel types of carriers and microreactors with designed properties because they exhibit controllable permeability and surface functionality.[2,3] This should enable many applications in drug delivery, the food and cosmetic industries, or biotechnology. Another most important attribute of the capsules is the variety of mechanical properties that are available, since they can be made either of very flexible organic materials or of organic/inorganic composites, as well as exclusively inorganic materials (e.g., SiO_2, TiO_2, Fe_2O_3). For the latter case, an organic/inorganic composite has been calcined, thus removing the organic component.[4,5] Sintering of the inorganic particles leads to hollow but porous inorganic capsules. However, the permeability of these inorganic capsules is not controllable, which strongly limits their application. Hence, what is needed is a composite material where the inorganic fraction yields mechanical strength to withstand, for example, drying and osmotic pressure, and the organic fraction allows for controllable permeability. Beyond that, the inorganic component may also contribute specific optical,[6] magnetic,[7,8] and sorption properties.

In this work we report an elegant and direct way to prepare capsules under ambient conditions with inorganic particles as building blocks glued together by a pH-sensitive polyelectrolyte. By means of three examples we demonstrate controllable permeability in combination with mechanical strength. Alternatively YF_3, magnetic Fe_3O_4, and calcium hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ inorganic/organic shells were used as examples of this new type of microcontainer, to demonstrate the general fabrication approach, mechanical properties, and the release activity of the inorganic composite capsules after redispersion. YF_3 shells can find application as adsorbents for rare earth ions, Fe_3O_4 shells are of practical importance in delivery systems due to their magnetic activity, while calcium hydroxyapatite shells can also be interesting in bioceramics, as an adsorbent for biomaterials, and as a chemical sensor, catalyst, and bone-repairing agent.

To synthesize composite inorganic/organic capsules, poly(styrene sulfonate) (PSS)/poly(allylamine hydrochloride) (PAH) polyelectrolyte capsules[2] containing PAH macromolecules were initially used as template microreactors. A suspension of $MnCO_3$ particles (1 mL, 3.6 μM, 5×10^8 particles per cm^3)[9] was mixed with a solution of citric acid (5 mL, 5 mM). Then an aqueous solution of PAH (0.7 mL, 1 $mg\,mL^{-1}$) was added while stirring, which formed a water-insoluble PAH/citrate complex on the surface of the template particles. The deposition of the first PAH/citrate layer was followed by layer-by-layer assembly of polyelectrolyte PAH/PSS multilayers using PAH (1 $mg\,mL^{-1}$) solution and PSS (2 $mg\,mL^{-1}$) solutions. After formation of the PAH/PSS shells, the $MnCO_3$ core was dissolved in 0.1 M HCl and hollow capsules composed of the inner thick PAH/citrate layer and outer PAH/PSS layer were formed. A more detailed description of the synthesis of hollow PAH/PSS capsules can be found elsewhere.[2,3,10]

The positive charge of the inner PAH layer, which is covered by the outer PAH/PSS shell, is compensated by negatively charged citrate ions; this results in a stable PAH/citrate complex.[3] The citrate ions can be replaced by other anions which can act as a precipitating agent to synthesize insoluble inorganic material exclusively inside the polyelectrolyte capsules. Exposing PAH/citrate–PAH/PSS capsules to a solution containing 0.01 M NaOH, 0.1 M H_3PO_4, or 0.1 M HF results in the rapid substitution of citrate ions to OH^-, PO_4^{3-} or F^- ions, and the formation of PAH/OH^-–PAH/PSS, PAH/PO_4^{3-}–PAH/PSS or PAH/F^-–PAH/PSS capsules. The presence of PO_4^{3-} and F^- ions in the capsule volume was confirmed by atomic absorbance spectroscopy; the absence of citrate ions after substitution was proved by FTIR spectroscopy. Thus, by such a simple procedure, PAH/PSS capsules containing the precipitating agent were obtained (Figure 1; stage a and b). These "initial" PAH/PSS capsules irreversibly collapse upon drying to form flat films (see scanning electron microscopy (SEM, Gemini Leo 1550) image in Figure 1).

After anion replacement the polyelectrolyte capsules were treated with 0.5 M $FeSO_4$ and 0.5 M $Fe_2(SO_4)_3$ (OH^--containing capsules), 1 M $CaCl_2$ adjusted to pH 9 by NaOH (PO_4^{3-}-containing capsules), or 0.1 M $Y(NO_3)_3$ (F^--containing capsules) solutions to deposit water-insoluble Fe_3O_4, hydroxyapatite or YF_3 particles, respectively, inside the capsules (Figure 1; stage c). The inorganic scaffold in the capsule interior prevents capsule collapse by forming micrometer-sized capsules with spherical morphology in the dry state, which are reminiscent of those of the original polyelectrolyte capsule in solution (see SEM image in Figure 1). Folds and creases spreading from one inorganic composite capsule to another are observed demonstrating partial shrinkage of the capsule shell. Wide-angle X-ray scattering analysis confirmed the presence of a weakly crystalline inorganic phase inside the polyelectrolyte capsules with traces of the corresponding metal oxides (Fe_2O_3, Y_2O_3); for $Ca_{10}(PO_4)_6(OH)_2$, a small amount of $CaPO_4$ was detected.

As has already been documented,[11] the PAH/PSS complex is unstable in strong alkaline (pH > 12) solution and can be dissolved. To remove the outer PAH/PSS shell, the resulting PAH/inorganic–PAH/PSS polyelectrolyte capsules loaded with inorganic material were added to 0.2 M NaOH solution for 24 h (Figure 1; stage d). SEM images of the capsules after PAH/PSS dissolution show individual spherical particles without polyelectrolyte material overlapping adja-

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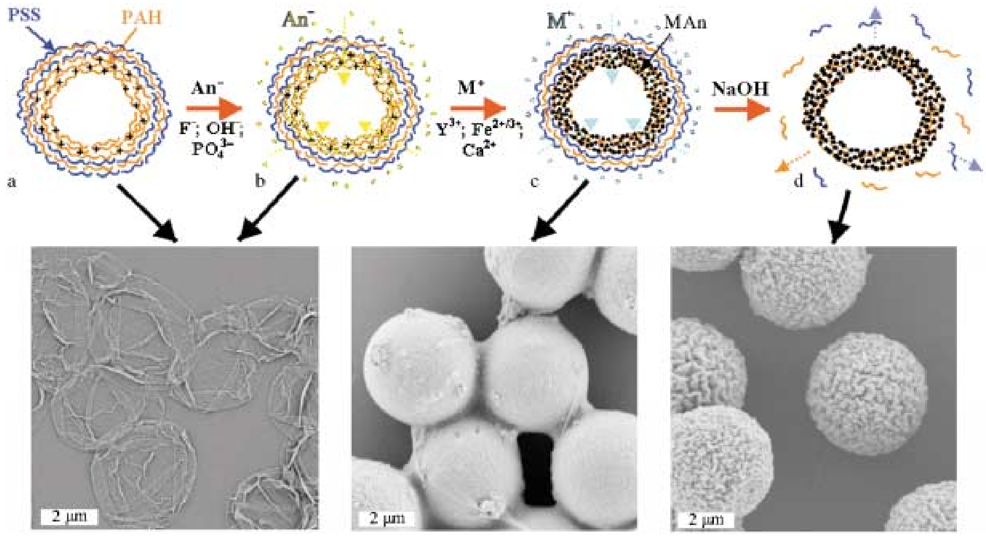

Figure 1. Schematic illustration of the preparation of inorganic/organic hollow capsules. $An^- = F^-$, OH^-, or PO_4^{3-}; $M^+ = Y^{3+}$, $Fe^{2+/3+}$, or Ca^{2+}; MAn = YF_3, Fe_3O_4, or hydroxyapatite; below: scanning electron microscopy images of the YF_3 capsules at different preparation stages (see text for details).

cent capsules (Figure 1, and Figure 2 a, b). Partial reduction of the capsule size and folding of the particle surface can be explained by minor shrinkage of the capsules after drying.

Raman microscopy and UV/Vis spectroscopy were employed to determine the extent of the dissolution of the outer PAH/PSS complex. 99 % of the PSS used for shell assembly was recovered from the supernatant solution after washing out the capsules after NaOH treatment. Raman spectra from individual capsules recorded after PAH/PSS dissolution using a Raman microscope indicated the absence of PSS bands, however, signals from the inner PAH layer were found. Thus, it can be concluded that the resulting inorganic capsules consist of inorganic particles connected to each other by PAH from the inner PAH/anion layer.

To obtain information about the inner structure of the composite inorganic capsules, they were ultramicrotomed into thin slices (30–100 nm) and analyzed with a transmission electron microscope (Zeiss EM 912 Omega). As shown in Figure 2 d–f, the composite inorganic capsules are hollow and inorganic particles form a shell-like structure that prcipitates on the inner side of the initial polyelectrolyte shell where PAH, which acts as a source of precipitating anions, exhibits the highest concentration. A continuous 30–150 nm layer consisting of 7–10 nm particles was observed for all of the inorganic/polymer capsules that were fabricated.

Composite inorganic–polymer capsules have higher mechanical stability compared to the polyelectrolyte examples. Besides their shape persistence after drying, the capsules are stable to ultrasonic treatment; processing inorganic capsules in an ultrasonic bath for 1 h does not affect their surface morphology or permeability properties. A mechanical force applied to the composite capsule through a cantilever leads, at first, to their reversible elastic deformation; a further increase of the force results in irreversible plastic deformation of the inorganic capsules (deformed YF_3 composite capsules are represented in Figure 2 c). The strength of the force that must be applied to initiate plastic deformation of the

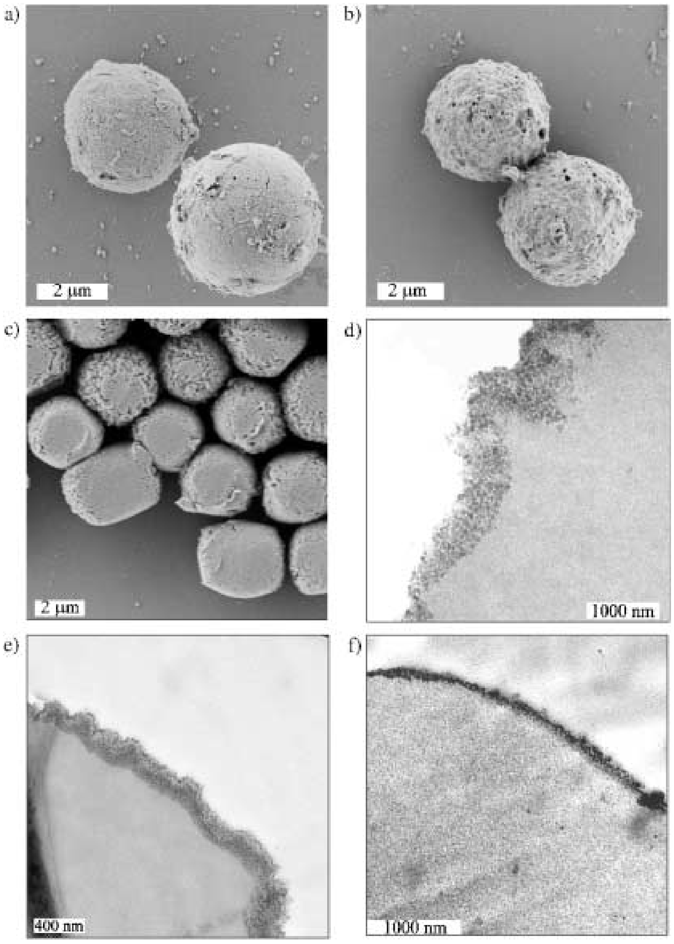

Figure 2. Scanning electron microscopy images of a) Fe_3O_4/PAH capsules; b) hydroxyapatite/PAH capsules; c) YF_3/PAH capsules that have undergone plastic deformation. Transmission electron microscopy images of d) ultramicrotomed Fe_3O_4/PAH capsules; e) hydroxyapatite/PAH capsules; f) YF_3/PAH capsules.

inorganic composite capsule depends on the inorganic nanomaterial synthesized.

Composite inorganic/organic capsules can incorporate with various organic and bioorganic materials (e.g., drugs, polymers, and enzymes) in a controlled manner. For this purpose, permeability and release properties were studied employing dextran (molecular weight = 2000 kDa) labeled with fluorescein isothiocyanate, which acts as a probe for YF_3/PAH capsules. The experimental procedure was as follows: YF_3/PAH capsules were added to a buffer solution with an appropriate pH value (2 or 8) and, after 5 min, were mixed with the labeled dextran solution. Fluorescence images were acquired using a Leica TSC SP fluorescent confocal microscope (see Figure 3). The YF_3/PAH capsules with dextran were shown to have an open formation at pH 5, while at pH 10, all inorganic/organic capsules are closed and the dextran molecules are captured inside. Changing the pH value again to give a more acidic media results in opening the capsule shell and the release of dextran molecules into the surrounding solution. A similar permeability versus pH dependence was observed for "initial" PAH/PSS capsules with no inorganic material at their interior.[12] Thus, one can conclude that inorganic/PAH capsules possess the main advantage of polyelectrolyte capsules, that is, controlled permeability. Drying dextran-containing YF_3/PAH capsules does not influence the controlled release properties (Figure 3). In the dried state the fluorescence from captured dextran molecules was observed. Further redispersion of dried inorganic/organic composite capsules in acidic and alkali media showed the preservation of their controlled-permeability properties. Under acidic conditions (pH 2) YF_3/PAH capsules release dextran molecules into the surrounding solution, while at pH 8 dextran molecules remain within the capsules. The possibility of switching the open/closed state of the inorganic/organic capsules, together with their stability upon drying or mechanical deformation, combine to provide a powerful tool for controlling the release of the organic materials, which may find applications for the protection, delivery, and storage of substances with unstable formulations. The capsules are thus suitable for applications where purely inorganic capsules obtained by the complete removal of organic components (calcination)[5] can not be envisaged. All the encapsulation procedures developed previously for polyelectrolyte capsules[3,6,8,10,12] can be applied for the inorganic/organic capsules presented herein.

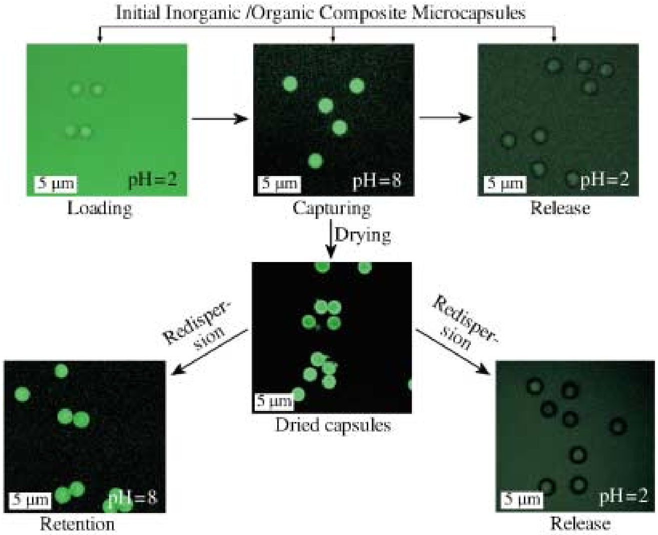

Figure 3. Permeability of YF_3/PAH capsules towards dextran molecules (molecular weight = 2000 kDa) labeled with fluorescein isothiocyanate. Measurements of the permeability of YF_3/PAH capsules before drying, in their dried state, and after redispersion in solutions with appropriate pH values were made using confocal fluorescent microscopy. The figure demonstrates that controlled permeability properties are retained in the composite inorganic/organic capsules after drying.

A versatile approach for the synthesis of new inorganic/organic composite capsules has been developed in this study. These inorganic capsules have both the advantages of inorganic materials (i.e., high mechanical stability) and conventional polyelectrolyte capsules (i.e., the controlled release/uptake properties of the capsule shell resulting from changes in, amongst others, pH value and ionic strength). Such possibilities have been demonstrated in this paper with the example of the controllable encapsulation and release of a polysaccharide (dextran). Defined characteristics (optical, magnetic, and mechanical) can be attributed to the composite capsules by varying the inorganic nanocomponent. Besides the common applications of polyelectrolyte capsules in controlled release, these composite inorganic/organic capsules can also be used as mechanically stable microreactors for enzymatic reactions and synthesis employing gas-phase reagents, in the form of hollow catalytically active microcontainers. The inorganic part can also find medical application that, together with encapsulated drug material, can provide synergetic curing effects (e.g., the application of hydroxyapatite-containing capsules in bone repair). Moreover, due to the preservation of the initial spherical shape and controlled-release properties upon drying, the inorganic/organic capsules can be employed as protective solid microcontainers for biochemical compounds that are unstable in solution or under UV/Vis irradiation, which can then be redispersed in solution to release the encapsulated compound in a controlled manner. In addition, the release properties of the inorganic/organic capsules can be adjusted mechanically by applying mechanical forces.

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