pH-Responsive nanocapsules from silylated copolymers†

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We introduce here a concept allowing the synthesis of smart nanocapsules without a surfactant. Copolymers with masked carboxylic acid groups are desilylated during the nanocapsule preparation and this leads to pH-responsive and self-stabilized nanocounters encapsulating a large amount of hydrophobic substances. The nanocapsules can be either disrupted for release applications or reversibly aggregated by lowering the pH of the dispersion. The concentration of the nanocapsules in water can be increased by more than 6 times by isolating the nanocounters at low pH and re-dispersing them at high pH values.

Due to their high loading capacity, nanocapsules with a liquid core are the colloidal morphology of choice for the encapsulation of liquid chemicals.3 Nanocapsules are prepared by a large variety of methods, including self-assembly approaches2 and templating of either solid nanoparticles3 or submicron liquid droplets.4 Microcapsules5 and nanocapsules5b,c can also be prepared by triggering phase separation in droplets between a polymer (building the shell) and a liquid (forming the core) by the evaporation of a solvent. On the contrary to the systems based on vesicles, this simple method allows the encapsulation of a large amount of hydrophobic liquid substances such as organic solvents5b and self-healing agents.2c Despite its popularity, this method suffers from important drawbacks, which are the presence of surfactant in the final dispersion and the very low concentration of the nanocapsules produced, i.e. typically (<5%). Because of their small sizes, nanocapsules cannot be easily filtered and centrifugation was shown to be detrimental to their structural integrity because of the inherent poor mechanical properties of nanocapsules with thin shells.6

Herein, we tackle simultaneously the aforementioned major issues by proposing a concept for the synthesis of smart nanocapsules without a surfactant that allows facile and repeatable separation of the nanocapsules from the aqueous continuous phase. The key point of our strategy is the design of a polymer with encoded processability that possesses enough functional hydrophilic groups to allow reversible aggregation and self-emulsification, but is still soluble in hydrophobic organic solvents. The requirements are a priori contradictory but can be solved by inducing a hydrophobic to hydrophilic transition in the polymer shell during the emulsification procedure, i.e., by creating a polymer shell with masked amphiphilic properties. Hydrophilic or and pH-responsive moieties can be masked by using trimethylsilyl protecting groups.7 The protecting group was advantageously used to allow the copolymerization of hydrophobic monomers with 2-trimethylsilyloxethyl acrylate or trimethylsilyl methacrylate to yield hydroxyf7b,c or carboxylic acid groups after desilylation.7c-f The method was found to be suitable for the fabrication of nanophase-separated amphiphilic conetworks.7f In a classical preparation of nanoparticles with the emulsion-solvent evaporation method5b,c a polymer is dissolved in a mixture of a non-solvent for the polymer and a good volatile solvent. The polymer solution is then emulsified in water with the help of a surfactant. A subsequent evaporation of the low boiling point solvent induces a phase separation between the non-solvent and the polymer to yield nanocapsules with controlled size and predictable shell thickness.

The amphiphilicity and pH-responsivity of the polymer shells were encoded in the chemical structure of the polymer by copolymerizing a hydrophobic monomer with monomers bearing a masked carboxylic acid, allowing a pH-switchability at relatively low pH values. Other reports have also used pH-responsive polymers to create core–shell structures and change the morphology of self-assembled structures. Wan et al. synthesized core–shell particles with a crosslinked polycationic shell and a polyglycerol core.8 A solid content of 2 to 4% could be obtained. Reversible morphological transitions between the micelles of hydroxyethylcellulose-graft-poly(acrylic acid) and

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hollow spheres could be induced by changes in the pH values. In our case, trimethylsilyl methacrylate (TMSMA) was copolymerized with various amounts of styrene (S) in solution by free-radical polymerization (experimental details in the ESI†) to obtain statistical copolymers as expected by the values of the monomer reactivity ratios. After purification, the copolymers of S and TMSMA (13, 29, and 48% TMSMA) could be dissolved in a mixture of chloroform and hexadecane. The solution was then added to a certain amount of basic aqueous solution, stirred, and further homogenized by sonication. The desilylation of the P(S-stat-TMSMA) copolymer occurred during the emulsification and yielded P(S-stat-MAA) as shown in Fig. 1 (top). The kinetics of desilylation was monitored by 1H-NMR spectroscopy (Fig. 1, bottom) and revealed that almost complete desilylation (91%) occurred after 24 h. A prolonged time in the presence of the basic solution completely removed the silyl groups from the copolymers. After 1 h of emulsification and just before the sonication step, ~50% of the protected groups were desilylated.

The in situ desilylation provided amphiphilic properties to the copolymer and allowed the stabilization of the droplets and the nanocapsules after the evaporation of the chloroform. Other organic solvents can be used with the conditions that they dissolve the polymer, that they are not miscible with water, and that they can be evaporated before water. The colloids were found to be colloidally stable and displayed a hydrodynamic diameter of 205 ± 80 nm as measured by dynamic light scattering (DLS). The successful formation of core–shell nanoparticles with a shell thickness of ~20 nm was evidenced by transmission electron microscopy in the dried state when using the copolymers P(S0.87-stat-TMSMA0.13) and P(S0.71-stat-TMSMA0.29) as precursors for the shell formation (Fig. 2A and B). However, too many TMSMA units in the copolymer are detrimental to the nanoparticle structure. Less defined structures, i.e. a mixture of nanocapsules and nanoparticles, were hence formed with P(S0.52-stat-MAA0.48) owing to the higher solubility of the desilylated copolymer in water (Fig. S1†). 29% of MAA units in the copolymer shell are already a remarkably high amount that cannot be reached by directly using a copolymer of styrene and methacrylic acid because of the non-solubility of the latter copolymer in chloroform. Therefore, the strategy for the in situ desilylation of the chloroform-soluble copolymers is necessary to fabricate a polymer shell enriched with a high amount of MAA. The method could be in principle used for other monomer units with pH-switchable groups that are not well soluble in organic solvents. To the best of our knowledge, this is the first reported solvent-emulsion evaporation process that yields nanocapsules without a surfactant. The procedure is very versatile since monolithic nanoparticles (monophasic solid nanoparticles) could be synthesized by the same method (ESI, Fig. S2†) by using a much lower amount of non-solvent.

Because the masked units yielded carboxylic acid groups, the amount of charges on the shell, and therefore the efficiency of the electrostatic stabilization, depends on the pH of the dispersion. Macroscopic inspections of the dispersion with a desilylated P(S0.71-stat-TMSMA0.29) shell at high and low pH evidenced stabilization and destabilization of the dispersions of nanocapsules, respectively (Fig. 3A). The flocculations and re-dispersions were found to be reversible. The pH-responsive behavior was further investigated by the DLS measurements performed on the dispersions subjected to different pH values. The size of the polydisperse aggregates was found to be larger than 1 μm at pH = 3 (Daggregates ~ 10.9 ± 8.0 μm for P(S0.71-stat-TMSMA0.29) nanocapsules, Fig. S3†) and could be switched back to ~ 300 nm by increasing the pH again.

![Fig. 1](image1.png)  
**Scheme of the reaction of desilylation of the copolymer (top), and a plot of the amount of remaining TMSMA groups versus time for the preparation of surfactant-free P(S0.71-stat-TMSMA0.29) nanocapsules (bottom) at room temperature in 0.02 mmol mL⁻¹ aqueous solution of NaOH. Samples were taken from stirred surfactant-free emulsions (●) and from the resulting dispersion of nanocapsules after sonication and evaporation (▲). The inset shows the section of the 1H-NMR spectra in the range of the signal for the TMS group.**

![Fig. 2](image2.png)  
**TEM micrographs of the desilylated nanocapsules prepared via a surfactant-free emulsion-solvent evaporation technique with A: P(S0.87-stat-TMSMA0.13), B: P(S0.71-stat-TMSMA0.29), C: SEM micrograph of the P(S0.87-stat-TMSMA0.13) nanocapsules with encapsulated dicyclopentadiene.**
The destabilization and redispersion of the P(S_{0.71-stat-TMSMA_{0.29}}) nanocapsules can be monitored visually and by turbidimetry (A), and by DLS (B). C: Schematics of the aggregation–redispersion of the nanocapsule dispersion upon switching of the pH value.

Fig. 3

contain a very low amount of dispersed phase (~6% in Fig. 4A). It was previously demonstrated that the structural integrity of nanocapsules with thin shells can be damaged by centrifugation. We showed that the switching of colloidal stability can be efficiently used to concentrate the nanocapsule dispersion. The nanocapsules were destabilized, filtered, and the separated solid could be redispersed to yield concentrated nanocapsule dispersions (Fig. 4A) with ~32% dispersed phase, i.e. a storage capacity of 160 mg mL^{-1} of hydrophobic liquids. Experiments performed by directly preparing the nanocapsules with 23 and 18 wt% dispersed phase failed to yield stable dispersions. Indeed, a large amount of dispersed phase favors coalescence between the droplets and gelation occurs during the tentative emulsification procedure. The concept of separation and concentration was exemplary demonstrated for nanocapsules encapsulating a fluorescent dye (Fig. 4B). The switchable nanocapsules were also used to encapsulate monomers and catalysts. Since the seminal work of White et al. showing the concept of autonomous self-healing materials, non-responsive nanocontainers for the encapsulation of monomers and catalysts for ring-opening metathesis polymerization (ROMP) have been proposed. Our surfactant-free method was used to separately encapsulate dicyclopentadiene as the monomer and a Grubbs–Hoveyda 2nd generation catalyst, both suitable for a ROMP self-healing reaction (Fig. 5). The nanocapsule dispersion was aggregated and redispersed and the amount of encapsulated DCPD (dicyclopentadiene) was found to remain constant (~80% of the initial amount), meaning that no loss of encapsulated substances occurred during the switching of the pH (details in the ESI†). Consequently, despite the swelling/collapse of the polymer shells due to pH changes, the structural integrity of the capsule walls was maintained and the shells still fulfilled the function of protection of the liquid core against coalescence. The pH-responsivity can be hence utilized for switching reversibly the nanocapsules...
from a collection of individual nanocapsules to a large macroscopic object.

However, the switching did not allow the release of the core in aqueous solution, a feature that can be interesting for some applications. This is due to the very low solubility of the encapsulated liquid core in water. On the other hand, an efficient encapsulation cannot be carried out with aqueous continuous phases if the core is too hydrophilic. To solve this issue, we proposed to employ a liquid core displaying a pH-switchable stability in water. Oleic acid was selected as the core and could be encapsulated at pH = 3 in nanocontainers with $D_0 = 230 \pm 80$ nm (ESI†). At this pH, oleic acid has a poor surface activity and solubility in water. In this case, the carboxylic acid groups of the shells are also mostly protonated and therefore sodium dodecyl sulfate was employed to allow for an electrostatic stabilization of the nanocapsules. An increase in the pH resulted in deprotonation of the acid, which rapidly diffused to the continuous phase, hence destroying the nanocapsule structure because its hydrophobic core was converted to a water-soluble substance. After switching the pH back to pH = 3, nanocapsules could not be observed anymore. Collapsed aggregates with much smaller sizes were indeed detected by TEM (Fig. S8†). These structures were the result of aggregated collapsed chains of desilylated P(S0.71-stat-TMSMA0.29). Therefore, it was also possible to induce a non-reversible response by varying the pH and to release the liquid core out of the nanocapsules. The described method represents an alternative to the release of substances upon pH switch from microparticles fabricated by the layer-by-layer procedure. 13

The proposed synthetic approach is unique in the sense that it combines two novelties in colloid science. Firstly, this is the first synthesis of nanocapsules by the emulsion-solvent evaporation process in the absence of a surfactant. Secondly, the pH-responsive stability is controlled by the chemistry of the polymer shell that is defined in situ during the self-emulsification process. The reversible aggregation allows the separation of the nanocapsules without evaporation or centrifugation and therefore the structural integrity of the nanocounters is preserved.

Finally, the possibility of preparing nanocapsules without a surfactant and subsequently concentrating them in water by switching the pH is environmentally friendly. The containers can be used to encapsulate hydrophobic liquids that present a high interfacial tension with water. Nanocapsules can be concentrated without evaporation of water, which is energy demanding. Furthermore, energy and resources dissipated in transport are saved by the fact that the nanocapsules can be separated directly after their production and redispersed where they are used. This simple proposed synthetic strategy could also be used with other shells by desilylating other functions such as alcohols, or, to a larger extent, by deprotecting other groups, although the deisilylation step may be longer and the reaction conditions have to be adapted to the protecting groups. 14 The masked groups could be introduced in other copolymer structures to prepare nanocapsules for biomedical applications.

Notes and references

1 W. Meier, Chem. Soc. Rev., 2000, 29, 295.
2 (a) H. Huang, E. E. Remsen, T. Kowalewski and K. L. Wooley, J. Am. Chem. Soc., 1999, 121, 3805; (b) F. Chocet, S. Lecommandoux, Y. Yanoun and H.-A. Klok, Angew. Chem., Int. Ed., 2002, 41, 1340; (c) R. Haag, Angew. Chem., Int. Ed., 2004, 43, 278; (d) Y.-S. Yoo, J.-H. Choi, N.-K. Oh, W.-C. Zin, S. Park, T. Chang and M. Lee, J. Am. Chem. Soc., 2004, 126, 6294; (e) E. G. Bellomo, M. D. Wyrsza, L. Pakstis, D. J. Pochan and T. J. Deming, Nat. Mater., 2004, 3, 244; (f) J. Du and Y. Chen, Angew. Chem., Int. Ed., 2004, 43, 5084; (g) K. J. Zhou, Y. G. Wang, X. N. Huang, K. Luby-Phepls, B. D. Sumer and J. M. Gao, Angew. Chem., Int. Ed., 2011, 50, 6109.
3 (a) G. Sukhorukov, A. Fery and H. Mohwald, Prog. Polym. Sci., 2004, 30, 885; (b) R. J. White, K. Tauer, M. Antonietti and M. M. Titirici, J. Am. Chem. Soc., 2010, 132, 17360; (c) C. Li, W. Zhu, H. Yang, Q. An, C.-A. Tao, W. Li, J. Cui, Z. Li and G. Li, Angew. Chem., Int. Ed., 2011, 50, 4947.
4 (a) C. Scott, D. Wu, C. C. Ho and C. C. Co, J. Am. Chem. Soc., 2005, 127, 4160; (b) D. Crespy, M. Stark, C. Hoffmann-Richter, U. Ziener and K. Landfester, Macromolecules, 2007, 40, 3122.
5 (a) A. Loxley and B. Vincent, J. Colloid Interface Sci., 1998, 208, 49; (b) Y. Zhao, K. Landfester and D. Crespy, Soft Matter, 2012, 8, 11687; (c) Y. Zhao, J. Fickert, K. Landfester and D. Crespy, Small, 2012, 8, 2954.
6 J. Fickert, M. Makowski, M. Kappl, K. Landfester and D. Crespy, Macromolecules, 2012, 45, 6324.
7 (a) H. Mori and A. H. E. Müller, Prog. Polym. Sci., 2003, 28, 1403; (b) A. Mühlebach, S. G. Gaynor and K. Matyjaszewski, Macromolecules, 1998, 31, 6046; (c) G. Makrikosta, D. Georgas, E. Siakali-Kioulafa and M. Pitsikalis, Eur. Polym. J., 2005, 41, 47; (d) D. N. Andreev, D. N. Asinovskaya and N. A. Solovskaya, Russ. Chem. Bull., 1972, 21, 1361; (e) W. Mommam and J. Ferbitz, Macromol. Chem. Phys., 2002, 203, 2616; (f) B. Ivan, M. Hanaszt, G. Erdodi, J. Scherble, R. Thoman and R. Mühlaut, Macromol. Symp., 2005, 227, 265.
8 D. Wan, Z. Li and J. Huang, J. Polym. Sci., Part A, 2005, 43, 5458.
9 H. Dou, M. Jiang, H. Peng, D. Chen and Y. Hong, Angew. Chem., Int. Ed., 2003, 42, 1516.
10 S. R. White, N. R. Sottos, P. H. Geubelle, J. S. Moore, M. R. Kessler, S. R. Sriram, E. N. Brown and S. Viswanathan, Nature, 2001, 409, 794.
11 (a) A. C. Jackson, J. A. Bartelt, K. Marczewski, N. R. Sottos and P. V. Braun, Macromol. Rapid Commun., 2011, 32, 82; (b) J. Fickert, C. Wohonnaas, A. Turschatow, K. Landfester and D. Crespy, Macromolecules, 2013, 46, 573.
12 R. D. Kulikarni and P. Somasundaran, Colloids Surf., 1980, 1, 387.
13 C. S. Peyratout and L. Dahne, Angew. Chem., Int. Ed., 2004, 43, 3762.
14 K. Jarowicki and P. Kocienski, J. Chem. Soc., Perkin Trans. 1, 2001, 2109.