Polymer Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Polym. Chem.*, 2016, **7**, 4330

Received 20th May 2016,
Accepted 7th June 2016

DOI: 10.1039/c6py00878j

www.rsc.org/polymers

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 nanocontainers 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 nanocontainers 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.[1] Nanocapsules are prepared by a large variety of methods, including self-assembly approaches[2] and templating of either solid nanoparticles[3] or submicron liquid droplets.[4] Microcapsules[5a] and nanocapsules[5b,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 solvents[5b] and self-healing agents.[5c] 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-trimethylsilyloxyethyl acrylate or trimethylsilyl methacrylate to yield hydroxyl[7b,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 method,[5b,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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†Electronic supplementary information (ESI) available. See DOI: 10.1039/c6py00878j

hollow spheres could be induced by changes in the pH values.[9] 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.[7c] 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 ^{1}H-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($S_{0.87}$-*stat*-$TMSMA_{0.13}$) and P($S_{0.71}$-*stat*-$TMSMA_{0.29}$) as precursors for the shell formation (Fig. 2A and B). However, too many TMSMA units in the copolymer are detrimental to the nanocapsule structure. Less defined structures, *i.e.* a mixture of nanocapsules and nanoparticles, were hence formed with P($S_{0.52}$-*stat*-$MAA_{0.48}$) 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.

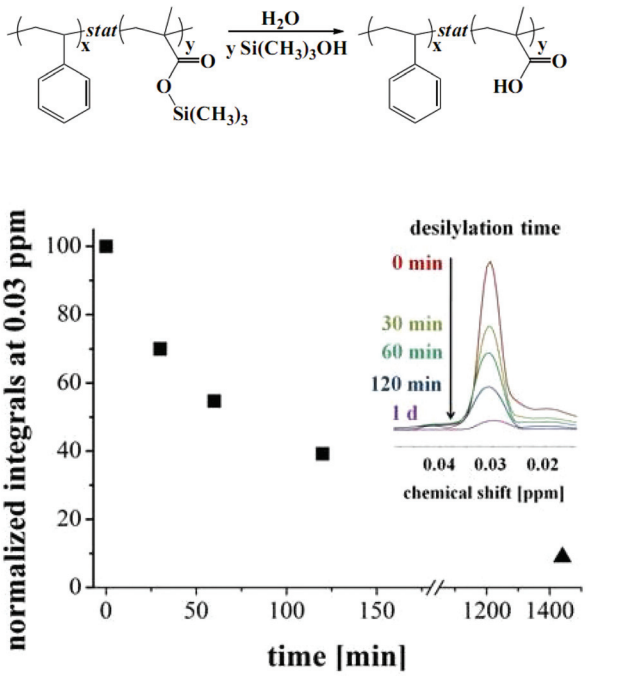

Fig. 1 Scheme of the reaction of desilylation of the copolymer (top), and a plot of the amount of remaining TMSMA groups *versus* time for the preparation of surfactant-free P($S_{0.71}$-*stat*-$TMSMA_{0.29}$) nanocapsules (bottom) at room temperature in 0.02 mmol mL^{-1} aqueous solution of NaOH. Samples 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 ^{1}H-NMR spectra in the range of the signal for the TMS group.

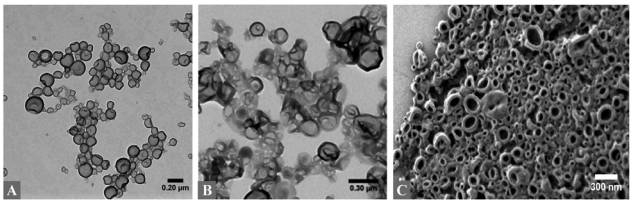

Fig. 2 TEM micrographs of the desilylated nanocapsules prepared *via* a surfactant-free emulsion-solvent evaporation technique with A: P($S_{0.87}$-*stat*-$TMSMA_{0.13}$), B: P($S_{0.71}$-*stat*-$TMSMA_{0.29}$). C: SEM micrograph of the P($S_{0.87}$-*stat*-$TMSMA_{0.13}$) nanocapsules with encapsulated dicyclopentadiene.

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($S_{0.71}$-*stat*-$TMSMA_{0.29}$) 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 ($D_{aggregates}$ ~ 10.9 ± 8.0 μm for P($S_{0.71}$-*stat*-$TMSMA_{0.29}$) nanocapsules, Fig. S3†) and could be switched back to ~ 300 nm by increasing the pH again

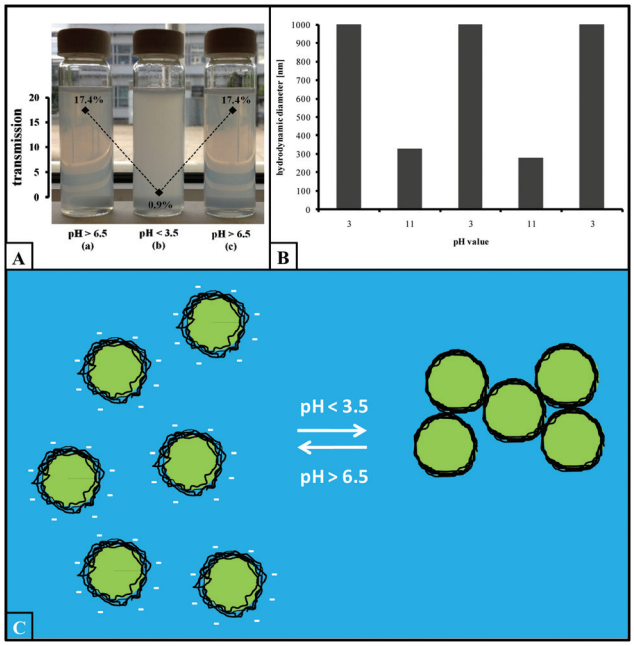

Fig. 3 The destabilization and redispersion of the P($S_{0.71}$-*stat*-$TMSMA_{0.29}$) nanocapsules can be monitored visually and by turbidimetry (A), and by DLS (B). C: Schematics of the aggregation–redispersion of the nanocapsule dispersion upon switching of the pH value.

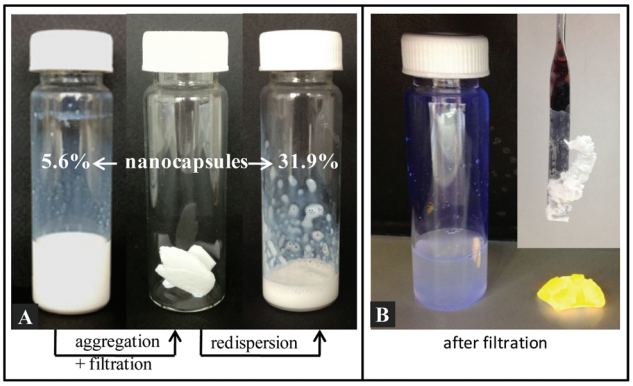

Fig. 4 The aggregation and subsequent redispersion allow increasing the concentration of the P($S_{0.71}$-*stat*-$TMSMA_{0.29}$) nanocapsules in water (A). The nanocapsules can be used to encapsulate organic molecules, for instance a fluorescent dye. After pH-triggered aggregation, the dye is present in the residue as identified by irradiating (λ = 366 nm) the filtrate and the residue (B). The inset shows the appearance of the residue under normal sunlight.

(Fig. 3B). The transition was found to be fully reversible, *i.e.* 100% of the nanocapsules could be redispersed after aggregation, as proved by the turbidity measurements. The transmission of the redispersed nanocapsules was independent of the number of cycles.

Lower amounts of methacrylic units in the copolymer shell do not allow the switching of the colloidal stability. Indeed the hydrodynamic diameters of the nanocapsules of the desilylated P($S_{0.87}$-*stat*-$TMSMA_{0.13}$) (Fig. S4a†) and P($S_{0.91}$-*stat*-$MAA_{0.09}$) prepared by free-radical copolymerization of styrene and methacrylic acid (Fig. S4b†) remained constant. This demonstrates further the unique character of the synthetic strategy for the synthesis of hydrophobic nanocapsules with pH-responsive aggregation. Indeed, copolymers with a higher amount of methacrylic acid are not soluble in chloroform and therefore the *in situ* desilylation or any form of deprotection of a carboxylic acid is necessary to yield nanocapsules with a pH-responsive stability *via* this simple emulsion-solvent evaporation method.

To prove that the switching was controlled by the electrostatic stabilization displayed by the negatively charged nanocapsule shells, further experiments were performed by adding a non-ionic block copolymer surfactant to the dispersions (Fig. S5†). Steric stabilization of the nanocapsules occurred efficiently at concentrations of the block copolymer surfactant above 4 mg mL^{-1} (Fig. S6†), for which the switching effect upon pH variation was no longer observed.

The last major drawback of the emulsion-solvent evaporation technique is that the colloids produced by this method 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.[6] 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,[10] non-responsive nanocontainers for the encapsulation of monomers and catalysts for ring-opening metathesis polymerization (ROMP) have been proposed.[5c,6,11] 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. S7†). 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_h = 230 ± 80 nm (ESI†). At this pH, oleic acid has a poor surface activity and solubility in water.[12] 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($S_{0.71}$-*stat*-$TMSMA_{0.29}$). 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 microcapsules 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 nanocaspules without evaporation or centrifugation and therefore the structural integrity of the nanocontainers 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 desilylation 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.

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