

Robust and Readily Functionalized Microcapsules from Interfacial Click Polymerization of Amphiphilic Alternating Copolymers

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Electronic Supplementary Information

Abstract The preparation and functionalization of polymeric capsules attract intense attention due to their application in various areas. Herein we presented an amphiphilic alternating copolymer (ACP)-based microcapsule which is both robust and readily-functionalized through interfacial click polymerization. A water-in-oil emulsion was constructed to act as the reaction medium, the hydrophilic 1,3-butadiene diepoxide (BDE) in water phase reacted with the oleophilic 1,4-dibutanedithiol (BDT) in oil phase at the water-oil interface to form the amphiphilic ACP named poly(2,3-dihydroxy butylene-*alt*-butylene dithioether) (abbreviated as P(DHB-*α*-BDT) below), which would deposit *in situ* to form the micro-sized capsules. Significantly, the dried capsules are robust enough to be rehydrated once the water was added and almost restored their original morphologies. Further elucidation showed that the Young's modulus of these capsules exceeded 1 GPa. As long as we know, it is the first time for the mechanical properties of the ACP-based microstructures being investigated. Besides, functionalization could be achieved simultaneously with the formation process. As a proof of concept, positive-charged capsules were successfully obtained through click copolymerization. Stemming from the unique characteristics of amphiphilic ACPs which combined both merits of click chemistry and interfacial reactions, all these features of the current method as well as the resultant capsules may promote the application of the polymeric capsules.

Keywords Click chemistry; Interfacial reaction; Amphiphilic alternating copolymer; Microcapsule; Young's modulus

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INTRODUCTION

Polymeric capsules are regarded as an important type of polymeric particles.^[1–4] Being constituted of a polymeric membrane with an enclosed hollow cavity, the polymeric capsules are widely applied in various fields, such as biomedicine, microreactors, biotechnology, and synthetic chemistry.^[5–10] Nowadays, polymeric capsules have evolved from simple containers to multifunctional platforms, which are constructed using diverse components such as man-made polymers, biomacromolecules, and other functional units.^[11,12] Therefore, the preparation and functionalization of polymeric capsules have become extremely significant. Many methods have been devised to prepare and further functionalize polymeric capsules.^[13–16] Among them, the layer-by-layer (LbL) strategy is one of the most frequently used methods.^[17,18] Different batches of polymers are coated or grafted consecutively onto the surface of a sacrificial template through covalent or non-covalent interactions. Afterwards, the

sacrificial templates were dissolved, leaving a solid shell with a hollow cavity. In this way, capsules can be elaborately prepared with precisely controlled sizes and compositions. Interfacial polymerization is another widely adopted pathway to prepare polymeric capsules.^[19–23] In general, interfacial polymerization is conducted in a heterophase system such as the oil-in-water (O/W) emulsion. The two types of monomers are dissolved beforehand in the oil droplets and water phase, respectively, and further react (e.g., ionic polymerization, radical polymerization, polycondensation, and polyaddition) at the water-oil interface to obtain polymers, which would deposit *in situ* to form a spherical membrane wrapping on the surface of the oil droplet. Such an interfacial polymerization methodology has been successfully employed to fabricate various microcapsules at the micro- and nanoscale.^[24–29] However, this method also suffers from some drawbacks. First, there are still relatively high requirements for polymerization, together with the occurrence of side reactions or the existence of small molecular residuals. Second, post-modification is frequently used to functionalize the capsule obtained from this method, complicating the overall preparation process. Third, to date, the categories of polymers constituting the capsules are still waiting to be expanded.

Recently, the emergence of click chemistry has alleviated

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these problems and provided a facile pathway for the preparation of polymeric capsules.^[30–37] The high efficiency and modular nature of click chemistry could eliminate the high reaction requirements, minimize side reactions and residuals, and combine the preparation and functionalization of the resultant polymeric nanoparticles into one step.^[38,39] Significantly, using click copolymerization, a novel kind of polymer named amphiphilic alternating copolymers (ACPs) could be prepared, and these ACPs could self-assemble into various particles with intriguing morphologies such as nanotubes, vesicles, and hierarchical superstructures with ultrathin and uniform feature sizes.^[40–49] Moreover, these morphologies are irrelevant to their molecular weights (MWs) and molecular weight distributions (MWD). This intriguing characteristic could be ascribed to the unique “loop” or “bridge” folding conformations that the ACP chains have adopted within the assemblies.^[50] Consequently, many intriguing properties that had not been observed previously, such as the ultra-large size transformation under stimuli, could be obtained.^[51–53] Both the experimental and simulation results confirmed that these facts stem from their unique amphiphilic alternating architectures.^[50,54]

Inspired by the unique characteristics of amphiphilic ACPs, we herein present ACP-based microcapsules utilizing the interfacial click polymerization method. The experimental details for the preparation of the primary capsules are shown in Fig. 1. Firstly, 1,3-butadiene diepoxide (BDE) aqueous solution was dispersed in *n*-hexane as spherical droplets to form a water-in-oil emulsion (W/O). Span-80 (2 wt% *n*-hexane) was used as the surfactant. Subsequently, oleophilic 1,4-dibutanedithiol (abbreviated as BDT) was added to initiate click polymerization between the dithiol groups of BDT and the diepoxy groups of BDE at the water-oil interface. The resultant ACP poly(2,3-dihydroxybutylene-*alt*-butylenedithioether) (abbreviated as P(DHB-*α*-BDT) below) was deposited on the water-oil interface *in situ* to form a solid membrane. Consequently, micro-sized capsules were successfully prepared. Owing to the intrinsic merits of click chemistry and interfacial reactions, the resultant capsules are scalable prepared at room temperature without the need for a specific temperature or inert gas protection. Moreover, these capsules could be readily functionalized simultaneously with their formation process utilizing click copolymerization by adding a third monomer. More significantly, the dried capsules obtained in

the current study were sufficiently robust to restore their original morphologies under rehydration. Therefore, we investigated the Young's modulus of these capsules and obtained values above 1 GPa (1.305 and 1.111 GPa, respectively), which may be a consequence of the alternating amphiphilic architectures of the ACPs. To the best of our knowledge, this is the first study exploring the mechanical properties of amphiphilic ACPs. All these advantages endow the as-prepared capsules with an elongated shelf-life, enhanced mechanical stability, and increased accessibility of preparation/functionalization, all of which are of great significance for many applications such as drug delivery and cosmetics.^[55–57]

EXPERIMENTAL

Materials

All reagents were purchased and used directly: 1,4-dibutanedithiol (BDT>95%, TCI), 1,3-butadiene diepoxide (BDE 95%, Alfa Aesar), *n*-butylamine (99%, Adamas), potassium carbonate (analytical grade, Greagent), *n*-hexane (analytical grade, Greagent), and span-80 (reagent grade, Adamas). Deionized (DI) water was used throughout the experiments.

Preparation of Capsules

BDE (85 μ L) was dissolved in deionized water (1 mL) to form a homogeneous solution. The aqueous solution was added to a 50 mL single flask equipped with a magnetic stirring bar. Subsequently, 9 mL of *n*-hexane, in which 0.119 g of span-80 was dissolved, was added to the flask under vigorous stirring. Subsequently, the mixture was subjected to an ultrasound treatment for 1 min to form a water-in-oil emulsion. Finally, 115 μ L of BDT was added to the mixture. The reaction continued for 4 h.

Redistribution of Capsules in Water

The capsules obtained in the last step were separated from the reaction mixture by centrifugation and washed with *n*-hexane repeatedly. After purification, the capsules were dried in vials under atmospheric conditions. For redistribution, 10 mL of deionized water was added to the vial, and the mixture was stirred vigorously to obtain spherical capsules that were redistributed in water.

Preparation of Amino-functionalized Capsules

The preparation of amino-functionalized capsules followed a pathway similar to that of the primary capsules. BDE (102 μ L) was dissolved in deionized water (1 mL) to form a homoge-

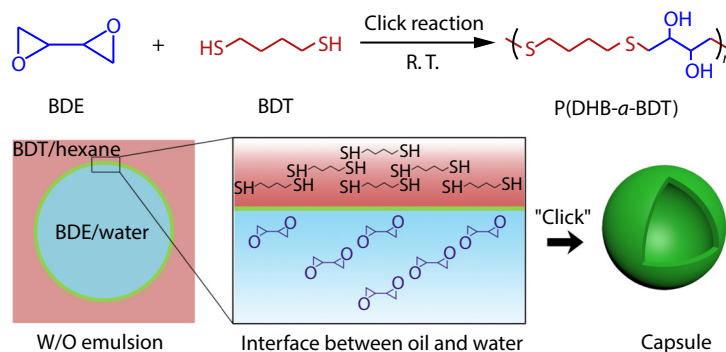


Fig. 1 Scheme for the preparation of amphiphilic alternating copolymer-based capsules based on interfacial click polymerization between 1,3-butadiene diepoxide (BDE) and 1,4-dibutanedithiol (BDT).

neous solution. The aqueous solution was added to a 50 mL single flask equipped with a magnetic stirring bar. Subsequently, 9 mL of *n*-hexane, in which 0.119 g of span-80 was dissolved, was added to the flask under vigorous stirring. Subsequently, the mixture was subjected to an ultrasound treatment for 1 min to form a water-in-oil emulsion. Finally, 115 μ L of BDT and 20 μ L of *n*-butylamine were added. The reaction continued for 4 h.

Characterization

Optical microscopy (OM): the microscope was a DM-4500B microscope (Leica, Germany). A drop of the sample solution was dipped onto the glass slide and observed directly (in liquid state), or dried in atmosphere for 48 h and observed under a microscope (in the dried state). **Scanning electron microscopy (SEM)** measurements were performed on a Nova NanoSEM 450 (FEI, USA). A drop of the sample solution was dipped into a silica wafer and dried at room temperature or freeze-dried for 48 h. A thin layer of gold (Au) was coated onto the surface of the samples before characterization. To observe the recovered capsule, a drop of the redispersed solution was dipped onto a silicon wafer, which was pre-cooled with liquid nitrogen. The water was immediately freeze-dried overnight before characterization. **Transmission electron microscopy (TEM)** measurements were conducted on a Tecnai G2 Spirit Biotwin (FEI, USA). A small drop of the diluted sample solution was dipped onto a carbon-coated copper grid and stained with phosphotungstic acid aqueous solution (3%). The grid was then dried at room temperature for 24 h.

Atomic force microscopy (AFM): the measurements were carried out on a BioScope Resolve scanning probe microscopy (SPM) system (Bruker, USA) in PeakForce tapping mode. Young's modulus of the capsule membrane was obtained using an MFD 3D atomic force microscope (Oxford, UK). Gel permeation chromatography (GPC) GPC measurements were carried out using an HLC-8320GPC (TOSOH, EcoSEC GPC System) at 313 K with *N,N*-dimethyl formamide (DMF) as the mobile phase at a flow rate of 0.6 mL/min. Poly(ethylene oxide) (PEO) and poly(methyl methacrylate) (PMMA) were used as the calibration standards. ^1H -nuclear magnetic resonance (NMR) spectra were recorded using an AVANCE III HD 400 (400 MHz) spectrometer (Bruker, Germany) with dimethyl formamide- d_7 (DMF- d_7) as the solvent at 293 K. Tetramethylsilane (TMS) was used as the internal standard. **Zeta potentials:** the measurements were conducted using a Nano ZS90 instrument (Malvern Instruments Ltd., UK).

RESULTS AND DISCUSSION

As soon as the onset of click polymerization began, some precipitates came into being gradually. After the reaction, their morphology was investigated firstly by the optical microscopy (OM). According to the OM images in the liquid state (Fig. 2a) and dried state (Fig. 2b), the as-prepared precipitates were micro-sized spherical particles with hollow interiors. We further evaluated the sizes of these particles by counting 100 particles and the statistical result showed that the average diameter of these particles is $(4.94 \pm 0.53) \mu\text{m}$ (Fig. S1 in the electronic supplementary information, ESI). This diameter matches well with the average diameter of the water droplets within the water-in-oil emulsion before the reaction $((5.01 \pm 0.55) \mu\text{m})$ as shown in Fig. S2 in ESI). Thus, we assumed that these spherical particles

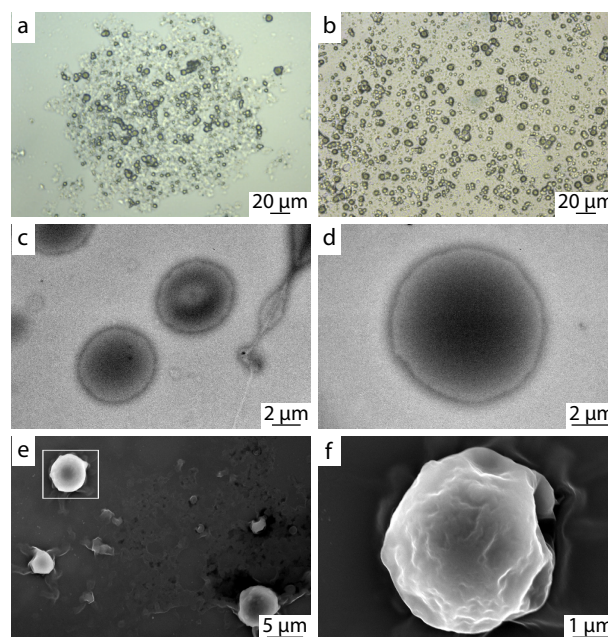


Fig. 2 Morphologies of the as-prepared particles after interfacial click polymerization. The optical microscopy (OM) images of the particles after reaction at liquid state (a) and dried state (b) respectively; Detailed morphologies of the as-prepared particles after interfacial click polymerization by transmission electron microscopy (TEM) (c, d) and scanning electron microscopy (SEM) (e, f). The specific particle indexed by the white pane in (e) are enlarged as (f). Some wrinkles could be found on the surface of this particle under the electronic beam of the SEM instrument.

were intrinsically microcapsules formed through click polymerization between the BDE and BDT monomers at the oil-water interface.

We further employed TEM and SEM to study the detailed morphologies of these particles. The corresponding TEM images in Figs. 2(c) and 2(d) show the presence of solid membranes. Moreover, a distinct contrast between the outer membrane and the inner cavities could also be clearly discerned. In the meantime, SEM image of these particles (Fig. 2e) demonstrates that the particles were soft and tended to collapse onto the substrate upon drying. In addition, the enlarged image shows that for a single particle, some wrinkles appeared on the electronic beam of the SEM instrument (Fig. 2f). We further put these particles under reduced pressure overnight and took them for the SEM measurement. The corresponding SEM images are demonstrated in Figs. 3(a) and 3(b). All particles collapsed and the membranes collapsed onto the substrate. This indicates that these particles had hollow interiors inside the membranes. In all, based on the proofs above, it could be confirmed that the particles obtained after interfacial click polymerization are micro-sized capsules with a solid membrane and a hollow cavity inside. AFM was used to measure the thickness of the membrane, and the resulting image is shown in Fig. 3(c), which contains some fully collapsed capsules. Since the hollow space inside the capsule was fully compressed under reduced pressure, the height profile (Fig. 3d), indicated by the white line in Fig. 3(c), represents the thickness of the two layers of the membrane ($h=249 \text{ nm}$). Thus, the monolayer thicknesses of the

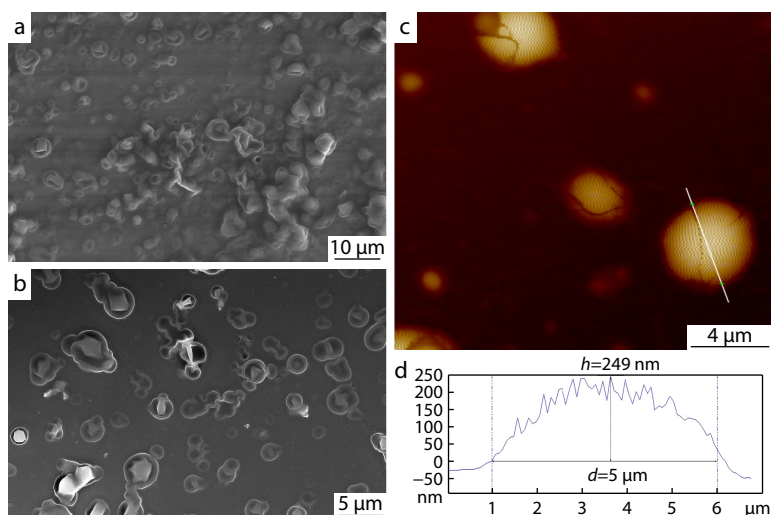


Fig. 3 Morphological characterizations on the collapsed microcapsules. (a, b) SEM images of the collapsed capsules; (c) AFM image of the fully collapsed capsules; (d) The height profile of the microcapsule as indexed by the white lines in (c).

capsule membrane locate around 125 nm.

Taking advantage of the high efficiency of click chemistry and interfacial reactions,^[38,39,58–64] the capsules could be prepared on a large scale (Fig. S3 in ESI). This makes us more convenient to collect capsules to characterize their molecular structures. The number-average molecular weight (M_n) of these capsules was 3400 Da according to the gel permeation chromatography (GPC) trace (Fig. S4 in ESI). $^1\text{H-NMR}$ spectroscopy (Fig. S5 in ESI) is consistent with previous reports^[46,47] and shows that these capsules are composed of amphiphilic alternating copolymers named P(DHB-*α*-BDT) with a molar ratio of hydrophilic DHB and hydrophobic BDT segments of 1:1, which keeps consistent with our previous reports.^[40,46] Evidently, it is the click reaction between the epoxy groups of BDE monomers and the thiol groups of BDT monomers at the water-oil interface that drives the formation of the P(DHB-*α*-BDT)s, which would deposit *in situ* to form the capsules, as illustrated in Fig. 1. Despite the relatively low M_n , it has been proved-through both the computer simulation and the experimental results-that the morphologies of ACP-derivate objects are independent from their molecular weights and weight distributions as long as the degree of polymerization exceeds a critical value.^[44,50] This is also one of the most exclusive characteristics of the ACPs. Moreover, the average diameter of the as-prepared capsules could be easily adjusted by adjusting the volume ratio of the oil phase to the water phase within the W/O emulsion. For example, if the volume fraction of the oil phase decreased from 90% (oil-water volume ratio: 9:1) to 60% (oil-water volume ratio: 6:4), the diameters of the resultant capsules would decrease to approximately 2 μm (Fig. S6 in ESI).

Significantly, one advantage of the current capsule is its robustness, which makes the morphological restoration of dried capsules in water much easier. The as-prepared capsules collapsed and existed as solids after complete drying. Once these solids were redispersed in water and vigorously stirred, a homogeneous cloudy solution could be obtained. We took it for OM observation and the resultant images are shown in Fig. 4. In the water phase, there are micro-sized particles with hollow interior (Fig. 4a), keeping consistent with the OM im-

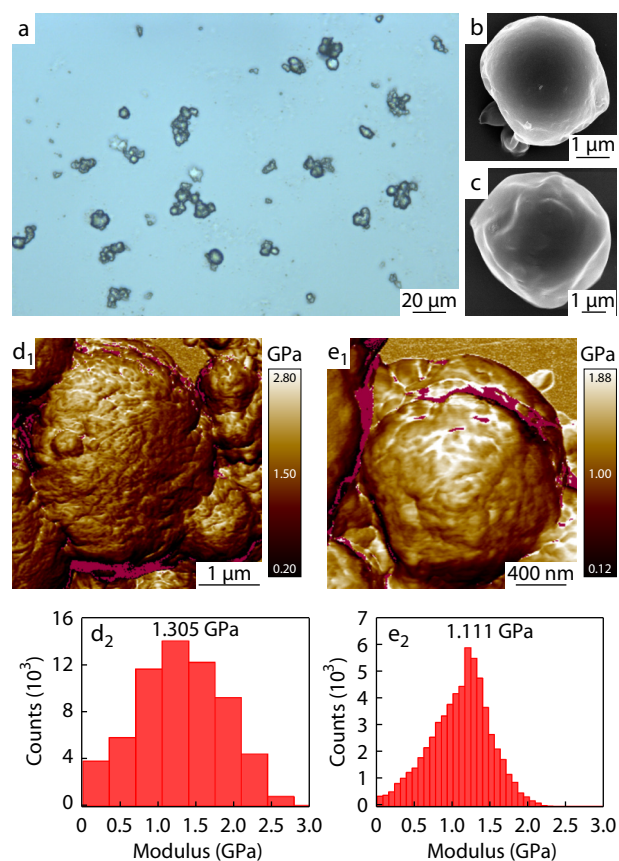


Fig. 4 Robustness of the capsules. The spherical morphology restored after the dried capsules redispersed in water. (a) The corresponding OM image of the recovered capsules in water; (b, c) SEM images of two single recovered capsules; AFM images of two capsules in the modulus mode (d_1 and e_1) and their statistical distributions of Young's modulus (d_2 and e_2) respectively. These two capsules are in contact and their AFM image at the lower magnification is shown as Fig. S8 (in ESI).

ages in Fig. 2. Thus, the capsules which have already collapsed after the drying process could recover their capsular morphologies successfully once they were redispersed in water. Further SEM images (Figs. 4b and 4c) show that the membrane of these recovered capsules fully recovered, almost no physical damages existed. Moreover, the capsules experiencing five “freeze drying and rehydrating” cycles still remain their original morphologies, and could disperse stably in acidic (pH=4) and basic (pH=10) aqueous solutions (Fig. S7 in ESI).

To gain deeper insight into the morphology recovery phenomenon, we utilized AFM at modulus mode to explore their micro-mechanical properties. The Young's moduli of the as-prepared capsule membrane are shown to be 1.305 GPa and 1.111 GPa, respectively (Figs. 4d₁, 4d₂, and 4e₁, 4e₂ with their low magnification image in Fig. S8 in ESI). Such high values are even comparable to some typical high-performance polymeric membranes like polybenzimidazole (PBI), polyimide (PI), etc (Table S1 in ESI).^[65–68] As far as we know it is the first time that the mechanical performance of the amphiphilic ACP-based microstructures was studied. Such high modulus may be ascribed to the unique composition of capsular membrane endowed by the folding manners of the ACP chains within the membrane. As the capsule is formed at oil-water interface, the hydrophilic segments of amphiphilic ACPs, *i.e.*

the soft DHB units, would separate from the hydrophobic segments, *i.e.* the BDT units. According to previous studies, the amphiphilic ACPs tend to adopt a loop or bridge conformation during the microseparation process, leading to assemblies with ultrathin feature sizes.^[50] Such kind of microphase-separations is believed to be advantageous to the optimization of mechanical performances,^[69] while the ultra-small feature sizes of the ACPs may further strength this trend. Besides, there might be other factors like the elasticity of the capsular membrane that influence morphology recovery. Moreover, the hydroxyl groups along the DHB segments of ACPs have high affinity with water and would also promote the recovery process. The investigation on detailed mechanism is still in progress. In all, this characteristic makes current capsules suitable for medical applications like long-lasting drug carriers, which call for redispersion of the freeze-dried powders in aqueous medium and restoration of the capsular morphology before use.^[70–75]

Another advantage of the current capsules is demonstrated below. Owing to the modular nature of the click chemistry, the capsules herein could be readily functionalized during their formation process to endow capsules with specific functions. As a proof of concept, herein we took *n*-butylamine as a third monomer to take part in the click copolymerization to get amino-functionalized microcapsules with positive charges. The corresponding scheme is illustrated in Fig. 5.

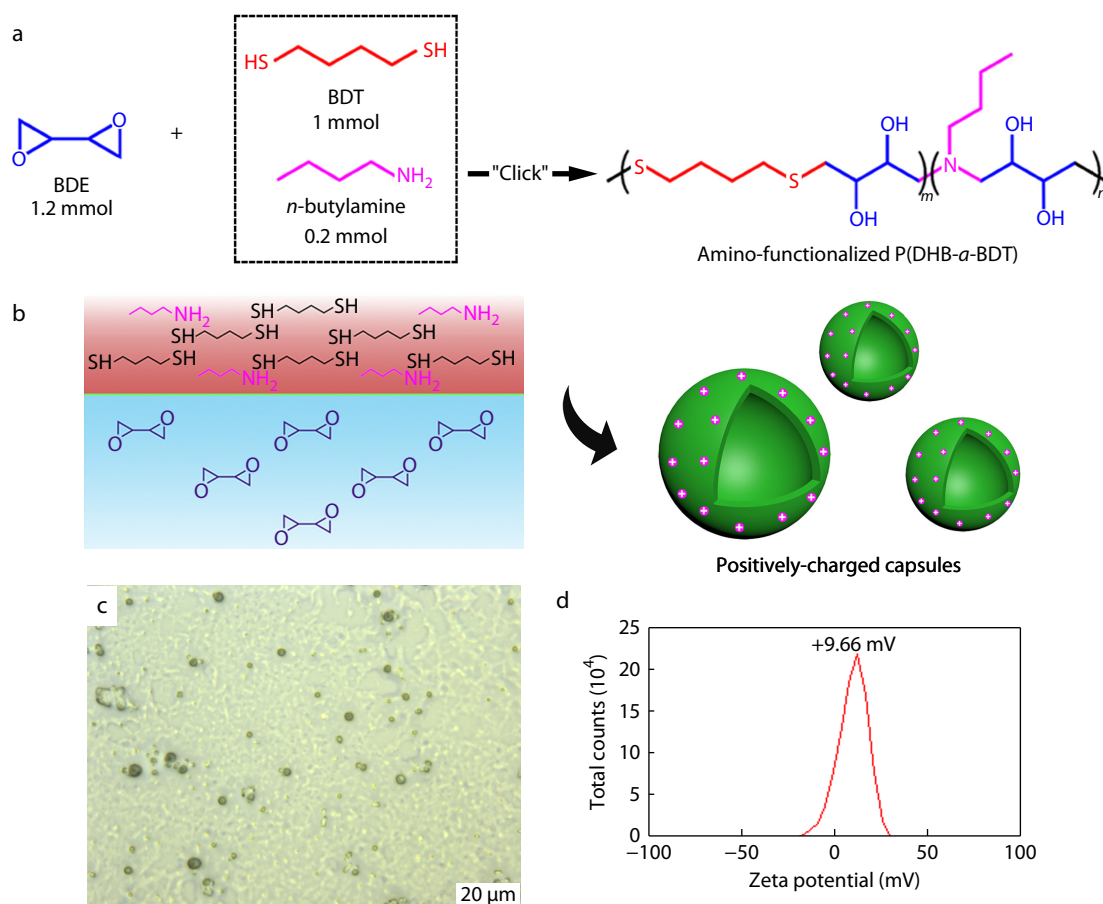


Fig. 5 Readily functionalization of the capsules through click copolymerization. (a) The scheme for click copolymerization of amino-functionalized alternating copolymers; (b) Scheme for the preparation of positively charged capsules through click copolymerization; (c) OM image of the amino-functionalized capsules; (d) Zeta potential of the as-prepared amino-functionalized capsules.

Firstly, BDE aqueous solution was distributed in *n*-hexane in the form of micro-sized droplets with span-80 acting as the surfactant. Consequently, water-in-oil emulsion (W/O) was built. Afterwards, *n*-butylamine and BDT were added into the emulsion to initiate the click reaction at water-oil interface (Fig. 5a). In this way, amino-functionalized microcapsules with positive charges on the surface could be prepared successfully, just as schematically illustrated in Fig. 5(b). The OM image of the as-prepared particle suspended in *n*-hexane is shown in Fig. 5(c), the coexistence of membrane and the inner cavity on every single particle validates the formation of capsule structures. Moreover, the SEM image and statistical analysis (Fig. S9 in ESI) show that both the morphologies and the diameters of these capsules remain almost the same with those obtained previously (Figs. 1 and 2). Furthermore, GPC measurements (Fig. S10 in ESI) and ¹H-NMR (Fig. S11 in ESI) confirm that these capsules are made from amino-functionalized amphiphilic ACP named P[(DHB-*α*-BDT)-*co*-(DHB-*α*-BA)], and there is average one BA unit on every single polymeric chain. Obviously, during this process, the epoxy groups of the BDE monomers could react with the thiol groups of BDT and amine groups of the *n*-butylamine simultaneously, and the resultant P[(DHB-*α*-BDT)-*co*-(DHB-*α*-BA)] would deposit on the interface to form capsules. Due to the protonation of amine groups within BA units along the polymer chains, surfaces of these capsules are positively charged. The corresponding zeta potential measurement demonstrated a positive charge of +9.66 mV (Fig. 5d). Moreover, the modulus of the amino-functionalized capsules was measured to be 1.164 GPa (Fig. S12 in ESI), which convinced that the functionalization at current status has almost no adverse effect on the values of modulus. In all, the current experiment has demonstrated the readily-functionalized characteristic of our capsules, *i.e.* preparation and functionalization could be conducted simultaneously. Following this way, we further prospect that the future of capsules in this study lies in the integration of functional monomers of various categories, such as biomacromolecules and the decorated metal/inorganic nanoparticles. The resultant functionalized capsules have the potential to be used as basic vehicles for biomedicine, cosmetics, etc.

CONCLUSIONS

In this study, we have presented an interfacial click polymerization-derivative method, which is both facile and highly efficient, for the preparation and functionalization of amphiphilic alternating copolymer-based microcapsules. Once rehydrated, the dried capsules were sufficiently robust to restore their original morphologies in water. The Young's modulus of these capsules was investigated, demonstrating, for the first time, the micro-mechanical properties of amphiphilic ACPs with a Young's modulus over 1 GPa. All these characteristics, which are endowed by the alternating sequences of the hydrophilic and hydrophobic segments, make the capsule in this study a general and powerful platform to be applied on diverse aspects, such as the vectors of biomedicines and cosmetics, cell mimics, and intelligent materials.

Conflict of Interests

The authors declare no interest conflict.

Electronic Supplementary Information

Electronic supplementary information (ESI) is available free of charge in the online version of this article at <http://doi.org/10.1007/s10118-025-3504-6>.

Data Availability Statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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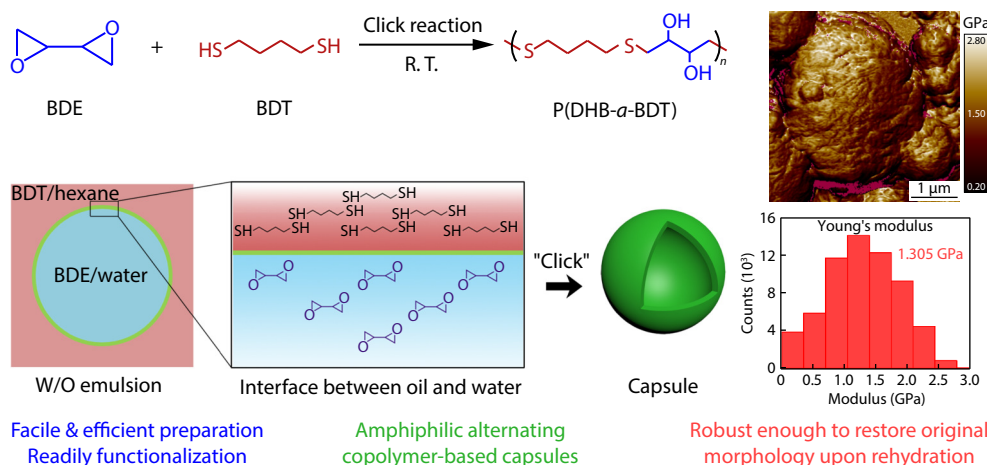
Graphical Abstract

Robust and Readily Functionalized Microcapsules from Interfacial Click Polymerization of Amphiphilic Alternating Copolymers

Qing-Song Xu, Min-Jiang Zhu, Xiu-Ting Li, Jie Dong, Xin Zhao, Qing-Hua Zhang and Yong-Feng Zhou

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A novel kind of amphiphilic alternating copolymer-based capsules are scalable prepared and functionalized by interfacial click polymerization owing to the merits of click chemistry. The dried capsules show high modulus values exceeding 1 GPa and are sufficiently robust to restore their original morphology once rehydrated.



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