Using Host-Guest Chemistry to Tune the Kinetics of Morphological Transitions Undertaken by Block Copolymer Vesicles

Hao Yao[†, ‡], Yin Ning[‡], Craig P. Jesson[‡], Jia He[†], Renhua Deng[‡], Wei Tian*[†], Steven P. Armes*[‡]

[†]School of Science, Northwestern Polytechnical University, Xi'an, 710072, P. R. China.

[‡]Department of Chemistry, University of Sheffield, Brook Hill, Sheffield, South Yorkshire, S3 7HF, UK.

ABSTRACT: Host-guest chemistry is exploited to tune the rate at which block copolymer vesicles undergo morphological transitions. More specifically, a concentrated aqueous dispersion of poly(glycerol monomethacrylate-co-glycidyl methacrylate)-poly(2-hydroxypropyl methacrylate) P(GMA-co-GlyMA)-PHPMA diblock copolymer vesicles were prepared via polymerization-induced self-assembly (PISA). The epoxy groups in the GlyMA residues were ring-opened using a primary amine-functionalized *β*-cyclodextrin (NH_2-*β*-CD) in order to prepare *β*-CD decorated vesicles. Addition of azobenzene-methoxypoly(ethylene glycol) (azo-mPEG) to such vesicles results in specific binding of this water-soluble macromolecular reagent to the *β*-CD groups on the hydrophilic P(GMA-co-GlyMA) stabilizer chains. Such host-guest chemistry induces a morphological transition from vesicles to worms and/or spheres. Furthermore, the rate of this morphological transition can be tuned by UV/visible light irradiation and/or guest molecule competition. This novel molecular recognition strategy offers considerable scope for the design of new stimulus-responsive diblock copolymer vesicles for targeted delivery and controlled release of cargoes.

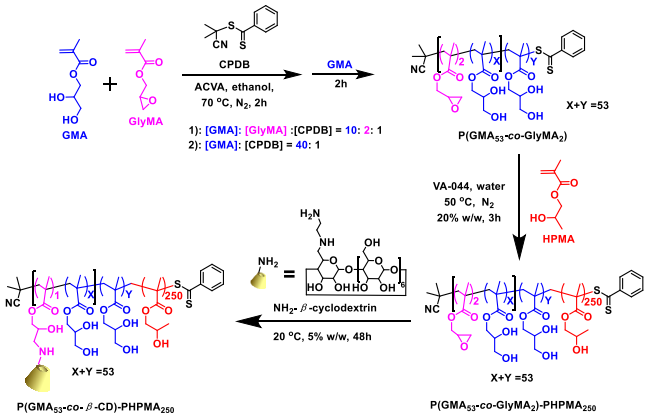
In the past two decades there has been substantial and sustained interest in the field of diblock polymer nano-objects owing to their many diverse potential applications, including use as nanoreactors, Pickering emulsifiers and drug delivery vehicles.[1-11] In principle, tuning the hydrophilic/hydrophobic balance of an amphiphilic diblock polymer enables a wide range of morphologies to be obtained in dilute aqueous solution, including spherical micelles, cylindrical micelles (e.g., rods or worms), or vesicles.[9-11] In particular, stimulus-responsive nano-objects can be designed that undergo a morphological transition on exposure to external stimuli such as pH, temperature, light or added salt.[12-19] For example, there are various literature examples of vesicle dissociation to afford molecularly-dissolved copolymer chains, whereby the membrane-forming hydrophobic block is rendered hydrophilic in situ.[20-24] More recently, vesicle-to-worm or vesicle-to-sphere morphological transitions have been reported, which can also be used to release payloads.[25-28] These latter transitions are typically the result of a subtle reduction in the geometric packing parameter arising from the response of either the stabilizer block or the membrane-forming block toward a change in pH or temperature.[27, 29-35] There are also a few reports concerning vesicles that undergo morphological transitions after selective binding to specific analytes.[25, 26, 36-40] In this context, the time scale required for the loss of the vesicular morphology clearly plays a critical role in determining the rate of release of the encapsulated cargo.[27, 28, 38] On the other hand, dynamic reversible host–guest chemistry has been proposed as a versatile and powerful means for designing vesicles exhibiting new properties and functions.[41-54] In particular, cyclodextrin (CD)-based inclusion complexes are sensitive to external stimuli, such as pH, redox chemistry and light irradiation. In principle, this offers an interesting opportunity to design next-generation stimuli-responsive nano-objects. However, as far as we are aware, there is only one example of using host-guest chemistry to tune a block copolymer morphological transition.[46] In this case, free CD is used to aid solubilization of a water-immiscible monomer (styrene), which results in the formation of hollow nanotubes via an intermediate vesicle morphology.

In contrast, herein we demonstrate that host-guest chemistry can be utilized to tune the rate of change in morphology for an aqueous dispersion of CD-functionalized diblock copolymer vesicles. More specifically, we use polymerization-induced self-assembly (PISA)[55-65] to prepare a series of precursor diblock copolymer vesicles in concentrated aqueous solution that contain a minor fraction of glycidyl methacrylate (GlyMA) comonomer in the stabilizer block. Such pendent epoxy groups are then reacted with a primary amine-functionalized *β*-CD using epoxy-amine chemistry[66-68] (see Scheme 1). Moreover, taking advantage of the well-known inclusion complex formed by *β*-CD and azobenzene,[47-54] these *β*-CD derivatized vesicles can interact with azobenzene-functionalized methoxy-capped poly(ethylene glycol) (azo-mPEG) via host-guest chemistry. Compared to the precursor vesicles, thermally-induced vesicle-to-worm/sphere morphological transitions are significantly faster when conducted in the presence of the azo-mPEG analyte. More importantly, the corresponding rate at which such morphological transitions occur can be fine-tuned by irradiation using either UV or visible light or via addition of competitive guest molecules (see Scheme 2). This versatile host-guest approach enables excellent control to be achieved over the rate of loss of the original vesicle morphology, which is the key to achieving controlled release of encapsulated actives from such nanocapsules.

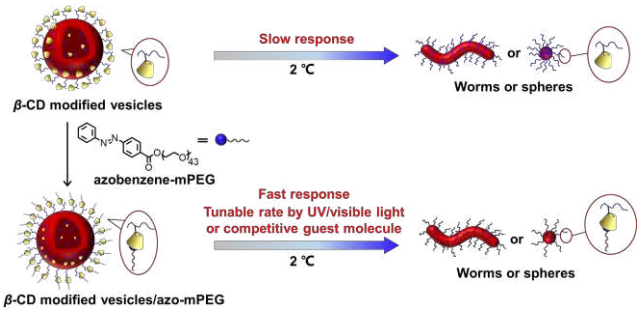
A near-monodisperse P(GMA_{53}-co-$GlyMA_2$) macro-CTA (M_w/M_n = 1.14) containing approximately two glycidyl methacrylate repeat units per copolymer chain was first synthesized by RAFT copolymerization of GMA and GlyMA in ethanol using 2-cyano-2-propyl dithiobenzoate (CPDB) as a chain

transfer agent and 4,4'-azobis(4- cyanopentanoic acid) (ACVA) initiator. Two units of GlyMA were statistically copolymerized with just ten units of GMA, followed by chain extension with a further forty GMA units. This strategy ensured that the pendent epoxy groups of the GlyMA repeat units were located close to the terminus of the PGMA stabilizer. The crude P(GMA_{53}-co-$GlyMA_2$) macro-CTA was purified by precipitation into excess dichloromethane.

Scheme 1. (A) Synthesis of P(GMA_{53}-co-$GlyMA_2$) macro-CTA via initial RAFT statistical copolymerization of GMA and GlyMA followed by GMA hompolymerization. This macro-CTA was then chain-extended via RAFT aqueous dispersion polymerization of HPMA to form P(GMA_{53}-co-$GlyMA_2$)-$PHPMA_{250}$ vesicles via polymerization-induced self-assembly (PISA). These precursor vesicles are then derivatized via epoxy-amine chemistry by reacting NH_2-β-CD with the pendent GlyMA residues to produce β-CD-decorated vesicles.



Scheme 2. Illustration of the thermally-induced vesicle-to-worm (or vesicle-to-sphere) morphological transitions undertaken by β-CD-decorated vesicles (see Scheme 1) in the presence or absence of azo-mPEG. The latter water-soluble analyte forms an inclusion complex with the β-CD moieties via host-guest chemistry.



End-group analysis via ^{1}H NMR spectroscopy indicated a mean degree of polymerization (DP) of approximately 55 (including two GlyMA units) for this purified macro-CTA (Figure S1). This water-soluble macro-CTA was then chain-extended via RAFT aqueous dispersion polymerization of HPMA at 20% w/w solids and 50 °C. A target DP of 250 for the core-forming PHPMA block produced a turbid, free-flowing copolymer dispersion. According to ^{1}H NMR analysis, the HPMA polymerization reached very high conversion (> 99%). Furthermore, DMF GPC analysis (Figure 1A) indicated a high blocking efficiency and a relatively narrow molecular weight distribution (M_w/M_n < 1.30), as expected on the basis of our previous reports. [9, 69, 70] Well-defined pure vesicular morphologies were confirmed by transmission electron microscopy (TEM) studies, see Figure 1B.

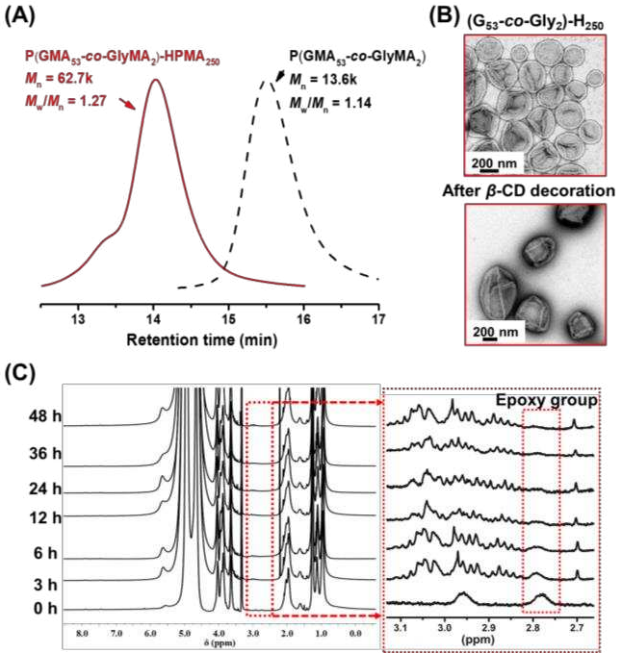


Figure 1. (A) DMF GPC curves obtained for a P(GMA_{53}-co-$GlyMA_2$) macro-CTA (dashed curve) and the corresponding P(GMA_{53}-co-$GlyMA_2$)-$PHPMA_{250}$ diblock copolymer (red curve). (B) TEM images obtained for the P(GMA_{53}-co-$GlyMA_2$)-$PHPMA_{250}$ precursor and β-CD-functionalized vesicles. (C) ^{1}H NMR spectra obtained at various time points following reaction of NH_2-β-CD with P(GMA_{53}-co-$GlyMA_2$)-$PHPMA_{250}$ after dilution using CD_3OD. The reduction in the epoxy signal intensity at 2.79 ppm indicated that the primary amine of the NH_2-β-CD reacts with the pendent epoxy groups in the P(GMA_{53}-co-$GlyMA_2$) stabilizer chains.

The as-prepared 20% w/w aqueous vesicular dispersions described above were diluted to 5% w/w solids prior to post-polymerization derivatization with NH_2-*β*-CD using a NH_2-*β*-CD/GlyMA molar ratio of 1.0. This epoxy-amine reaction was conducted at 20 °C for 48 h. Its progression was monitored by ^{1}H NMR spectroscopy (see Figure 1C). The integrated epoxy signal was reduced to 6% of its original value within 12 h and had almost entirely disappeared after 48 h. In control experiments conducted in the absence of any NH_2-*β*-CD, the P(GMA_{53}-co-$GlyMA_2$)-$PHPMA_{250}$ precursor vesicles were stirred at 20 °C and the epoxy signals retained at least 90% of their original integrated intensity after 48 h (Figure S3). This indicated that the majority of the original epoxy groups should be available to react with NH_2-*β*-CD via ring-opening nucleophilic addition. The resulting aqueous dispersion of vesicles was then dialyzed against water for two days to remove any unreacted NH_2-*β*-CD. End-group analysis by ^{1}H NMR spectroscopy studies performed in d_6-DMSO indicated approximately one *β*-CD unit per copolymer chain by comparing the integrated aromatic end-group signals at 7.2-7.4 ppm to that of the 2,3-hydroxyl group of the NH_2-*β*-CD moiety at 5.72 ppm (Figure S4). This suggests that up to half of the epoxy groups actually undergo hydrolysis to afford GMA residues.[71] This epoxy-amine reaction was also monitored by GPC, which indicated the formation of a high molecular weight shoulder (see Figure S5). In principle, the secondary amines formed via ring-opening of the epoxide group can react further with a second epoxide to form tertiary amines.[68] Given that there are relatively few epoxy groups per chain, this side reaction is more likely to proceed intermolecularly (i.e., involving two or more chains), rather than intramolecularly (i.e., within a single chain). TEM studies confirmed the expected pure vesicular morphology, with a mean vesicle membrane thickness of 17 nm (see Figure 1B). DLS studies yielded a mean hydrodynamic diameter of 370 nm for a dilute aqueous dispersion of such vesicles. Azo-mPEG was added to a 0.1 % w/w aqueous dispersion of the *β*-CD-functionalized vesicles (azo-mPEG/*β*-CD molar ratio = 1.0) at pH 7.6 prior to cooling from 20 °C to 2 °C. The evolution in copolymer morphology that occurred under such conditions was monitored over 10 h using DLS (see Figure 2A). The gradual reduction in apparent particle diameter indicated the formation of worms and/or spheres. The same DLS study was also performed in the absence of any azo-mPEG. The apparent particle diameter fell from 340 nm to less than 100 nm after 70 min at 2 °C in the presence of the azo-mPEG, while the same size reduction required more than 300 min in the absence of this analyte. In an additional control experiment, the addition of non-functionalized mPEG had no effect on the rate of reduction in particle diameter (see Figure 2A). Thus these experiments confirm that host-guest chemistry can be harnessed to induce a significantly faster response from thermoresponsive vesicles. Binding of the azo-mPEG analyte to the *β*-CD units increases the effective volume fraction of the stabilizer chains,[38] which in turn reduces the geometric packing parameter for the overall copolymer and hence drives vesicle dissociation to form worms and/or spheres.

This evolution in copolymer morphology was also studied by TEM. As shown in Figure 2B, using host-guest chemistry ensures that the vesicle membranes become plasticized within 5 min, with worm clusters being formed after 20-40 min and isolated worms being observed within 70 min. However, when cooling the *β*-CD-functionalized vesicles in the absence of any azo-mPEG, only worm clusters were observed within 70 min. Based on a recent study by Deng et al.,[38] the local maximum in particle size observed by DLS after ageing for around 10 min at 2 °C (see Figure 2A) could be interpreted as evidence for 'jellyfish' structures. However, TEM studies did not provide any evidence for such transient intermediates (Figure 2B). An alternative explanation may simply involve vesicle swelling, but further studies are required to confirm this hypothesis.

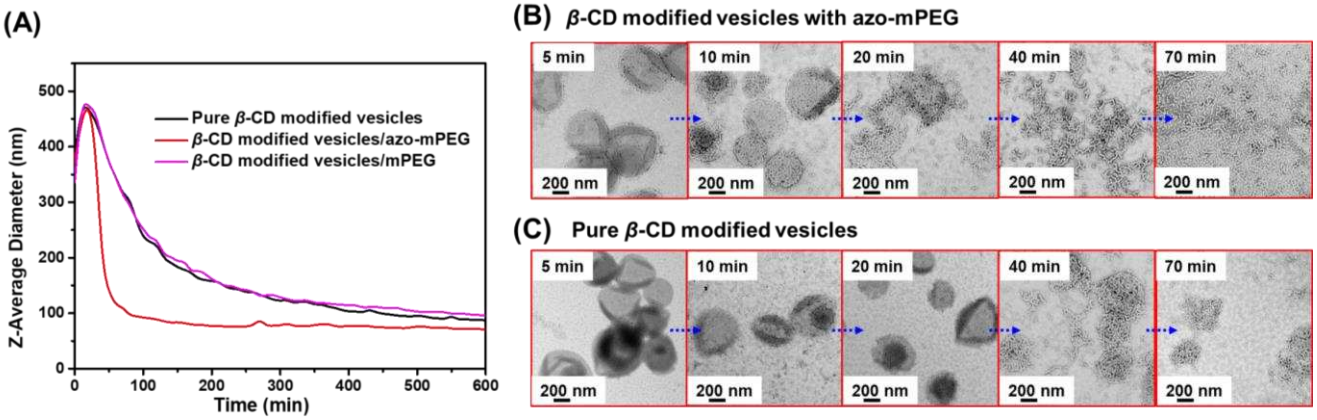


Figure 2. (A) Evolution in the apparent sphere-equivalent DLS diameter for a 0.10% w/w aqueous dispersion of *β*-CD-functionalized diblock copolymer nano-objects recorded over time in the presence of azo-mPEG (red curve); a control experiment conducted in the absence of any azo-mPEG (black curve) and a further control experiment conducted in the presence of non-functionalized mPEG (pink curve). Corresponding TEM images recorded for *β*-CD-functionalized diblock copolymer nano-objects indicating the various changes in copolymer morphology observed during these kinetic experiments: (B) in the presence of azo-mPEG or (C) in the absence of azo-mPEG.

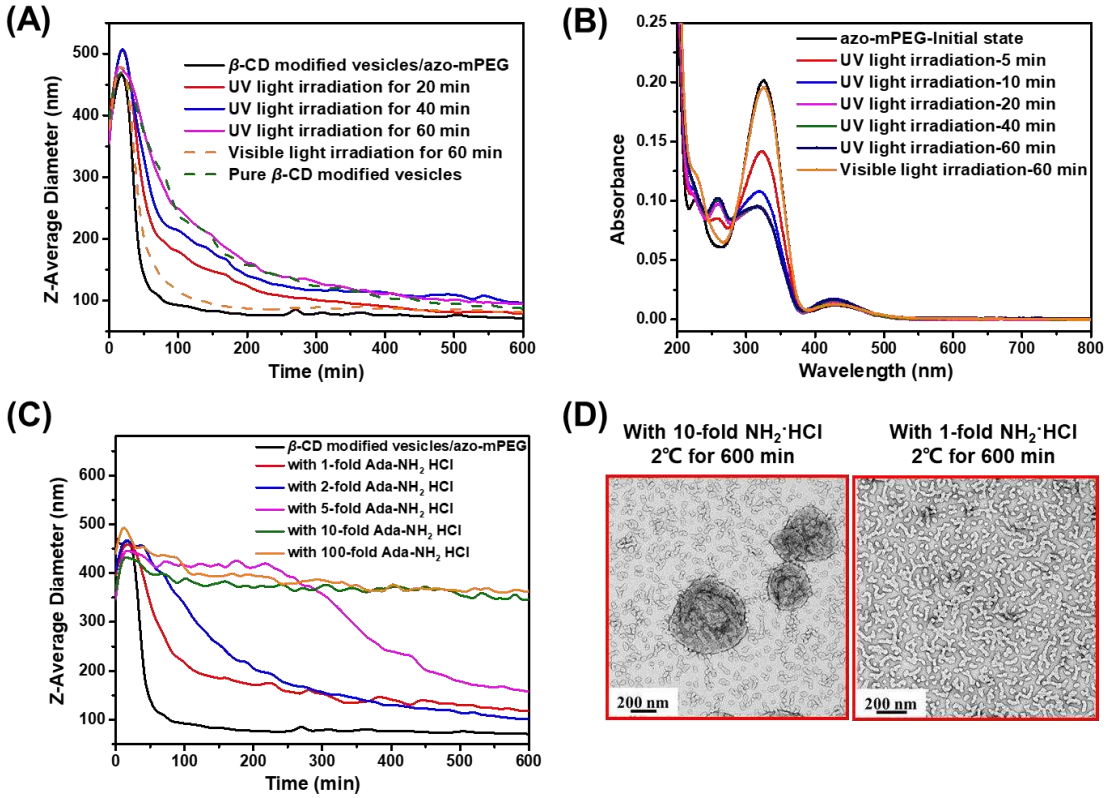


Figure 3. (A) Temporal evolution in the apparent sphere-equivalent DLS diameter for a 0.10% w/w aqueous dispersion of *β*-CD-functionalized diblock copolymer nano-objects during UV/visible light irradiation for various time periods in the presence of azo-mPEG (azo-mPEG/*β*-CD molar ratio = 1.0). (B) UV-visible absorption spectra recorded for the reversible photoisomerization of the azobenzene group in various aqueous copolymer solutions at 20 °C during irradiation with either UV or visible light (the azo-mPEG concentration was 2.5×10^{-5} M in all experiments). (C) Temporal evolution in the apparent sphere-equivalent DLS diameter for a 0.10% w/w aqueous dispersion of *β*-CD-functionalized diblock copolymer nano-objects in the presence of azo-mPEG and various amounts of adamantyl-NH_2·HCl. (azo-mPEG/*β*-CD molar ratio = 1.0 and adamantyl-NH_2·HCl/azo-mPEG molar ratio = 1.0, 2.0, 5.0, 10.0 or 100) (D) Corresponding TEM images recorded for a 0.10% w/w aqueous dispersion of *β*-CD-functionalized diblock copolymer nano-objects in the presence of azo-mPEG (azo-mPEG/*β*-CD molar ratio = 1.0 and adamantyl-NH_2·HCl/azo-mPEG molar ratio = 1.0 or 10) after cooling to 2 °C for 600 min.

Binding of the azo-mPEG analyte to the vesicles was investigated using both ^{1}H NMR and 2D NOESY NMR spectroscopy. It is well known that *β*-CD can interact with similar-sized tran-azobenzene-based guest molecules via hydrophobic interactions (see Figure S7A).[47-54] ^{1}H NMR spectra recorded for azo-mPEG with or without *β*-CD-functionalized vesicles dispersed in D_2O are shown in Figure S7B. Addition of an equimolar amount of azo-mPEG based on the *β*-CD moieties caused distinct spectral changes: all the aromatic proton signals assigned to the azo-mPEG broaden and shift downfield. These observations are consistent with binding of this analyte within the hydrophobic *β*-CD cavity.[54, 72] The nuclear Overhauser effect (NOE) is widely used in supramolecular chemistry: it involves transfer of nuclear spin polarization between species via cross-relaxation and is highly sensitive to the inter-proton distance. More specifically, no NOE can be observed if the inter-proton distance is larger than about 0.4 nm.[73] As shown in Figure S7B, intermolecular correlations between the H3 and H5 protons of *β*-CD at 3.5-4.0 ppm and the aromatic azo protons at 7.1-8.2 ppm confirm the formation of the expected host-guest complex.

The rate of change in copolymer morphology can be further tuned via irradiation using either UV or visible light. As determined by DLS studies (see Figure 3A), the rate of reduction in particle diameter (and hence the rate of morphological evolution) gradually decreased when increasing the UV light irradiation time from 20 to 60 min. Furthermore, the rate of reduction in particle diameter after 60 min visible light irradiation was almost the same as that of the *β*-CD-functionalized vesicles in the absence of any azo-mPEG. These observations indicate that the host-guest binding of azo-mPEG can be prevented via UV light irradiation. Conversely, after visible light irradiation for 60 min, the rate of reduction in particle diameter is more or less as that observed in the presence of azo-mPEG, confirming that the negative effect of UV irradiation can be counteracted. These observations can be rationalized in terms of the well-known photoisomerization behavior of the azobenzene group, whose cis and trans isomers display markedly different binding affinities for *β*-CD. For example, the association constants for the 1:1 inclusion complex of *β*-CD with trans-azobenzene and cis-azobenzene are 5.36×10^3 M^{-1} and 3.15×10^2 M^{-1}, respectively.[53] Herein, the photoisomerization of azobenzene group was studied by UV-visible spectroscopy. The two absorption bands at approximately 323 and 432 nm can be ascribed to the π-π* (H-aggregate) of the trans

isomer and n–π* (J-aggregate) of the cis isomer, respectively.[53]

After irradiation with UV light at 365 nm for 15 min, the 360 nm absorption band became notably attenuated, while the 450 nm band increased slightly, see Figure 3B. Both features were restored after exposure to visible light, indicating that UV irradiation of azobenzene causes a conformation change from the trans isomer to the cis isomer, with the trans isomer being reformed on exposure to visible light.[72] Moreover, ^{1}H NMR spectroscopy studies confirmed that the proton signal assigned to cis-azobenzene increased markedly after UV irradiation and the corresponding trans-azobenzene proton signal reappeared after visible light irradiation (see Figure S6).

Finally, the effect of competitive guest molecules on the rate of evolution in copolymer morphology was evaluated. According to our previous work,[54] adamantane can form inclusion complexes with *β*-CD and its *β*-CD binding constant is significantly higher than that of the azobenzene/*β*-CD complex. Herein, water-soluble adamantyl-NH_2·HCl was used as a competitive guest for the *β*-CD-functionalized vesicles, with the aim being to tune the rate of morphological transition by reducing the efficacy of the azo-mPEG binding species. As shown in Figure 3C, the rate of reduction in apparent particle diameter (and hence the rate of evolution in copolymer morphology) can be gradually retarded by increasing the adamantyl-NH_2·HCl concentration by a factor of five. Furthermore, this morphological transition could be suppressed by using an adamantyl-NH_2·HCl/azo-mPEG molar ratio of 10 (for an azo-mPEG/*β*-CD molar ratio of 1.0). This is also confirmed by TEM studies, see Figure 3D. Under these latter conditions, adamantyl-NH_2·HCl binds within the *β*-CD instead of azo-mPEG while the excess adamantyl-NH_2·HCl acts as a salt and causes charge screening of the single cationic charge conferred per stabilizer chain, which might otherwise lead to a sufficient reduction in the packing parameter to drive the morphological transition.[31, 35]

In summary, we demonstrate that host-guest chemistry can be used to tune the rate of thermally-induced morphological transitions for *β*-CD-functionalized diblock copolymer vesicles. Binding of a water-soluble azo-mPEG analyte to such vesicles leads to a significantly faster change in copolymer morphology compared to the *β*-CD-functionalized vesicles alone. Moreover, the rate at which such morphological transitions occur can be further fine-tuned via UV/visible light irradiation or the use of competitive guest molecules. This molecular recognition strategy offers considerable scope for the targeted delivery and controlled release of encapsulated cargoes from vesicles in aqueous solution.

ASSOCIATED CONTENT

Supporting Information.

Included are details of all materials, methods, and experimental procedures utilized in this work alongside copolymer characterization and additional NMR data of the azo group after irradiation using either UV or visible light.

AUTHOR INFORMATION

Corresponding Author

*E-mail: s.p.armes@shef.ac.uk (S.P.A.).
*E-mail: happytw_3000@nwpu.edu.cn (W.T.).

Notes

The authors declare no competing financial interest.

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