Photoswitchable polyurethane based nanoaggregates for on-command release of noncovalent guest molecules

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ABSTRACT

The self-assembly of light responsive amphiphilic polymers has been of great interest in spatially and temporally controlled drug delivery applications. In this article, we report the design, synthesis and characterization of amphiphilic main chain azobenzene polyurethane as well as its self-assembly in aqueous milieu. This polymer self-assembles into micellar nanostructure (investigated by dynamic light scattering and scanning electron microscopy imaging) and shows hydrophobic guest sequestration with high encapsulation stability (probed by FRET experiment). The photoswitching (trans-to-cis) of these nanoaggregates has been investigated by irradiation with UV light (λ = 365 nm), which results significant change in the hydrophobic environment and molecular arrangement in the micellar core. This leads to encapsulated guest release in a controlled manner as probed by UV-vis spectroscopy. Furthermore, we demonstrated tumor-relevant pH (~6.5-6.8) induced surface charge modulation (neutral to positive) by zeta potential measurements. The light responsive guest release and pH-specific charge modulation, we believe, will have significant impact in development of delivery systems for targeted and controlled delivery of drug molecules.

GRAPHICAL ABSTRACT

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1. Introduction

The design of amphiphilic macromolecules are of great interest due to their applications in various fields of materials and biomedical science, for example, drug delivery,[1–6] gene transfection,[7–10] cell imaging,[11,12] tissue engineering,[13–15] nanoreactors[16–18] and biomimetics etc.[19–21] Specifically, in the context of drug delivery applications, stimuli responsive amphiphilic polymers including homopolymers, block-copolymers, random copolymers, graft copolymers and hyperbranched polymers are widely used as they are capable of self-assembling into various supramolecular nanostructure such as micelles,[22–25] vesicles[26–28] and liposomes,[29–31] which can keep the drug molecules noncovalently sequestered in one set of conditions and release them under another. Since toxicity and degradability is one of the major issues in drug delivery applications it is better to investigate stimuli responsive characteristics in the amphiphilic polymers with biocompatible and biodegradable backbone. Many biodegradable polymers such as polypeptide, polyamide, polyester, polycarbonate and polyurethane are in commercial use, but we focused on designing stimuli responsive polyurethane because of the following reasons: (i) ease of polymer synthesis; (ii) formation of stable nanoassemblies due to H-bonding nature of the backbone; (iii) outstanding biocompatibility and biodegradability, which are well documented in the literature.[32–35]

The release of guest molecules from the nanoassemblies can be triggered by both exogenous (variations in temperature, light, ultrasound and magnetic field)[36–42] and endogenous
(pH, redox gradients and enzyme)[43–49] stimuli. Among these stimuli, light responsive guest release is interesting as it provides a pathway for releasing the molecules on-command, which allows temporal and spatial control.[50–52] Integration of photochromic units with the amphiphilic copolymers converts these macromolecules into light controlled delivery systems.[53,54] Azobenzene is one of the well known and widely investigated photoresponsive groups due to their rapid, reversible and high quantum yield photoswitching properties. Under UV or visible light irradiation, it undergoes trans-to-cis isomerization, which results in an increase in the dipole moment of the molecules.[55,56] This isomerization induced property change is the key motivation in designing azobenzene containing polymers as macromolecular scaffold for on demand release of guest molecules. There are several reports on amphiphilic polymers with azobenzene side chain,[57–61] but only a few examples of amphiphilic main chain azobenzene polymers[62,63] including single azobenzene unit at the junction of two polymer blocks[64–66] have been reported in the literature. To the best of our knowledge, there is no prior report on polyurethane based amphiphilic main-chain azobenzene polymer for light responsive on command guest release. Hence, we wanted to explore the area of amphiphilic main chain azobenzene polymer toward the application of remote controlled drug release. We hypothesized that trans to cis photoswitching of azobenzene units would reduce the hydrophobicity of the core of the nanoassemblies formed by the azobenzene polymer and convert the compact nanostructure to loosely aggregated structure, which should concurrently release the guest molecules in a controlled fashion. To test this hypothesis we have designed and synthesized amphiphilic polyurethane integrated with azobenzene unit on the polymer main chain. The hydrophilic tetraethylene glycol side chains are periodically attached to the polymer backbone by a pH responsive tertiary nitrogen atom. The multiple copies of azobenzene units on the polymer backbone would make it light responsive in nature. The guest molecules would make it light responsive in nature. The guest molecules would make it light responsive in nature.

2. Experimental

2.1. Materials

All the reagents were purchased from commercial sources and used without further purification unless mentioned. The solvents for NMR spectroscopy such as CDCl₃ and DMSO-d₆ were purchased from the Sigma Aldrich. HPLC grade water for spectroscopic study was purchased from SRL chemicals. Acetonitrile, DCM, DMF and THF solvents for the reaction was purchased from Merck and dried in the laboratory using the established protocol. All the chemicals including 3- bromo propanol, diethanol amine, tetraethylene glycol, triethyl amine, potassium iodide, benzyl alcohol, hexamethylenediisocyanate and DABCO used for the monomer and polymer synthesis were purchased from Sigma-Aldrich.

2.2. NMR characterization

The Bruker DRX-300 (300 & 400 MHz) was used to record ¹H-NMR spectra at room temperature. All the chemical shifts are given in ppm (δ) units relative to tetramethyilsilane (singlet δH = 0.00). Calibration was achieved using the residual solvent signal of chloroform at δH = 7.27. Analysis followed first-order and the following abbreviations were used throughout the text: s = singlet, br. s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet.

2.3. FT-IR characterization

The PerkinElmer Spectrum 100 FT-IR spectrometer was used to record the IR spectra. The sample was mixed with KBr and then a pellet was prepared and placed in the chamber inside the instruments, and the spectrum was recorded at room temperature.

2.4. Gel permeable chromatography

The GPC measurements were done using Waters GPC equipped with a Waters 515 HPLC pump and a Waters 2414 refractive index (RI) detector using DMF solvent respectively. Molecular weight and PDI were calculated with respect to poly(methyl methacrylate) (PMMA) standards. The column temperature and flow rate were maintained at 35°C and 1 mL/min, respectively. Polymer sample of a measured quantity (3 mg) was dissolved in 1 mL of DMF and sonicated for 3 min. Then the homogeneous solution was obtained by keeping the solution at room temperature for few hours. The prepared polymer solution was then filtered using a membrane filter with 0.22 μm pore size. Next, the solution was injected into the GPC column to obtain the molecular weight of the polymer.

2.5. Fluorescence microscopy studies

For the fluorescence microscopic experiment, DiI and Pyrene encapsulated polymer solution was placed on a cleaned glass slides, and then another cover glass was placed on it. Finally, images were recorded on a fluorescence microscope (OLIMPUS BX-51) in 10 x magnification.
2.6. Isothermal titration calorimetric (ITC) experiments

Microcal-200 ITC ultrasensitive isothermal titration micro-calorimeter was used to perform ITC experiment. In a typical ITC experiment, the reference cell was filled with deionized water and the sample cell was filled with the aqueous solution of the polymers (80-45 μM, 1 μL injection volume, and number of injections 40). The 24 sample was injected with a gap of 120 s between each addition with continuous stirring at 400 rpm. The MicroCal Origin software package (ver. 7.0) was used for data analysis. Experimental temperature = 25°C. The free energy (ΔG) of micellization can be calculated by equation 1 given below, where CAC, T and R are the critical aggregation concentration, temperature and universal gas constant respectively. The entropy (ΔS) of micellization can be calculated from Gibb’s-Helmholtz equation (eq. 2).

\[ ΔG = RT \ln(CAC) \] (1)
\[ ΔG = ΔH - TΔS \] (2)

2.7. Determination of critical aggregation concentration (CAC)

At first, in screw-capped vial, a measured amount of a solution of DiI dye in acetone (20 μL, 1 mM) was placed. A polymer solution was added to the DiI containing vials, and the mixture was sonicated and allowed to stand for 6 hours before spectroscopic analysis. The final concentration of DiI was maintained at 2 × 10^{-6} M. The absorption intensity of the encapsulated DiI at 560 nm was plotted against the concentration of polymer, and the inflection point of such a plot was taken as the CAC for all the polymers. All the experiment were done by using quartz cuvette of 1 cm path length.

2.8. Dynamic light scattering (DLS)

Malvern Nanozetasizer (NANO-ZS) was used for the DLS measurement. The 0.02 mM polymer sample was used for the DLS measurements. The data was recorded at 25°C before UV and after UV irradiation.

2.9. Zeta-Potential measurement

Malvern Nanozetasizer (NANO-ZS) was used for the DLS measurement. Here, phosphate buffer of pH 7.4 and 6.6 are used to measure zeta potential of polymer solution of concentration 0.02 mM.

2.10. DiI Dye release study

A measured amount of a solution of DiI dye in acetone (20 μL, 1 mM) was placed in two vial and to this a polymer solution of known concentration (1 mL, 0.02 mM) was added, stirred for 4 hours at room temperature to evaporate the acetone and obtain a homogeneous solution. Next, one dye-encapsulated solution was used for absorption measurement to check the extent of dye encapsulation at different time intervals. Another one is irradiated by UV light for 3 mins and check the absorption at different time intervals. All the experiments were done by using quartz cuvette of 1 cm path length.

The percentage of dye release was calculated from the change in absorption intensity of DiI at 520 nm by using the equation

\[ \text{% of DiI release} = \left\{ \frac{(A - A_0)}{A_0} \right\} \times 100 \]

where A0 is the initial absorption intensity and A is the absorption intensity at different time intervals.

2.11. Calculation of dye encapsulation efficiency and encapsulation capacity

The dye encapsulation efficiency and dye encapsulation capacity were calculated by absorption spectroscopy using following equations:

\[ \text{EE(%) =} \frac{\text{weight of dye in micelles/weight of dye in feed}}{\times 100} \]
\[ \text{EC(%) = weights of dye in micelles/weight of dye in loaded vesicle} \times 100\% \]

2.12. Scanning electron microscopy (SEM) and atomic force microscopy (AFM)

Pico plus 5500 AFM instrument was used for collecting AFM images. SEM images were collected from the SEM instrument of model ZEISS EVO 18. One drop of polymer solutions (both before and after UV irradiation) was placed on silicon wafer and dried in air for 12 hours before images were taken.

2.13. X-Ray diffraction measurements

The XRD measurements were recorded on a powder X-Ray diffractometer (Rigaku Smart lab) and the source was Cu Ka radiation (λ = 0.15406 nm) with a voltage and current of 40 kV and 30 mA respectively. In a typical XRD experiment, solid polymer was placed on a XRD holder. And the data was recorded from 1° to 60° with a sampling interval of 0.02° per step.

3. Results and discussion

3.1. Synthesis and characterization

Commercially available diethanolamine was treated with tetraethylene glycol mono methyl ether acrylate to synthesize hydrophilic diol monomer (M_H) and on the other hand 4, 4′ dihydroxy azobenzene was reacted with 1, 3 dibromo propane to prepare azobenzene based diol monomer (M_Azo). Next, both the monomers were condensed with hexamethylene diisocyanate in presence of a catalytic amount of 1,4-diazabicyclo[2.2.2]octane (DABCO) and dry THF solvent to produce main-chain azobenzene polyurethane PU_{Azo} (Scheme 1) by a step-growth polymerization technique. In the polymerization of diisocyanate monomer (mole fraction = N_{R1B}) and diol monomers (mole fraction = N_{AA}),
benzyl alcohol (mole fraction = \( N_{A_1} \)) was used as a mono-functional impurity (MFI) with a specific ratio satisfying the relationship 2 \( N_{BB} = 2 N_{AA} + N_{A^*} \) (where \( N \) stands for mole fraction of each component, \( N_{AA} = \) Summation of mole fraction of \( M_{H} \) and \( M_{Azo} \) monomers) to ensure capping of all the chain ends.\(^{[74,75]} \) In the course of the reaction, MFI was added after 2 hours of reactions, so that growth of the polymerization can be stopped in the range of desired molecular weight. The MFI would cap the polymer chain ends, which would arrest the chain growth. To confirm the formation of polymer from the monomers, gel permeation chromatography (GPC) measurement was carried out and the molecular weight (\( M_n \)) of the product was found to be 8,700 gm/mol with PDI of 1.60, which establishes formation of polymer.\(^{[74,75]} \) Further, the polymer was structurally characterized by \(^1\)H-NMR and IR spectroscopy (Figure S2 and S3). In \(^1\)H-NMR, the polymer \( PU_{Azo} \) shows a few characteristics peaks of urethane –NH at \( \delta = 7.20 \) ppm and \( \delta = 7.25 \) ppm. In addition, two new peaks at \( \delta = 3.95 \) ppm and 2.95 ppm for \(-CH_2\) protons in \(-CH_2-O-CO-NH\) and \(-CH_2-NH-CO-O-\) respectively confirms formation of polyurethane. In FT-IR spectrum, the urethane –NH and carbonyl stretching appear at 3320 cm\(^{-1}\) and 1690 cm\(^{-1}\) respectively as shown in Figure S3. All the above discussed measurements suggest formation of polyurethane from disocyanate and diol monomers.

### 3.2. Self-assembly and thermodynamics studies

The polymer nanoassemblies were formed in a nanoprecipitation technique by drop-wise addition of water to the DMSO solution (~6% DMSO in H\(_2\)O) of \( PU_{Azo} \) polymer. The nanoaggregates formation and guest encapsulation was pictorially represented in Scheme 1. The dynamic light scattering (DLS) measurement revealed formation of nanoassemblies with an average hydrodynamic diameter of 120 nm, (Figure 1b) which corroborates well with the diameters of spherical micelles (100-110 nm) found in scanning electron microscopy (SEM) by analysis of dried samples of \( PU_{Azo} \) (Figure 1c). A slight smaller size in SEM measurement can be attributed to the shrinkage of the particle\(^{[26,76]} \) while drying the aqueous drop cast of the samples for the measurements. Atomic force microscopy (AFM) images (Figure S4) also well matched with the size and morphology found in SEM measurement. To support the formation of spherical micelles with azobenzene moieties inside the core, we performed \(^1\)H-NMR of polymer \( PU_{Azo} \) in deuterium oxide (D\(_2\)O) and DMSO-d\(_6\) solvents and compared the results (Figure S5). \(^1\)H-NMR of polymer \( PU_{Azo} \) in DMSO-d\(_6\) showed signals from both hydrophilic and hydrophobic segments, whereas in D\(_2\)O, it showed signals only from tetraethylene glycol monomethyl ether (TEG) block, thus indicating formation of an assembly where hydrophobic azobenzene and hexamethylene segments are buried in the core domain of micellar nanoassembly.\(^{[77]} \) Further, to test its nanocontainer property, pyrene was used as a hydrophobic fluorescent probe, which is not soluble in water unless a hydrophobic compartment is provided. This showed intense absorption and fluorescence in presence of micellar solution, which suggests formation of nanocontainers for hydrophobic molecules like pyrene in water (Figure S6). Here, the ratio (I\(_1\)/I\(_3\)) of first (I\(_1\)) and third (I\(_3\)) vibrational peaks (calculated from pyrene’s emission spectrum) was found to be 1.40, which closely matched with the value for pyrene in CH\(_2\)Cl\(_2\) (I\(_1\)/I\(_3\) = 1.37), thus suggesting \( PU_{Azo} \) micellar core has moderate nonpolar environment, which resembles with the polarity of CH\(_2\)Cl\(_2\).\(^{[78]} \) Pyrene encapsulation was visually...
justified by optical polarization microscopy images, which showed blue emitting particles (Figure S6). Next, to determine the critical aggregation concentration (CAC), another hydrophobic dye 1,1\textsuperscript{0}-dioctadecyl-3,3,3\textsuperscript{0},3\textsuperscript{0}-tetramethyl-indocarbocyanine perchlorate (DiI), was used as a model guest molecule. In a typical experiment, DiI concentration was kept constant and polymer concentration was varied from low to high concentration and DiI absorption was recorded. With the increase in polymer concentration, DiI absorption intensity was found to be increased, which can be attributed to the formation of micelles with increasing polymer concentration and encapsulation of DiI dye (Figure 1a). The inflection point from the plot of absorption intensity of DiI at a particular wavelength ($\lambda = 560$ nm) vs concentration of polymer solution was considered as critical aggregation concentration (CAC = 7.9 $\mu$M) (Figure 1a inset), which corroborates well with the CAC (8.5 $\mu$M) found from isothermal titration calorimetry experiment (ITC) (Figure 1d and 1e). The DiI encapsulation was also justified by OPM images showing red emitting particles (Figure 1f). The low CAC and smaller micellar size suggests formation of very compact nanostructure and high tendency of aggregation in water via supramolecular cross-linking by $\pi-\pi$ stacking (azobenzene moieties) and H-bonding (urethane functionalities) interactions. To get more insight into the self-assembly, we established a comprehensive thermodynamic profile for the self-assembly of PU\textsubscript{Azo} polymer in water by isothermal titration calorimetric (ITC) experiment. The heat change associated with the disassembly of the self-assembled structure can be recorded in ITC experiment and from this data, enthalpy of micellization and other thermodynamic parameters associated with the self-assembly process can be calculated using the equations reported in the literature.\cite{79,80} The ITC dilution experiment of PU\textsubscript{Azo} polymer solution at 25 $^\circ$C, reveals an exothermic heat flow, which eventually saturates beyond a certain concentration (designated as CAC) as there is no more disassembly of micelles. The exothermic heat change ($\Delta H = -0.6$ kcal/mol) indicates disassembly process is enthalpically favorable and self-assembly is an enthalpically disfavored process ($\Delta H = 0.6$ kcal/mol), (Figure 2a) which is previously found for other polymeric systems as well.\cite{80} The entropy of assembly ($\Delta S = 20.8$ cal/mol/K) was found to be positive, which implies the assembly though is enthalpically disfavored, but entropically favorable, thus making the overall self-assembly a spontaneous process with a free energy ($\Delta G$) value of $-5.6$ kcal/mol (Figure 2b). The entropy driven process can be attributed to the release of urethane bounded water molecules to the bulk during the self-assembly process. In the non-assembled state, the water molecules remain engaged in H-bonding with the urethane linkers, but they are expelled during the process of self-assembly as the self-assembled structure is stabilized by the preferable H-bonding between urethane linkers and $\pi-\pi$ stacking (here between azobenzene $\pi$-chromophores) as evidenced by computational chemistry\cite{67} and X-Ray diffraction study ($d = 3.8$ Å corresponds to $\pi-\pi$ stacking distance) (Figure S7).

### 3.3. Photoresponsive behavior of the nanoassemblies

The photoisomerization of the PU\textsubscript{Azo} polymer in water was recorded by UV/Vis spectroscopy and the irradiation of the sample to achieve the isomerization was done by a mercury low pressure UV lamp ($\lambda = 365$ nm, 16 W). Before irradiation, the azobenzene remains as trans isomer in the solution and it gives two characteristic bands, one strong band at 360 nm corresponding to $p-p$ transition and one weak band at 450 nm corresponding to $n-\pi^*$ transition. The broader nature of the bands in the UV/Vis spectroscopy
indicates the presence of aggregated form of the azobenzene moieties. Upon UV irradiation, a remarkable decrease in absorbance at 360 nm and the increase in absorbance at 450 nm were observed (Figure 3a). This can be attributed to the photoisomerization of the trans-isomer (light yellow color solution) to the cis-isomer (yellow color solution) accompanied by the changes of the molecular organization and the polarity of micellar core (Figure 3b). After 3 mins of irradiation, no further changes in UV-Vis spectrum were observed, specifying that a photo stationary state was reached. In dark the thermal cis to trans back isomerization happens and here it takes 5 hours for complete recovery from cis to trans as probed by the UV/Vis spectroscopy (Figure 3c). The structural change due to cis-trans isomerization has been shown in Figure 3e. To get more insight into the size and morphological change after irradiation, DLS in combination with SEM measurements were performed. The wrinkled and swelled nanoaggregates with a diameter of \( \sim 200 \) nm (double of the size of micelles before irradiation) were observed by SEM (Figure 3f) and this was found to be in good agreement with the hydrodynamic diameter (210 nm) measured by DLS study (Figure 3d).
of robust drug delivery platform to minimize undesired leakiness and premature drug release. In the guest release experiment, we noticed a minimal drug leakage due to (i) formation of stable nanocontainer via noncovalent crosslinking by π-π stacking and H-bonding interactions and (ii) stabilization of guest inside the core by π-π stacking interactions between azobenzene and guest molecules. The encapsulation stability was further demonstrated by well documented FRET experiment using two hydrophobic FRET pairs, 3,3′-dioctadecyloxacarbocyanine perchlorate (DiO, donor) and 1,1′-dioctadecyl-3,3′,3′-tetramethyl-indocarbocyanine perchlorate (DiI, acceptor) (Figure 5d for FRET solution image). Here both the FRET pair molecules were coencapsulated inside the micelles and donor molecule was excited at 450 nm, which results energy transfer from donor to acceptor molecules as they are within their Förster distance (Figure 5a). The strong acceptor emission at 580 nm was monitored over the 45 hours (Figure 5c) and very minimal spectral change suggested high encapsulation stability with the leakage coefficient (Λ) of 0.6 × 10^{-3} h^{-1} (Figure 5d). The encapsulation efficiency (EE = 77%) and encapsulation capacity (EC = 45%) (Figure S8) were also found to be higher because of enhanced guest encapsulation stability.

3.6. pH induced surface charge modulation

Positively charged nanoaggregate shows enhanced cellular uptake due to their high affinity toward negatively charged cell membrane, thus making them very useful in the area of cancer cell specific drug delivery. The acidic environment of tumor extracellular matrix (pH = 6.5-6.8) generates the nanocarrier endows with a fascinating feature of enhanced cellular uptake provided that it contains a specific functionality, which can be protonated at above mentioned acidic pH. This can introduce a selectivity nature of the nanocarrier toward cancer cells rather than normal cells as normal cells environment is neutral in nature (pH = 7.4). The lower extra cellular pH in the tumor tissue compared to normal tissue and blood is due to the hypoxia induced generation of excess lactic acid in the tumor microenvironment. There are many reports of charged nanoparticles in the literature including permanent charge, charge reversal from negative to positive and charge generation from neutral to positive etc. Among these three categories charge generation from neutral to positive at tumor
environment is superior as it can avoid the nonspecific interactions with proteins in the blood. As the present main-chain tertiary amine group with a pKₐ of ∼6.8 in the PU₉₇₀ polymer remain on the surface of the nanoaggregates, we assumed that nanoaggregates with multiple copies of tertiary amine on the surface will be positively charged at tumor extracellular matrix relevant pH (pH = 6.5-6.8). To check the pH induced surface charge generation, we carried out zeta potential measurements at pH 7.4 and 6.6, which showed surface charge modulation from nearly neutral (4.0 mV at pH 7.4) to moderately positive (18.0 mV at pH 6.6) (Figure S9). This environment specific charge modulation is expected to reduce the nonspecific interactions with proteins in the serum and increase the cellular uptake to cancer cells.

4. Conclusions

In this article we have demonstrated synthesis of amphiphilic main-chain azobenzene polymer by step growth polymerization technique. The polymer forms light responsive nanoaggregates in aqueous milieu, which can sequester hydrophobic guest molecules noncovalently. The nanoaggregates are stabilized by supramolecular cross-linking, thus resulting enhanced encapsulation stability (leakage coefficient as low as 0.6 × 10⁻³ h⁻¹) with high drug loading efficiency (EE) and capacity (EC). Upon UV irradiation for very short time (3 mins) the increase of membrane permeability followed by entrapped guest release in a controlled fashion was observed. The increasing membrane permeability can be attributed to (i) the increase in polarity of the micellar core owing to the change in net dipole moment associated with trans-to-cis photoisomerization as probed by spectroscopic technique using pyrene as a fluorescent probe; (ii) morphological transition from smaller compact to larger swelled nanoaggregates as established by SEM and DLS study. The nanoaggregates showed pH induced surface charge modulation, which is relevant to enhanced cellular uptake as the cell membrane with negative potential has high affinity toward positively charged nanoaggregates. Hence, the main-chain azobenzene polyurethane outlined here can be a potential smart material for biomedical applications such as cell specific on command drug release or cell imaging.

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