

Responsive Azobenzene-Containing Polymers and Gels

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Abstract— The photoviscosity effect in aqueous solutions of novel poly(4-methacryloyloxyazobenzene-co-N,N-dimethyl acrylamide) (MOAB-DMA) was demonstrated. The observed significant reduction in the zero-shear viscosity upon UV-irradiation of MOAB-DMA aqueous solutions was due to the dissociation of the interchain azobenzene aggregates. Such phenomena can be advantageously used in photoswitchable fluidic devices and in protein separation. Introduction of enzymatically degradable azo cross-links into Pluronic-PAA microgels allowed for control of swelling due to degradation of the cross-links by azoreductases from the rat intestinal cecum. Dynamic changes in the cross-link density of stimuli-responsive microgels enable novel opportunities for the control of gel swelling, of importance for drug delivery and microgel sensoric applications.

Index Terms:- Responsive gels, trans-4-methacryloyloxy azobenzene, 4,4'-di(methacryloylamino) azobenzene, cis-trans transitions, UV irradiation, azoreductase cleavage

I. INTRODUCTION

The azobenzene $-C_6H_4-N=N-C_6H_4-$ functionality is unique from the standpoint of being capable of changing conformation (photoisomerization) in response to the energy input from UV sources as well as the azo group being cleavable by enzymes (azoreductases) produced by microflora of the gastrointestinal tract (GIT).^{1,2} Hence, in the present work we explored both of these properties of the azobenzene functionality to create responsive polymers and gels. By creating amphiphilic polymers with azobenzene side chains that are prone to association in their *trans*- form and dissociation in the *cis*-form, we aimed at the “smart” aqueous, polymeric system with photoswitchable rheological and transport properties. Since the azobenzene group is extremely hydrophobic, it must be conjugated with a hydrophilic moiety in order for the resulting copolymer not to phase-separate from its aqueous solution. We chose N,N-dimethylacrylamide (DMA) as such a water-soluble moiety. On the other hand, having previously introduced self-assembling microgels of Pluronic and poly(acrylic acid) (PAA)^{3,4}, in the present work we set out to impart the biodegradation capability to

such microgels by using the azoaromatic cross-links. To this end, we synthesized an azoreductase-cleavable cross-linker, 4,4'-di(methacryloylamino)azobenzene, which could be cleaved by the enzyme, thus allowing the microgels to swell. Kinetics of swelling of such microgels responsive to the biological stimulus is reported herein.

II. EXPERIMENTAL SECTION

POLYMER SYNTHESIS

A. Materials

Nonionic copolymer Pluronic L92 was obtained from BASF Corp. and used without further treatment. Acrylic acid (99%), ethylene glycol dimethacrylate (EGDMA, 98%), N,N'-bis(acryloyl) cystamine (BAC, 97%, CAS 60984-57-8), 4-aminoacetanilide (99%), 4-allyl-2-methoxyphenol (eugenol, 99%), methacryloyl chloride (98+%), benzyl viologen (97%), dithiothreitol (DTT, 99%), tris(2-carboxyethyl)phosphine hydrochloride (TCEP, 98%), sodium hypochlorite solution (available chlorine, 13%), Ninhydrin Reagent solution, glycine hydrochloride (99%), 4-hydroxyazobenzene (98%), methacryloyl chloride (97%), N,N-dimethylacrylamide (99%), and 2,2'-azobisisobutyronitrile (initiator, AIBN, 98%) were purchased from Sigma-Aldrich Chemical Co. and used as received. Triethylamine (99%) was obtained from J.T. Baker and was also used without further treatment. Deuterated solvents were obtained from Cambridge Isotope Laboratories. All other solvents, buffers, and gases were obtained from commercial sources and were of the highest purity available.

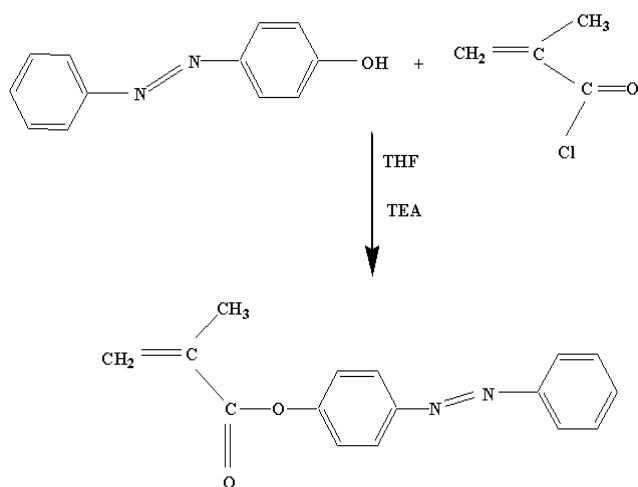
B. Synthesis of Photoresponsive Polymers

B.1. trans-4-Methacryloyloxyazobenzene (MOAB)

MOAB was prepared by condensation of 4-hydroxyazobenzene and methacryloyl chloride in THF, with triethylamine (TEA) acting as a promoter (Scheme 1). In brief, 4-hydroxyazobenzene (10 g, 50.0 mmol) was dissolved in 120 ml THF, to which triethylamine (acid scavenger; 7.11 ml, 50.6 mmol) and 2,6-di-*tert*-butyl-p-cresol (free-radical inhibitor, 5 mg) were added. The resulting solution was purged with nitrogen and stirred at room temperature for 30 mins. Methacryloyl chloride (15

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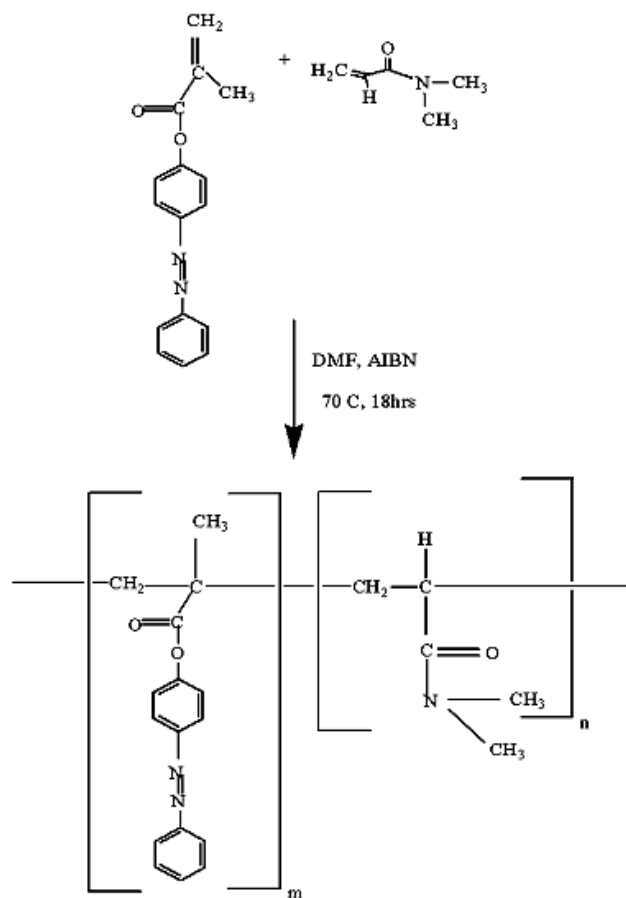
ml, 150 mmol) was then added gradually using a glass syringe while the solution was maintained at subzero temperature by placing it in an ice-cooled water bath. The formation of triethylammonium salt in the form of precipitate was observed immediately upon methacryloyl chloride addition. The reaction mixture was stirred for 48 h at r.t. The formed precipitate was filtered off, and the solution was diluted with mixture of chloroform and water (3:1) to convert the excess methacryloyl chloride into methacrylic acid. The organic layer was washed three times with distilled water to remove the polar compounds. Finally, the organic layer was dried on anhydrous Na₂SO₄, and the residual solvent was removed *ab vacuo*. The product was crystallized twice from n-hexane and dried under vacuum.



Scheme 1: Synthetic route to the preparation of *trans*-4-methacryloyloxyazobenzene (MOAB)

B.2. Copolymerization of dimethylacrylamide with *trans*-4-methacryloyloxyazobenzene

The obtained MOAB was copolymerized with a hydrophilic monomer, N,N-dimethylacrylamide (DMA) via free-radical polymerization using AIBN in DMF (Scheme 2). Namely, a solution containing MOAB (0.1 g, 3.8 mmol), N,N-dimethylacrylamide (0.154 ml, 15 mol) AIBN (5 mg, 2 wt %), and 0.15 ml of DMF was deoxygenated with nitrogen while in an ice-cooled water bath. The solution was then maintained at temperature of 70 °C for 18 hours. To complete the polymerization, the solution was then kept at 90 °C for 2 h. The obtained polymer was dialyzed for 48 h against deionized water using a 3500 Da MWCO membrane and then lyophilized.

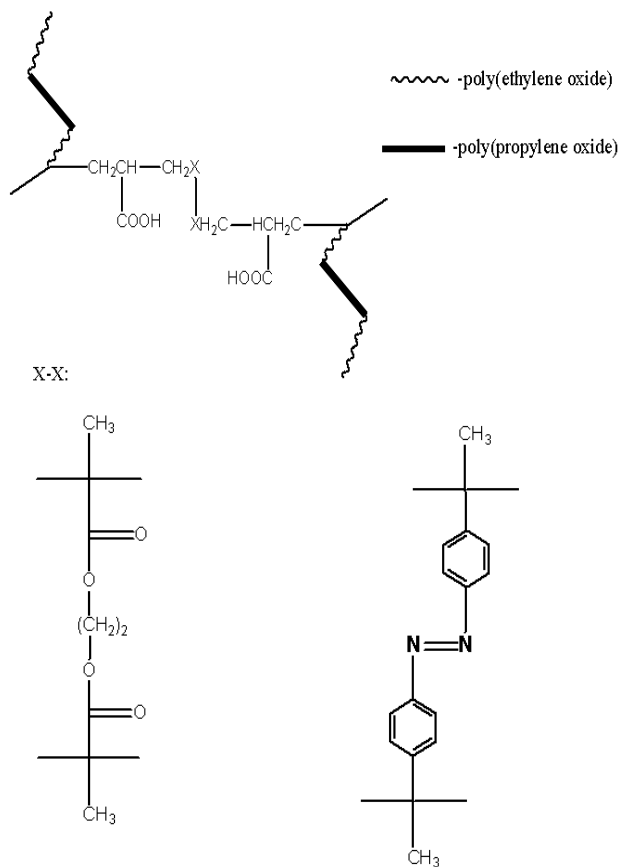


Scheme 2: Synthetic route of the MOAB-DMA copolymers

C. Synthesis of Gels with Biodegradable Cross-links

The azoaromatic cross-linker, 4,4'-di(methacryloylamino)azobenzene, was synthesized by reaction of 4,4'-diaminoazobenzene with methacryloyl chloride. The precursor, 4,4'-diaminoazobenzene, was obtained from 4-aminoacetanilide. Then the 4,4'-diaminoazobenzene (4.25 g, 20 mmol) was dissolved in 0.1 wt% 4-allyl-2-methoxyphenol solution in pyridine resulting in a 10 wt% solution. Methacryloyl chloride (5.9 mL, 60 mmol) was added drop-wise into the solution under stirring and the solution was kept at 60 °C under stirring for 1 h. Eugenol addition prevented a possible premature free-radical polymerization of methacryloyl chloride. The solution was then poured into 100 mL of chilled (4 °C) deionized water and the resulting mixture was acidified to pH 4 by addition of concentrated HCl. The precipitate was filtered under vacuum, washed with excess aqueous 5% NaHCO₃ and deionized water, dried and repeatedly recrystallized from ethanol. The chemical structure of 4,4'-di(methacryloylamino)azobenzene was confirmed by NMR [¹H NMR (400 MHz, Pyridine-d₅): δ 5.55 (*d*, =CH₂), 5.87 (*d*, =CH₂), 1.96 (*s*, H₃C-C=), 7.85 (*q*, H₄C₆) ppm] and elemental analysis [found (calculated): C: 68.83 (68.95), H: 5.81 (5.79), N: 15.89 (16.08)].

Microgels with azobenzene cross-links cleavable by azoreductases from the rat intestine microflora were synthesized by free-radical copolymerization of acrylic acid and 4,4'-di(methacryloylamino)azobenzene with simultaneous grafting of Pluronic chains on the forming network of poly(acrylic acid), in a free-radical procedure analogous to that described previously^{4,5}.



Scheme 3: Chemical structures of Pluronic-PAA microgels and cross-linkers copolymerized with the vinyl monomers.

In the Pluronic-PAA microgels, the cross-linking ratio, XL, was set at 0.1 and 1.0 mol% for the EGDMA and azoaromatic (Azo) cross-links, respectively as shown in Scheme 3. Using analogous procedures, but without Pluronic, a batch of poly(acrylic acid) microgels cross-linked by the azo-aromatic cross-linker was also synthesized (designated PAA-Azo). The cross-linking ratio, XL, was set at 0.1 and 0.56 mol% for the EGDMA and Azo, respectively, in the PAA-Azo microgels. The amount of the azobenzene cross-linking agent incorporated in the microgel particles was determined spectroscopically. The dry microgel particles (5-10 mg) were hydrolyzed in 2 M NaOH solution (5 mL) at room temperature for four days. The solution was then diluted with 5 mL dimethylsulfoxide and electronic absorbance at 443 nm was assayed. The concentration of the cross-linker in the microgel was expressed in mmol/g dry polymer using the

absorbance-concentration calibration curve developed with 4,4'-diaminoazobenzene in dimethylsulfoxide/2M NaOH (1:1) solution. The concentration of the cross-links in the microgels based on Pluronic L92 and PAA without Pluronic was found to be 72 ± 8.3 and 71 ± 5.8 $\mu\text{mol/g}$, respectively, which is in excellent agreement with the calculated concentration of 76 $\mu\text{mol/g}$.

D. Procedures

Proton NMR spectra of polymer solutions in CD_2Cl_2 were acquired on a Bruker AMX400 spectrometer. Gel Permeation Chromatography (GPC) was carried on the THF solvent column. UV-vis absorption spectra were obtained on a Hewlett-Packard HP 8453 spectrophotometer with a quartz cuvette (1 cm path length). The light source used to change the surfactant conformations was a 200 W mercury lamp (Oriel 6283) mounted in an arc lamp housing (Oriel 66902) and powered by an arc lamp power supply (Oriel 68910). Monochromatic UV light was obtained by using a 320 nm band-pass filter (Oriel 59800). Rheological measurements were performed using a controlled stress Rheolyst Series AR1000 Rheometer (TA Instruments) with a cone and plate geometry system (cone: diameter, 2 cm; angle, 2°, truncation, 57 μm). Temperature control (internal resolution 0.016 °C) was provided by two Peltier plates. Equilibrium flow experiments were conducted in a stepped ramp mode with the shear stress (0.6 Pa) as a controlled variable; likewise the creep measurement (retardation mode) was accomplished with a stress of 0.6 Pa. Microgel swelling was studied using a volumetric method as described previously⁵. In brief, single microgel particles were placed into glass capillary tubes (internal diameter 1.5-2.3 mm) using suction pressure applied by a filler/dispenser. The tubes were placed into a glass thermostatted cuvet and observed under a Nikon TMS Inverted Microscope equipped with a Model IV-550 Video Microscaler and a Hitachi Color Video Monitor. The boundaries of the spherical particles were fitted with the microscaler and the particle diameters were measured with an accuracy of ± 0.5 μm or better. Initially, the diameter (d_0) of a dry particle or a particle swollen under the initial pH and temperature was measured. The capillary tube was then either filled gently with water of appropriate pH, or the particle was removed from the initial tube and placed into another tube, which itself was then filled with a different solution or cell suspension. In the case of microgels with degradable cross-links, their swelling was studied only in buffer solutions deaerated by nitrogen bubbling. The diameter of the swollen particle (d_i) was videotaped and the diameter changes were measured at low speed replays. All measurements under given conditions were conducted in triplicate.

Testing of microgels with azoaromatic cross-links

Adult, pathogen-free male Sprague-Dawley rats (Harlan, 250-300 g) were sacrificed and midline incisions were made. The cecal segment of the intestine contents was cut open and its content was collected and dispersed in isotonic

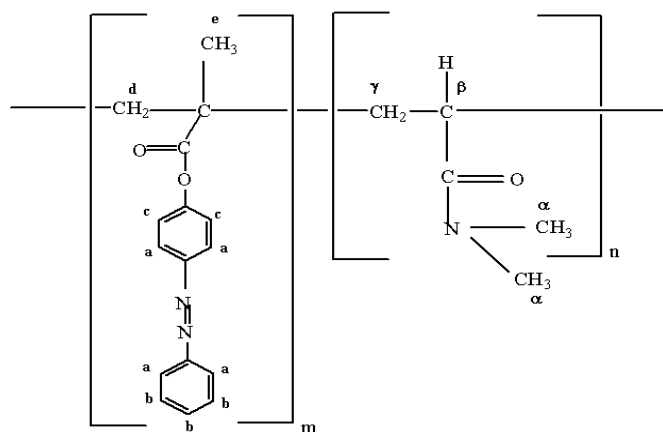
phosphate buffer (pH 7.4) that had been deoxygenated by nitrogen bubbling, resulting in a 10 w/w% suspension, which was lyophilized and kept dry on ice. In the microgel swelling experiments, a 6 mg/mL cecum suspension in isotonic phosphate buffer (pH 7.4) was prepared that contained 1.2 mM benzyl viologen and 2.5 mg/mL of α -D-glucose. The suspension was incubated at 37 °C under anaerobic conditions for 14 h and at time $t=0$ was added to microgel particles loaded into a capillary, which was subsequently sealed to prevent penetration of oxygen. The swelling kinetics were measured at 37°C as described above.

The concentration of pendant amino groups originating from the degrading cross-linker was measured spectroscopically using the ninhydrin method as described by Yeh et al.¹⁵. In brief, a 1 wt% microgel suspension was incubated under gentle shaking in a sealed vial containing 6 mg/mL cecum suspension in isotonic phosphate buffer (pH 7.4) at 37 °C. The suspension samples (1 mL each) were withdrawn intermittently; the microgels were removed from the samples using syringe filters (pore diameter, 5- μ m, Pall Corporation, East Hills, NY) and lyophilized. The dry samples (4-7 mg) were placed into a vial containing 1 M acetate buffer at pH 5.0 (1 mL) following addition of 1-mL ninhydrin solution, mixing, equilibration at 100°C for 15 min, and addition of 50% aqueous ethanolic solution (15 mL). The samples were then allowed to equilibrate at room temperature for 1-1.5 h and the amino group concentration was measured by assaying electronic absorbance at 570 nm. Glycine aqueous solution was used to develop calibration curves, generated simultaneously with the assay samples.

In the microgel degradation experiments, microgels pre-swollen in isotonic phosphate buffer were added to a 6 mg/mL cecum suspension in isotonic phosphate buffer (pH 7.4) containing 1.2 mM benzyl viologen and 2.5 mg/mL of α -D-glucose, to result in 1 wt% microgel suspension.

RESULTS AND DISCUSSION

E. Photoresponsive Polymer Synthesis and Structure



Scheme 4: Structure of the MOAB-DMA polymer

Using ¹H NMR spectroscopy, we were able to verify the structure of the MOAB-DMA copolymers resulting from polymerization (Scheme 2).

The average number of azobenzene groups in the polymer was found from the ratio of the protons in the azobenzene moiety to the protons of the methyl group of DMA (See Scheme 4 and Fig.1 for the proton designations). At $n=1$, the NMR analysis yielded $m=0.185$, with the theoretical m value being 0.2. That is, our copolymer contained 22.1 wt% of the hydrophobic azobenzene groups. The weight-average molecular weight of this copolymer was found to be 18 kDa. This copolymer species was water-soluble, while an analogous copolymer with a theoretical m value of 0.3 appeared to be water-insoluble.

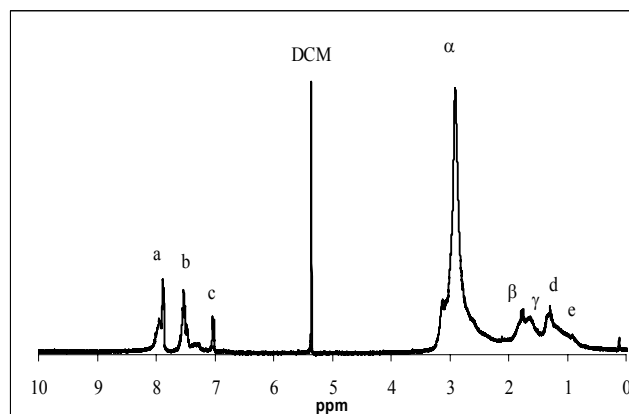


Figure 1: ¹H NMR (400 MHz) spectra of MOAB-DMA in CD₂Cl₂. Protons are labeled as shown in Scheme 3.

F. Photo-Induced Polymer Assembly

Since the azobenzene group incorporated in the MOAB-DMA copolymers changes its conformation reversibly when illumination is switched between UV and visible light¹, we anticipated that the copolymer would undergo conformational changes upon irradiation.

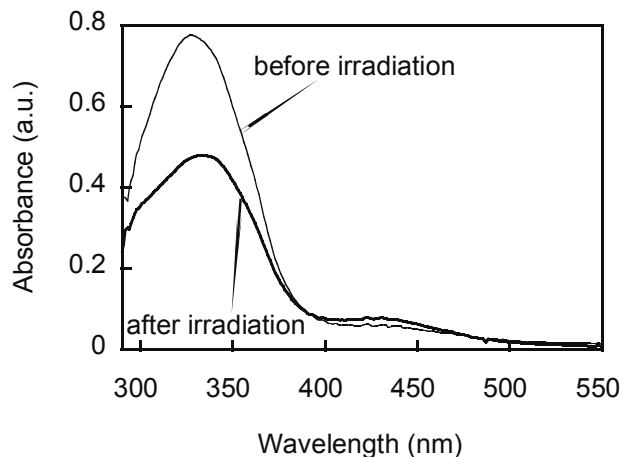


Figure 2: UV/Vis Absorption spectrum for the *trans* and *cis* copolymer solution in DI water (0.0045 wt%).

Fig.2 illustrates such changes. The intensity of the absorption band centered at 330 nm corresponding to the $\pi \rightarrow \pi^*$ transitions decreased after about 30 min irradiation. Simultaneously, the $n \rightarrow \pi^*$ transition band around 440 nm (associated with the appearance of the cis- form of the azobenzene moiety in solution) increased. Upon exposure of the sample to daylight for 0.5 h the electronic spectra reversed to become identical to the ones prior to the UV irradiation, which proved the reversibility of the photoisomerization.

When the azobenzene molecule is attached chemically to a polymer chain as a side chain, photo-induced isomerization takes place. In the trans form, the azobenzene groups generate hydrophobic interactions between azobenzene groups on the same polymer chain, which tend to contract the polymer chain. On irradiation with UV light, cis isomerization takes place which tends to expand the polymer chain thus leading to increased viscosity^{7,8}. This photo-induced viscosification effect can be exploited in separation process.

Indeed, exposure of the MOAB-DMA aqueous solutions to the UV light resulted in a precipitous change of the solution rheological properties (Figs 3 and 4). The effect of irradiation on the property of 30 wt% MOAB-DMA solution to flow under shear is illustrated in Fig.3. The steep increase of the creep compliance after irradiation reflects upon the lower viscosity, resulting from the dissociation of the interchain azobenzene aggregates acting as physical cross-links affording the viscoelastic properties to the solution.

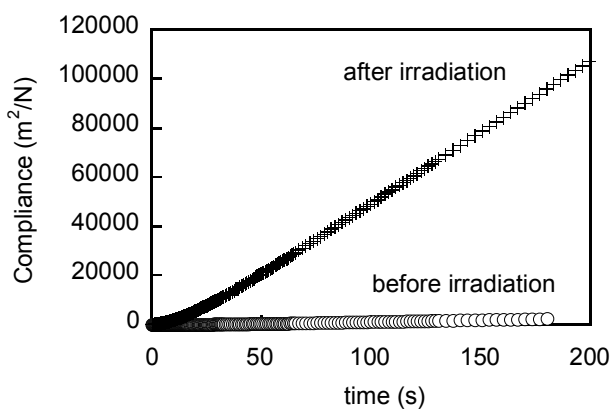


Figure 3: Creep experiment result showing creep compliance against time at shear stress of 0.6 Pa during retardation.

The compliance is given by

$$J(t) = \frac{\gamma(t)}{\sigma_0}$$

where, $\gamma(t)$ is the strain and σ_0 is the applied stress at $t=0$. The compliance J has the units of reciprocal of modulus but in general does not equal to $1/G$.

The zero shear viscosity (η_0) of the MOAB-DMA solutions was estimated from the creep experiments according to⁹:

$$\gamma(t) / \sigma_0 = J_e^0 + t / \eta_0$$

where t is the time, $\gamma(t)$ is the shear strain, σ_0 is the shear stress and J_e^0 is the steady state shear compliance. The η_0 values before and after irradiation were estimated to be 86.1×10^{-3} and 1.92×10^{-3} Pa.s respectively.

The solutions that were allowed to equilibrate at daylight showed a tendency to restore the original viscosity characteristic of the trans-conformation of the azobenzene groups conducive to the appearance of the associations (cross-links) (data not shown). Analogously, the equilibrium flow experiment demonstrated significant changes in the solution viscosity upon irradiation (Fig.4).

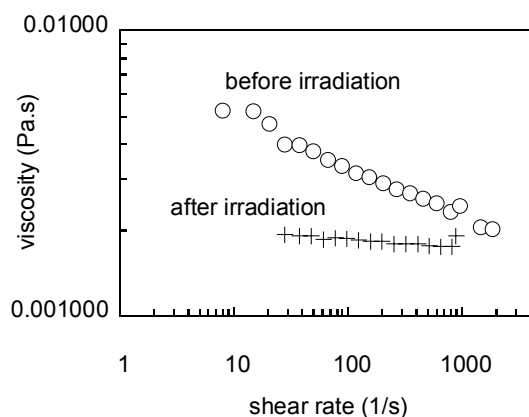


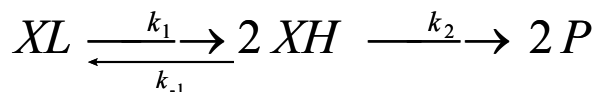
Figure 4: Equilibrium flow results showing viscosity of the solution against shear rate for constant shear stress of 0.6 Pa

These experiments demonstrate that the azobenzene-modified amphiphilic copolymers introduced in this work possess a significant “photoviscosity effect”⁷, with the associative cross-links altered by the UV irradiation. Aqueous solutions of such polymers could be applied as photoswitchable protein separation matrices and UV-sensitive rheology modifiers. It might well be that due to the significant changes in the conformation of these copolymers in solution related to their water-binding properties (i.e., hydrophobicity), the interfacial properties of the polymer solutions such as surface activity, spreading, solute binding, etc. can also be made photoresponsive. Work is currently underway to explore these possibilities.

Next, we explored how the azoaromatic moieties that we used as cross-links in the Pluronic-PAA microgels could be cleaved by azoreductases leading to the microgel volume changes.

Swelling of microgels with biodegradable azoaromatic cross-links

The process of swelling that is coupled with the cross-link reduction can be described by the following scheme, assuming that the cross-link (XL) cleavage and swelling can be presented as two separate steps:



Shrunken gel

Swollen gel

Under steady-state approximation, the kinetics of the disappearance of the shrunken gel are described simply by

$$-\frac{d[XL]}{dt} = \frac{1}{2} \frac{d[P]}{dt} = k_1[XL] - k_{-1}[XH]^2 = \frac{k_2}{2}[XH] \quad (1)$$

Since our L92-PAA microgels enable rapid polymer diffusion when the cross-linking density diminishes ($XL \ll 1$ mol%), we can assume that when a microgel that is initially equilibrium-swollen under non-reducing conditions is placed in a reducing medium and the microgel diameter changes are monitored, the cross-link cleavage will be rate-limiting (i.e., $-d[XL]/dt = k_1[XL]$) and the changes in XL will be proportional to the diameter changes ($[XL]_t \sim d_t - d_\infty$). As is shown below, the kinetic experiments with reversible cross-links were specifically designed to monitor the rate-limiting cross-link degradation. Hence, eqn(1) can be presented in its integral form as

$$\ln\left(\frac{[XL]_t}{[XL]_0}\right) = -k_1 t \quad (2)$$

Equation (2) allows for evaluation of the cross-link cleavage rate constant, k_1 , from the variation of the microgel diameter with time, when this degradation reaction is rate-limiting.

The Pluronic-PAA microgels can swell sufficiently in the neutral pH range characteristic of the lower part of the human GIT⁵, where the gels can be susceptible to the influence of enzymes such as azoreductases. The high degree of swelling enables sufficiently rapid diffusion of enzymes into the hydrogel, where the enzyme can facilitate the cleavage of biodegradable cross-links. Herein, we employed 4,4'-di(methacryloylamino)azobenzene as a cross-linker (Scheme 3) yielding aromatic azo bonds degradable by azoreductase activity.

Fig.5 depicts the effect of placing L92-PAA microgels, equilibrium-swollen in phosphate buffer, into a suspension of azoreductase-containing cecal contents of the rat intestine; similar experiments were performed using PAA microgels with no L92 content. The initial swelling rates for the azo-cross-linked microgels from the dry to the equilibrium-swollen state were faster than those for the EGDMA microgels for the same total cross-linking density, but that the equilibrium swelling of the EGDMA

microgels was higher than that of their azo-cross-linked counterparts. This observation is consistent with the supposition that the azo cross-linker provides more of a cross-linking effect than does EGDMA, possibly through some intra-molecular association between the aromatic rings of these cross-linkers yielding a higher effective cross-linking density within the gel particle.

When these microgels were placed in the cecum suspension, the swelling degree of the nondegradable microgels cross-linked by EGDMA did not change appreciably, while the microgels cross-linked by azobenzene swelled 1.5-fold in the cecum due to the azo-group degradation. The swelling kinetics in cecum followed eqn (2) in all cases, yielding linear fits ($R^2 > 0.97$) (Fig.6).

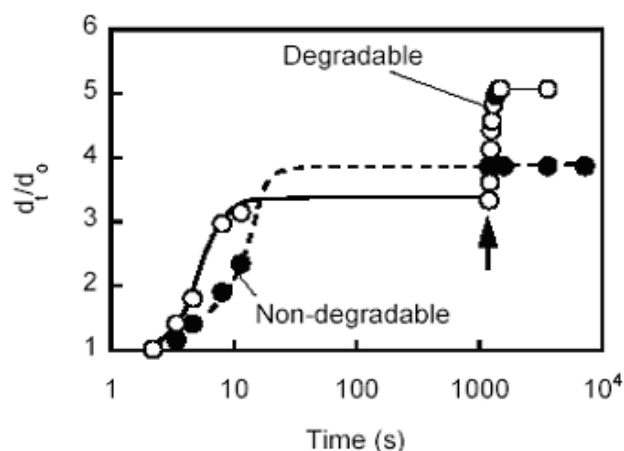


Figure 5: Swelling kinetics of non-degradable and degradable L92-PAA microgels at pH 7.4 and 37 °C. The non-degradable microgels were cross-linked by EGDMA (XL=1.1 mol%), while degradable microgels were cross-linked by both 4,4'-di(methacryloylamino)azobenzene (XL=1.0 mol%) and EGDMA (XL=0.1 mol%). The microgels were initially placed in an isotonic phosphate buffer and allowed to equilibrium swell, then at the time indicated by an arrow the microgels were placed in the cecum suspension.

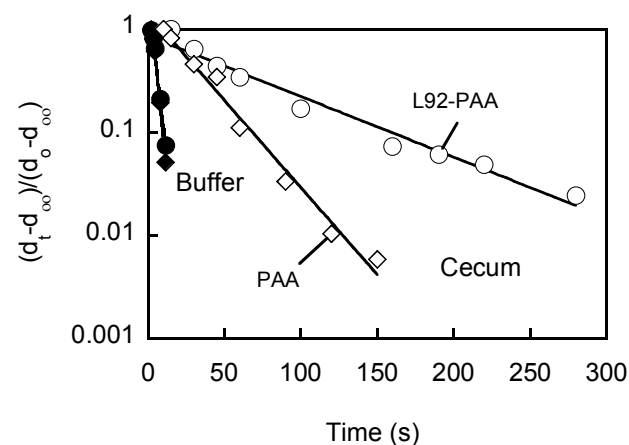


Figure 6:- Typical swelling kinetics of degradable L92-PAA and PAA microgels at pH 7.4 and 37 °C expressed in terms of eqns (1) and (4). The microgels were cross-linked by both 4,4'-di(methacryloylamino) azobenzene and EGDMA. The microgels

were initially placed in an isotonic phosphate buffer and allowed to equilibrium swell, and then at time t_2 were placed in a cecum suspension. The kinetics in cecum suspension is shifted by the time t_2 to the beginning of the axis for clarity of the presentation. Notably, the degradation-limited swelling in cecum was in all instances much slower than the diffusion-limited swelling in buffer, with the kinetic constants of $(1.5 \pm 0.4) \times 10^{-2}$ ($n=4$) and $(3.7 \pm 0.5) \times 10^{-2}$ ($n=3$) found for L92-PAA microgels and PAA microgels without Pluronic, respectively. An over 2-fold, statistically significant difference of identically cross-linked microgels with and without Pluronic can be attributed to the impeding effect of the Pluronic dangling chains on the microgel/water interface. The Pluronic polymers are protein-resistant, because hydrated hydrophilic PEO chains extend out into the solution inhibiting the protein adsorption by steric repulsion^{10,11}. Therefore, the diffusion of the azoreductase into the Pluronic-containing microgels might be inhibited, leading to the lower rate of the degradation-limited swelling.

To further elucidate differences between degradation rates of the Pluronic-modified and unmodified PAA microgels, an independent method of titration of the amino groups resulting from the azo group degradation, was used (Fig.7). The kinetics of the appearance of the amino groups measured by the ninhydrin assay (see Experimental section) afforded estimates of the effective rate of azo cross-link degradation, found to be 1.8×10^{-10} and 3.8×10^{-10} mol/h for the L92-PAA and PAA-based microgels, respectively. These results thus confirm the 2-fold faster degradation of the PAA-based microgels. Yeh at al.⁶ observed a rate of the azo groups degradation in rat cecum of about 2×10^{-9} mol/h in pH-sensitive hydrogels cross-linked by N,N'-(ω -aminocaproyl)-4,4'-diaminoazobenzene. A much slower degradation of the Pluronic-modified microgels in the colon, coupled with their mucoadhesive properties³, could provide means for a sustained, site-specific release.

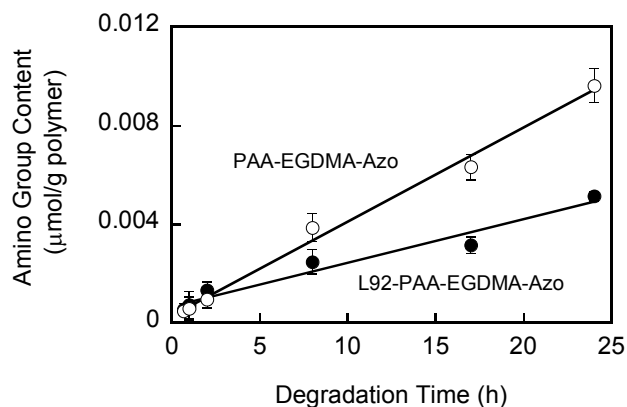


Figure 7: Kinetics of the appearance of the amino groups via degradation of the azobenzene in rat cecum suspension at 37 °C and pH 7.4. The amino groups were measured by ninhydrin assay (see Experimental section). The L92-PAA and PAA gels had

identical cross-linking density and were cross-linked by both 4,4'-di(methacryloylamino) azobenzene and EGDMA.

III. CONCLUSIONS

The photoviscosity effect in aqueous solutions of novel MOAB-DMA was demonstrated. A significant reduction in the zero-shear viscosity upon UV-irradiation due to the dissociation of the interchain azobenzene aggregates was observed. Such phenomena can be advantageously used in photoswitchable fluidic devices and in protein separation. Introduction of enzymatically degradable azo cross-links into Pluronic-PAA microgels allowed for control of swelling due to degradation of the cross-links by azoreductases from the rat intestinal cecum. The presence of Pluronics in the microgels structure can impede the enzyme diffusion into the microgel and further reduce the rate of swelling, which is an effect potentially conducive to sustained release during colon-specific drug delivery using degradable microgels. Dynamic changes in the cross-link density of stimuli-responsive microgels enable novel opportunities for the control of gel swelling, of importance for drug delivery and microgel sensoric applications.

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