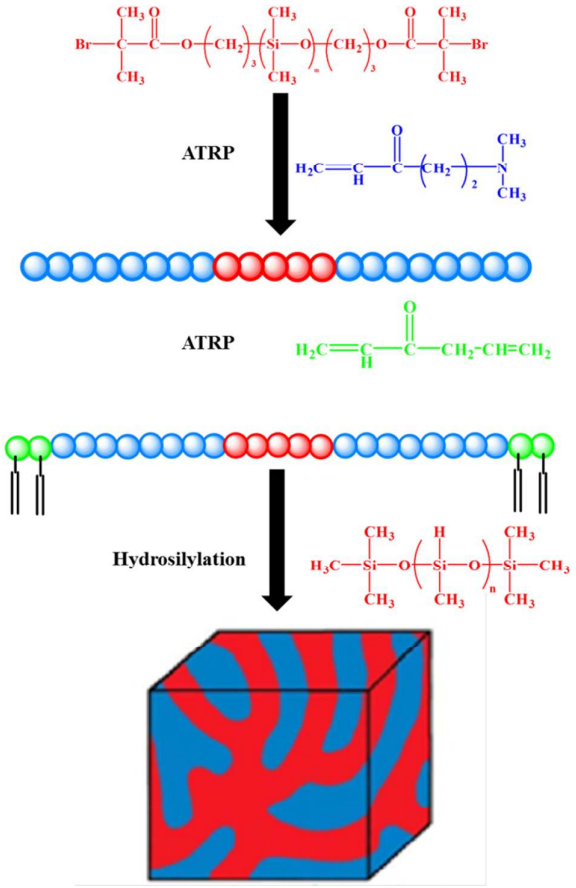
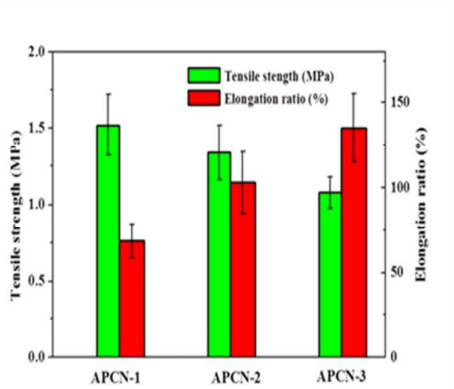
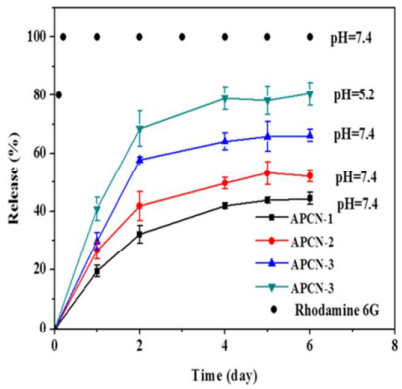
RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances







A series of pH-responsive amphiphilic conetworks were synthesized through cross-linking of well-defined amphiphilic pentablock copolymers via atom transfer radical polymerization.

PH Sensitive Amphiphilic Conetworks Based on End-Group Cross-linking of Polydimethylsiloxane Pentablock Copolymer and Polymethylhydrosiloxane

Ming Qiu,[a] Xin-Zheng Zhao,[a] Da-Peng Liu,[a] and Chun-Ju He[a]*

ABSTRACT: A series of pH-responsive amphiphilic conetworks (APCNs) were synthesized through cross-linking of well-defined amphiphilic pentablock copolymers via atom transfer radical polymerization (ATRP). A new ditelechelic polydimethylsiloxane macroinitiator was synthesized to initiate the polymerization of N, N-dimethylaminoethyl methacrylate. The resulting triblock copolymers show well-defined molecular weight with narrow polydisperisty, which are used as macroinitiator to incorporate allyl methacrylate to get the pentablock copolymers with allyl pendant groups. Then pentablock copolymers are fully cross-linked with polyhydrosiloxanes through hydrosilylation. The so-prepared APCNs exhibit unique properties of microphase separation of hydrophilic (HI) and hydrophobic (HO) phases with small channel size, a variable swelling capacity in media with different pH and polarity, a good mechanical property (1.3 ± 0.2 MPa) and outstanding oxygen permeability (300 ± 120 barrers). The properties of APCNs depend on the ratio of HI-HO, which can be regulated via precise synthesis of the triblock copolymers. The APCNs show well-controlled drug release to Rhodamine 6G upon varying the pH. Meanwhile, the controlled manner is also attributed to the well-defined molecular structure and tunable HI/HO composition of the APCNs.

Introduction

As the rapidly emerging novel materials that consist of covalently interconnected hydrophilic and hydrophobic polymer chains,[1-4] amphiphilic conetworks (APCNs) have many unique properties, such as swelling dependence on solvent, microphase separation structure and biocompatibility, which make them promising for applications in a wide variety of areas.[5-15]

The APCNs prepared from polydimethylsiloxane (PDMS)[16,17] have received great attention due to its own characteristics, i.e. excellent biocompatibility, high elasticity, heat resistance, low surface free energy, biological inertness as well as the highest oxygen permeability among all polymers, which shows a wide range of potential applications in intelligent polymer materials, soft contact lenses, biomedical materials, antifouling surfaces and biochemical sensors.[18,19] Poly(N, N-dimethylaminoethyl methacrylate) (PDMAEMA), one of well-investigated hydrophilic polymers with thermo and pH sensitivity,[20-24] have potential applications in drug delivery and release,[25,26] gene carrier,[27,28] and antibacterial surface.[29,30] Patrickios group[31-36] has prepared PDMAEMA-based APCNs with different architecture and studied their swelling property, degradation characteristics, storage and delivery of DNA. Therefore, an APCN consisting of PDMAEMA and PDMS segments is of great interest due to the distinguished characteristics of segment, its microphase separation, physiological inertness and biocompatible properties. However, there is no report about the synthesis of such a conetwork.

Most APCNs reported are synthesized by uncontrollable free radical

polymerization,[37-39] which inevitably leads to bad conformation regularity, structure defect or even loss of performance. To minimize the defects, more recently APCNs have been prepared by cross-linking polymer chains of well-defined length using controlled methods, such as quasiliving carbocationic polymerization (QLCCP), group transfer polymerization (GTP), reversible addition fragmentation chain transfer (RAFT) polymerization and atom transfer polymerization (ATRP).[35,40-43] Among these methods, ATRP has shown outstanding capability to prepare hrdrogels and APCNs with well-defined molecular structure and good mechanical properties,[42,44] and the use of macroinitiator has received much attention because it simplifies the synthesis step and has a high tolerance for functional groups and impurities.[45] In this study, polydimethylsiloxane di-2-bromoisobutyrate (Br-PDMS-Br) initiate the ATRP of DMAEMA (Scheme 1), and the resulting well-defined PDMAEMA-b-PDMS-b-PDMAEMA triblock copolymers is used as the macroinitiator for the ATRP of allyl methacrylate due to the preservation of active alkyl halide chain end. The introduction of poly (allyl methacrylate) (PAMA) units in the resulting pentablock copolymers guarantees the full cross-linking of the resulting APCN since the allyl pendant groups act as crosslinking sites with polymethylhydrosiloxane. The good water swelling property as a function of pH, excellent mechanical properties and interesting drug release profile of prepared APCN suggest a promising excellent carrier for controlled release.

Experimental Part

Materials. N, N-dimethylaminoethyl methacrylate (DMAEMA) and allyl

methacrylate (AMA) were purchased from Energy Chemical Co. and purified by passing through a babic silica column to remove the inhibitor. Hydroxypropyl polydimethylsiloxane (PDMS, M_n=4000 g/mol, PDI=1.41), polymethylhydrosiloxane (PMHS, M_n=6000 g/mol, PDI=1.40) and Karstedt's catalyst (3% Pt(0) in xylene) were purchased from Gelest and were used as received. Copper(I) bromide was purchased from Shanghai Chemical Reagent Plant and was purified according to a standard procedure.[46] N,N,N',N'',N''-pentamethyldiethylenetriamine (PMDETA), anhydrous magnesium sulfate ($MgSO_4$), Rhodamine 6G and 2-bromoisobutyryl bromide were purchased from Aldrich and used as received.

Synthesis of Macroinitiator Br-PDMS-Br. Hydroxypropyl polydimethylsiloxane (30 g, 7.5 mmol) and triethylamine (1.59 g, 15.8 mmol) were dissolved in 200 mL dry THF in a three-neck round bottomed flask. 2-bromoisobutyrate (3.45 g, 15.0 mmol) was added dropwise to the stirred solution at 0 °C for 1 h. The reaction was stopped after stirring at room temperature for 16 h, filtered to remove the triethylamine hydrobromide byproduct, and evaporated under vacuum. The resulting liquid was redissolved in hexane and washed with a saturated aqueous sodium hydrogen carbonate solution three times. The organic layer was dried by anhydrous magnesium sulfate. The final PDMS macroinitiator (Br-PDMS-Br) was obtained as a slightly yellow liquid with a yield of 95%. ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si, δ): 0.00 (m, 6H), 0.079 (s, 6H, $Si(CH_3)_2$), 0.87 (m, 2H, $SiCH_2CH_2CH_2$), 1.6 (m, 2H, $SiCH_2CH_2CH_2$), 4.33 (m, 2H, $SiCH_2CH_2H_2$), 1.96 (s, 6H, $BrC(CH_3)_2$).

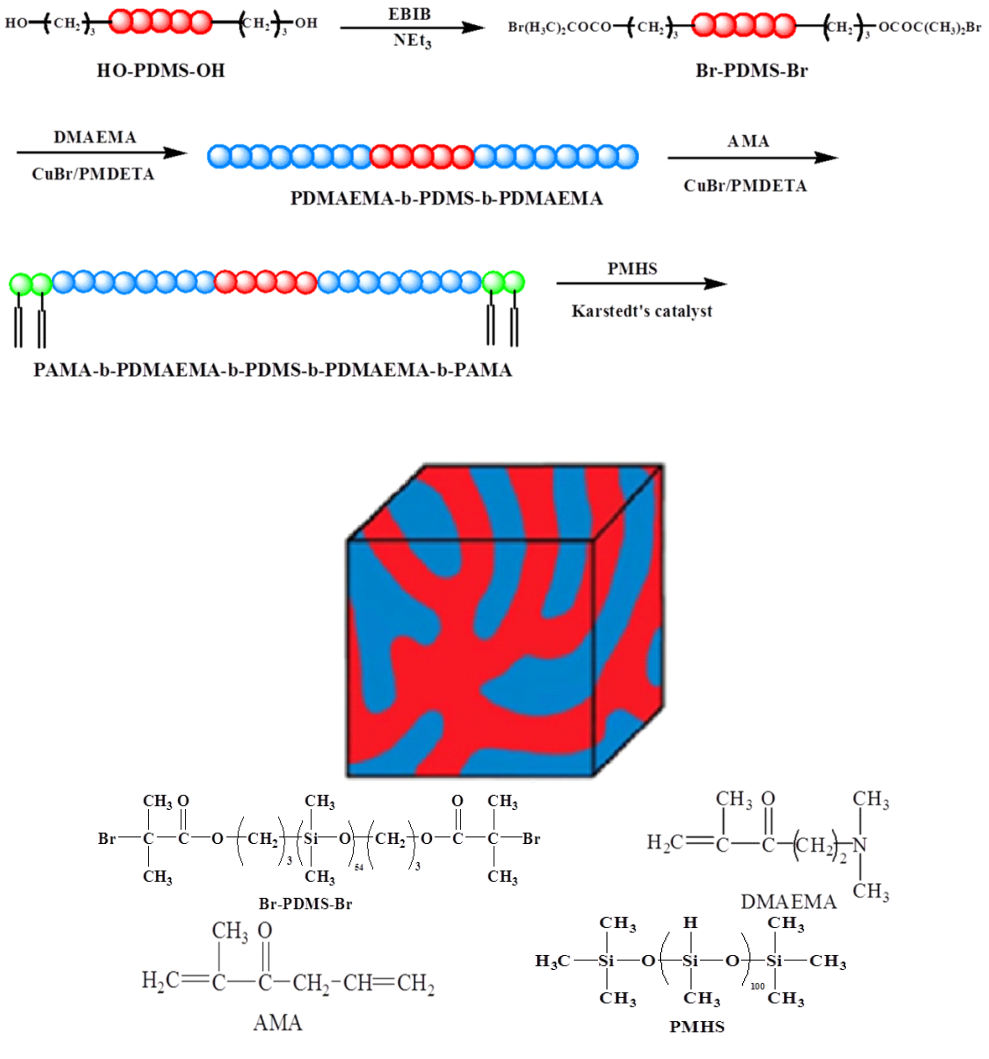
Synthesis of PDMAEMA-b-PDMS-b-PDMAEMA Triblock Copolymers. A series

of triblock copolymers were synthesized by ATRP. In a typical experiment, Br-PDMS-Br macroinitiator (1.00 g, 0.25 mmol), PMDETA (0.865 g, 0.5 mmol) and CuBr (0.072 g, 0.5 mmol) were added to a Schlenk flask (100 mL) equipped with a magnetic stirring bar and degassed three times. DMAEMA (7.85 g, 50 mmol) and isopropanol (15 mL) were then injected into the reaction flask. The flask was placed in a thermostated bath at 60 °C for 12 h. The mixture was then diluted in THF and passed through a basic alumina column to remove the copper residue and evaporated until dry. The crude product was redissolved in THF and precipitated in cold hexane twice, prior to being dried for 24 h in a vacuum oven. ^{1}H NMR (400 MHz, $CDCgl_3$, Me_4Si, δ)： 0.00 (m, 6H), 0.079 (s, 6H, $Si(CH_3)_2$), 1.1-0.94 (3H, m, $CH_2C(CH_3)CO$), 1.9-2.0 (m, 2H, $CH_2C(CH_3)CO$), 2.35 (m, 6H, $N(CH_3)_2$), 2.75 (m, 2H, $COCH_2CH_2N(CH_3)_2$), 4.13 (m, 2H, $COCH_2CH_2N(CH_3)_2$

Synthesis of PDMS-Based Pentablock Copolymers. The pentablock copolymers was synthesized using a molar feed ratio [AMA (0.6 g)]:[CuBr]:[PMDETA] of 50:1:1 in 8 mL isopropanol at 60 °C involved of 2 g triblock polymers for 18 h. The operations were used the same procedures as described above. ^{1}H NMR (400 MHz, $CDCgl_3$, Me_4Si, δ)： 0.00 (m, 6H), 0.079 (s, 6H, $Si(CH_3)_2$), 1.1-0.94 (3H, m, $CH_2C(CH_3)CO$), 1.9-2.0 (m, 2H, $CH_2C(CH_3)CO$), 2.35 (m, 6H, $N(CH_3)_2$), 2.75 (m, 2H, $COCH_2CH_2N(CH_3)_2$), 4.13 (m, 2H, $COCH_2CH_2N(CH_3)_2$, 4.46 (m, 2H, OCH_2CHCH_2), 5.30 (m, 1H, CH_2CHCH_2, allyl), 5.9 (m, 2H, CH_2CHCH_2, allyl).

Synthesis of Amphiphilic Conetworks. PAMA-b-PDMAEMA-b-PDMS-b-PDMAEMA-b-PAMA (1 g), PMHS (0.1 g) and Karstedt's catalyst (50 uL) was

dissolved in 20 mL toluene and the mixture was stirred at room temperature for 12 h. Then the homogeneous solution was poured into a Teflon mold (3×3cm) and placed in an oven at 60 ˚C for 24 h. After crosslinking, the formed film was extracted by THF, and dried in vacuo at room temperature.



Scheme1 Schematic diagram illustrating the preparation of pentablock copolymer via ATRP and crosslinking APCNs with PMHS.

Characterization Techniques

Proton Nuclear Magnetic Resonance Spectroscopy. ^{1}H NMR spectra was performed at room temperature on a Bruker Avance 400 instrument using $CDCl_3$

solutions with tetramethylsilane (TMS) as an internal standard.

Fourier Transform Infrared Spectroscopy. FT-IR spectra were obtained with a Nicolet Instrument Nicolet 8700 spectrometer. The sample was dispersed in a KBr disk.

Gel Permeation Chromatography. GPC was performed on a BI-MwA Gel Permeation Chromatography (Waters, Milford, MA), equipped with a light scattering instrument (Brookhaven, Holtsville, NY) at room temperature, using THF as the eluent at a flow rate of 0.8 mL/min with a polystyrene standard as the reference.

Determination of the Sol Fraction. The sol fraction was determined by extracting a freshly synthesized APCN with THF for 72 h. The sol fraction was calculated as the ratio of the mass of the extractable mixture divided by the mass of virgin conetwork.

$$Sol = \frac{m_0 - m_q}{m_0} \times 100\%$$

Where m_q is the dry mass of the extracted samples and m_0 is the dry mass of the virgin sample.

Measurement of the Swelling Ratio. Swelling experiments were carried out at room temperature by immersing a pre-weighed sample in an excess of distilled water, THF, hexane and aqueous solutions of various pHs, respectively. The extent of swelling was determined by periodically taking the samples from the solvent, removing the solvent adsorbed to the surfaces by blotting with tissue paper, and weighing equilibrium swelling ratio (S_w) was recorded when the weight of the swollen samples remained unchanged for 48 h. The swelling ratio was calculated as following equation:

$$S_w = \frac{m_t - m_0}{m_0} \times 100\%$$

Where m_t is the mass of the swollen samples and m_0 is the mass of the dry sample.

Measurement of the Degree of Ionization. The degree of ionization of APCN was calculated as the ratio of added HCl equivalents divided by the number of DMAEMA unit equivalents (calculated from the conetwork dry mass and conetwork composition) present in the sample. The acid titration curves were obtained by plotting the calculated degrees of ionization against the measured solution pH.

Tensile Strength and Elongation at Break. The tensile strength and elongation at a break of APCN were measured by Universal Testing Machine (KEXIN, WDW3020, China) in water-swollen state. The samples were formed into rectangles (6×2 cm) and the tensile speed was set at 10 mm/min. Each sample was measured three times, respectively, and the average value was obtained. The error is less than 5%.

Oxygen Permeability. Apparent oxygen permeability of APCN was determined at 35 ℃. The instrument used together with specifications and the operational principle were described in detail.[47] To obtain comparable results with different compositions, the membranes were of the same dimensions (4 cm × 4 cm × 0.2 mm) and measurements were carried out under the same conditions.

Atomic Force Microscopy. AFM images were recorded with a Veeco Dimension Icon Scanning Probe Microscope (Veeco Instruments) in tapping mode using silicon cantilevers from Mikromasch USA with resonance frequencies of about 160 kHz, spring constants of 10.0 N/m.

Loading and in vitro release of drug. The dried APCNs were immersed in 30 mL

aqueous solution of Rhodamine 6G (20 mg/ mL) at room temperature for 72 h. Then the samples swollen to equilibrium were taken out and washed with water to remove the drug residued on the surface. The APCNs loaded with drugs were dried under vacuum for 2 days. These samples were available for drug release experiments without any further treatment. The amounts of drug loading in the conetworks were estimated in an indirect way. Rhodamine 6G in the conetworks exhibited the same molar absorption coefficient (530 nm) in the UV spectra as the free drugs. The amount of drug loading and encapsulation effciency were calculated as following equation.

$$\text{durg loading (ug/g)} = \frac{(C_0 - C_t)V}{M}$$

$$\text{encapsulation efficiency (\%)} = \frac{(C_0 - C_t)V}{m}$$

Where C_0 and C_t are concentrations at different time (ug/mL), V is the volume of solution (mL), M is the weight of the conetwork (g), m is the weight of drug in feed (ug).

In vitro release studies were performed in water. The samples loaded with the drug were immersed in 50 mL water at pH 7.4 and 5.2, respectively. 3 mL of the solution was withdrawn from the release medium at intervals and replaced with 3 mL fresh water. The cumulative percentage of drug release was calculated as the average of three determinations and the standard deviations did not exceed 3%.

Results and Discussion

Scheme 1 illustrates the synthetic strategy for a novel family of APCNs. The first step is the synthesis of PDMS macroinitiator by coupling commercially available

hydroxypropyl polydimethylsiloxane with 2-bromoisobutyryl bromide. As far as PDMS-based copolymer is concerned there are few reports of controlled synthesis of amphiphilic block copolymers. Thus Meier et al. reported the synthesis of PDMS-based amphiphilic block copolymers via ATRP using PDMS-based macroinitiator.[48] Haddleton and co-workers reported the control synthesis of PDMS-based triblock copolymers.[49] Here, a triblock copolymer PDMAEMA-b-PDMS-b-PDMAEMA was synthesized via ATRP of DMAEMA using Br-PDMS-Br macroinitiators and CuBr/PMDETA catalyst system. The synthesis of pentable block copolymer with allyl groups on ends is the key for preparation of well-defined amphiphilic conetworks, therefor, the incorporation of AMA segment through ATRP using PDMAEMA-b-PDMS-b-PDMAEMA macroinitiator produced pentablock copolymer with well-defined molecular weight and narrow molecular weight distribution. AMA has a conjugated methacrylic and an unconjugated allylic group. The former group has higher reactivity to form copolymers with allyl pendant groups. The present research concerns the synthesis of APCNs by combining amphiphilic pentablock copolymers with the polymethylhydrosiloxane (PMHS) through hydrosilylation. There exists an average of 100 Si-H pendant bonds per PMHS chain available for hydrosilylation, which means that the PDMAEMA-b-PDMS-b-PDMAEMA acts as cross-linker for the PMHS chains. Therefore, the important difference between the conetworks obtained by free radical copolymerization of functional macromonomers and the present work is the specific average chain length and relatively narrow molecular weight distribution of the PAMA-b-PDMAEMA-b-PDMS-b-PDMAEMA-b-PAMA

chains in comparison with the broad distribution of the cross-linked chains in the conetworks prepared by conventional free radical copolymerization of telechelic macromonomers with low molecular weight monomers.

Polymer Synthesis

Well-defined PDMAEMA-b-PDMS-b-PDMAEMA triblock copolymers and PAMA-b-PDMAEMA-b-PDMS-b-PDMEMA-b-PAMA pentablock copolymers are summarized in Table 1. The triblock copolymers with different block lengths of PDMAEMA were synthesized by varying the reaction time. As the reaction time is increased from 12 to 24 h, M_n of the copolymer is increased from 13400 to 31000. The PDI of the triblock copolymers is increased only slightly from 1.18 to 1.24 and their GPC traces are all symmetrical monomodal (Figure 1), which indicates that no side-reactions occurred during the polymerizations. The relative wide PDI of PDMS macroinitiator, i.e.1.41, does not influence the low PDI of the resulting copolymer, which narrows down with increasing PDMAEMA chain length, indicating that the polymerization of DMAEMA proceeds in a controlled manner. As ATRP process occurs at a rate balance between activation (K_{act}) and deactivation (K_{deact}), the rate of reaction is not as high as radical polymerization reaction. When the conversion reaches a high level, the rate of propagation is slowed down considerably, the rate of any side reaction increases, leading to an increasing PDI of the final polymer. Pentablock copolymers were synthesized by ATRP using triblock copolymers as the macroinitiators. However, the chain length of triblock copolymers influences the activity of alkyl halide chain ends, the larger molecular weight of triblock copolymer

is, and the lower activity of alkyl halide is. Therefore, the number of AMA repeat units in the pentablock copolymers decreases with increasing PDMAEMA chain length, i.e. 40, 34 and 26, respectively. The PDI of the pentablock copolymers remain almost the same as the triblock copolymers, indicating the polymerization is controllable.

Table 1 Characterization of the PDMAEMA-b-PDMS-b-PDMEMA triblock copolymers and PAMA-b-PDMAEMA-b-PDMS-b-PDMEMA-b-PAMA pentablock copolymers synthesized by ATRP.

polymer structure[a,]	reaction Time (h)	$M_{n,cal}$[b] (kDa)	$M_{n,NMR}$[c] (kDa)	$M_{n,GPC}$[d] (kDa)	PDI
D_{30}-b-P_{54}-b-D_{30}	12	14.0	13.4	17.8	1.20
D_{61}-b-P_{54}-b-D_{61}	18	18.8	23.2	23.4	1.18
D_{86}-b-P_{54}-b-D_{86}	24	30.7	31.0	35.8	1.24
A_{20}-b-D_{30}-b-P_{54}-b-D_{30}-b-A_{20}	18	17.2	18.5	20.8	1.26
A_{17}-b-D_{61}-b-P_{54}-b-D_{61}-b-A_{17}	18	25.3	27.5	31.5	1.21
A_{13}-b-D_{86}-b-P_{54}-b-D_{86}-b-A_{13}	18	32.8	34.3	37.9	1.33

[a]D, DMAEMA; P, PDMS; A, AMA. The subscript means the number of the unit, calculated from the NMR.

[b]Calculated from ^{1}H NMR based on PDMS unit (6H at 0.09 ppm) , DMAEMA unit (2H at 4.1 ppm) , AMA unit (2H at 4.5 ppm).

[c]Determined by GPC measurement using polystyrene standards.

[d]Theoretical M_n= [monomer]/[initiator] × (monomer conversion) × (monomer molecular weight) + (initiator molecular weight).

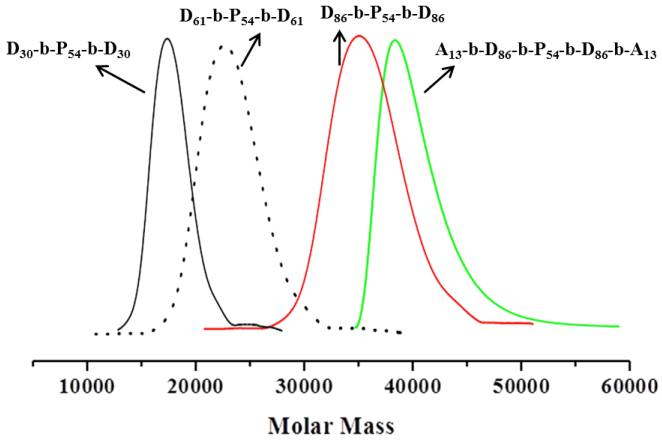
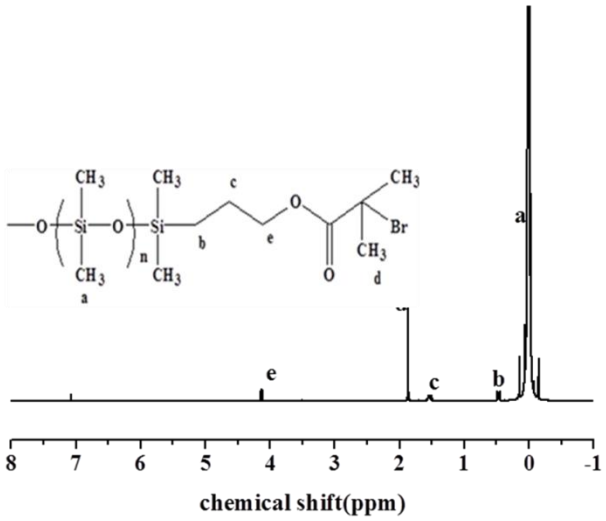


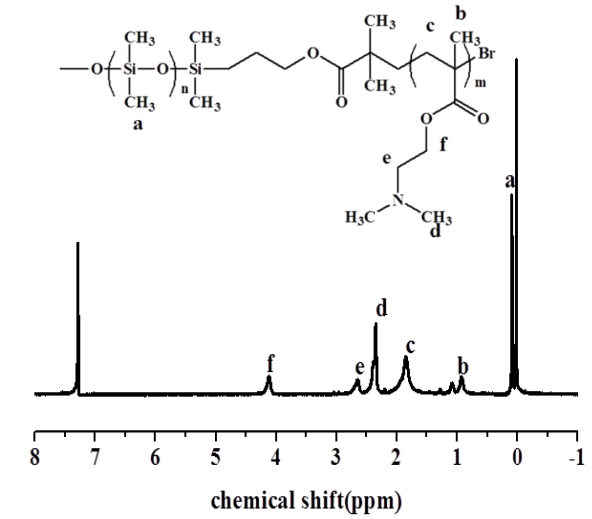
Figure 1. GPC traces of D_x-b-P_{54}-b-D_x triblock copolymers and A_{13}-b-D_{76}-b-P_{54}-b-D_{76}-b-A_{13} pentablock copolymer. D, P and A are further abbreviations for DMAEMA, PDMS and AMA, respectively. The subscript means the number of repeat units.

The compositions of the copolymers were first determined by ^{1}H NMR. Figure 2 (a) shows the ^{1}H NMR spectrum of the Br-PDMS-Br macroinitiator. The chemical shift at 1.92 ppm is assigned to the protons (d, BrC(C*H*$_3$)$_2$) of the 2-bromoisobutyryl groups. The chemical shift at 4.12 ppm is attributed to the protons adjacent to the oxygen moiety (e, OC*H*$_2$). From the area ratio of peak d and peak e, the extent of halogenation in the Br-PDMS-Br macroinitiator is determined to be 90.8%. Figure 2 (b) and (c) shows the ^{1}H NMR spectra of PDMAEMA$_{30}$-b-PDMS$_{54}$-b-PDMAEMA$_{30}$ and PAMA$_{20}$-b-PDMAEMA$_{30}$-b-PDMS$_{54}$-b-PDMAEMA$_{30}$-b-PAMA$_{20}$, respectively. The signals at 2.35, 2.63 and 4.12 ppm are mainly assigned to the methylene (d, NC*H*$_2$) and methyl (e, N(C*H*$_3$)$_2$) and methylene (f, COOC*H*$_2$) protons of the DMAEMA units. The chemical shifts at 4.50, 5.32 and 5.89 ppm correspond to the protons in allyl group of the AMA units, indicating the successful incorporation of

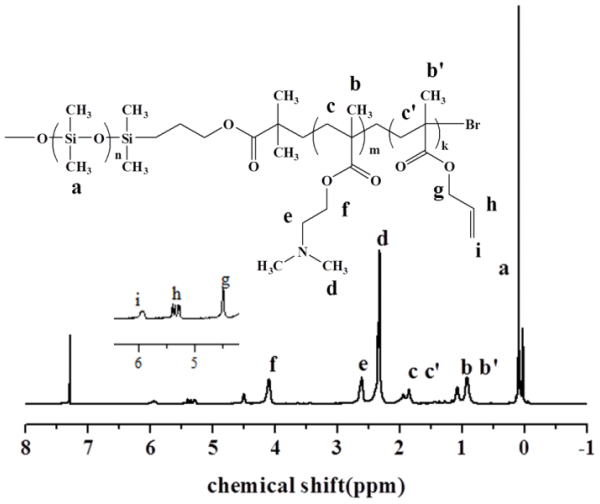
AMA. To further confirm the structure of copolymer, FT-IR measurement is utilized to characterize the block copolymer. Figure 3 shows the FT-IR spectras of D_{30}-b-P_{54}-b-D_{30} and A_{20}-b-D_{30}-b-P_{54}-b-D_{30}-b-A_{20}, respectively, where the three strong tertiary amide absorption bands at about 2825cm^{-1}, 2764 cm^{-1}, 1266cm^{-1} are associated with the DMAEMA block. The intensities of peak at about 1736 cm^{-1} increased significantly with the incorporation of AMA. The characteristic band of the AMA component at about 1640 cm^{-1} is observed in the FT-IR spectra of the A_{20}-b-D_{30}-b-P_{54}-b-D_{30}-b-A_{20}.



a



b



c

Figure 2. The ^{1}H NMR spectra of the (a) Br-PDMS-Br; (b) D_{61}-b-P_{54}-b-D_{61}; (c) A_{17}-b-D_{61}-b-P_{54}-b-D_{61}-b-A_{17} in CCl_3D.

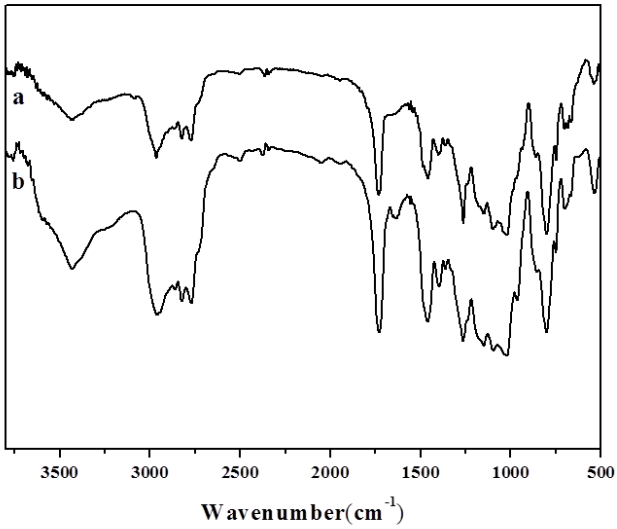


Figure 3. The FT-IR spectra of the (a) D_{61}-b-P_{54}-b-D_{61} and (b) A_{17}-b-D_{61}-b-P_{54}-b-D_{61}-b-A_{17}

Characterization of the APCNS

Sol Fraction of the Conetworks. Table 2 shows the compositions of APCNs and the sol fraction extracted from each conetwork. In all cases the sol fraction was relatively low, with the lowest value being as low as 4.5% and the highest 8.5%, indicating essentially complete crosslinking and control over the conetwork structure.

Table 2 Fabrication composition of conetworks and corresponding sol fraction percentage and thickness.

sample	block used (g)	PMHS crosslinker (g)	total DMAEMA (w %)	sol fraction (w/w %)	thickness (mm)
APCN-1	0.56	0.30	33.2	4.5	0.20 ± 0.02
APCN-2	0.80	0.30	50.7	6.3	0.19 ± 0.03
APCN-3	0.97	0.30	60.1	8.5	0.20 ± 0.04

Characterization of the Degree of Swelling of the APCNs. One of the most attractive characteristics of APCN is its property in different solvents due to the

existence of both HO and HI phases in conetworks. Figure 4 shows the S_w of APCN-3 in THF, neutral water and hexane. THF is a good solvent for both PDMS and DMAEMA, which APCN can fully swell. In contrast to THF, pure water is a good solvent for DMAEMA but poor for PDMS and AMA units, leading to lower S_w in neutral water than in THF. Figure 4(c) shows the swelling ratios of APCNs in hexane, which is a good solvent for PDMS and AMA but poor for DMAEMA. The S_w value of APCN-3 in hexane is smaller than that in neutral water as APCN-3 has more hydrophilic phase than hydrophobic phase.

Figure 5 shows both the degree of swelling and the calculated degree of ionization of APCN-3 against the solution pH. The S_w increased as the pH decreased. Because the DMAEMA units become protonated at low pH, which resulted in the establishment of an osmotic pressure within the conetwork from the counterions to the charged DMAEMA units and creation of electrostatic repulsions between the polymer chains.[31] The degrees of swelling and the calculated degrees of ionization of APCN-1 and APCN-2 have the same changing trend as the APCN-3. And the APCNs do not start to swell at the same pH, which influenced by their composition.

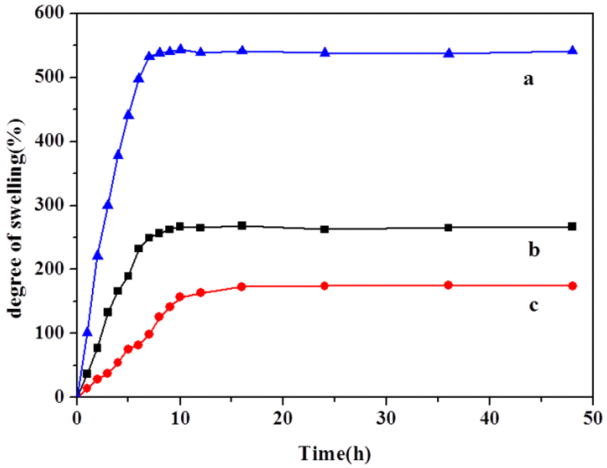


Figure 4. Degrees of swelling of APCN-3 in (a) THF, (b) H_2O and (c) hexane

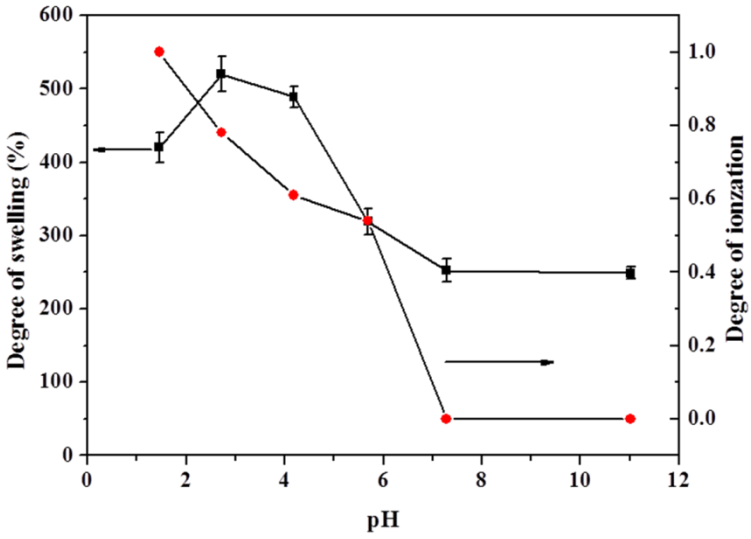


Figure 5. Aqueous degree of swelling and degree of ionization of the APCN-3 as a function of the solution pH

Effective pK_as of the conetworks. The effective pK_a values of the DMAEMA units in the conetworks were taken from Figure 5 and presented in Table 3. The pK_a of PDMAEMA is approximately 8, while the effective pK_a values of the DMAEMA units in all conetworks were significantly lower, at a range from 5.2 to 5.8, which is attributed to the polyelectrolyte effect, Donnan equilibrium and the reduction of the

conetwork dielectric constant induced by the presence of the hydrophobic units.[31] This phenomenon shows similar tendency with other conetwork studies.[31, 36]

Table 3 pK_as of the DMAEMA Monomer Repeating Units in the End-Linked Conetworks

sample	pK_a
APCN-1	5.2
APCN-2	5.7
APCN-3	5.8

Mechanical Properties of the Conetworks. As shown in Figure 6, the tensile strengths of all the APCNs exceed 1 MPa at water-swollen state, which are 3 times to other conetwork that contained DMAEMA and ε-caprolactone (CL) through ATRP reported in the literature, i.e., 0.37 MPa.[50] This phenomenon is mainly contributed to the existence of PDMS phase, which reinforced the hydroplilic PDMAEMA phase. Meanwhile, ATRP avoids the formation of inhomogeneity throughout the conetwork structure as usually encountered with an uncontrolled polymerization. Figure 6 shows a decrease in tensile strength and an increase in elongation ratio with increasing PDMAEMA block length into APCN.

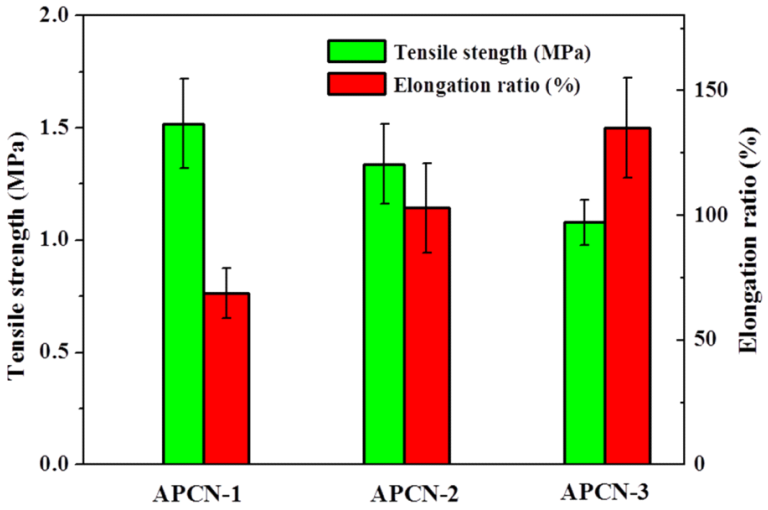


Figure 6. The mechanical properties of all APCNs.

Oxygen Permeability. High oxygen permeability is a key requirement for a biological device and we focus on this requirement when constructing the APCN. Figure 7 shows the apparent oxygen permeability of water-swollen PDMAEMA$_x$-*b*-PDMS$_{54}$-*b*-PDMEMA$_x$/PMHS membranes as a function of PDMAEMA segment chain length. The data are collected by using 0.2 mm thick membranes and the boundary layer effect is not taken into account. Therefore, the true permeability is slightly higher than those test values.

As shown in Figure 7, oxygen permeability is decreased from 420 to 181 barrers by increasing the PDMAEMA content from 33 to 61 %. This trend is not surprising in view of the high gas permeability of PDMS and low oxygen permeability of hydrogels. It is noteworthy that the oxygen permeability of the present APCN, even those containing relatively large amounts of PDMAEMA, are similar to the best commercial extended-wear soft contact lenses, i.e. 195±4 barrers.[51] Therefore, the resulting APCNs exhibit very high oxygen permeability.

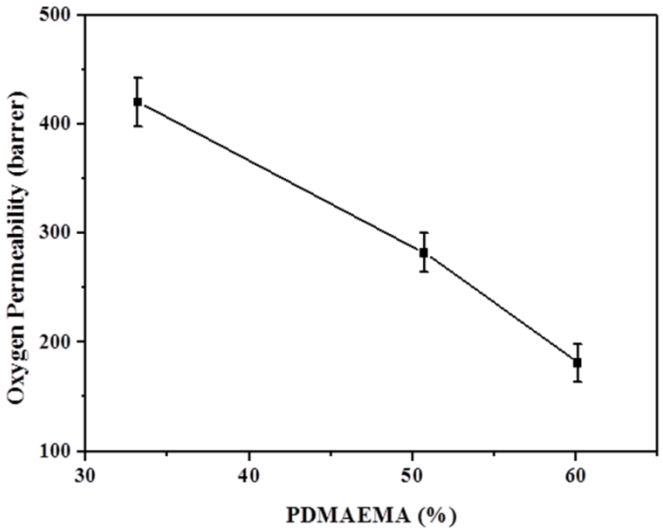


Figure 7. Oxygen permeability of APCNs as a function of PDMAEMA content (1barrer = 10^{-11} (cm2/s)(mL of O2 (STP))/(mL mmHg).

Atomic Force Microscopy. Atomic force microscopy (AFM) was used to visually investigate the morphology of the APCNs. Figure 8 displays the AFM images (phase mode) of the surface of the conetworks, which depicting the nanoscale phase separation. The soft PDMS appears darker. Brighter structures are related to the brittle PDMAEMA. It is obviously that APCN-3 has larger brighter domain than the APCN-1, which is in agreement with the fact that APCN-3 has a higher HI content.

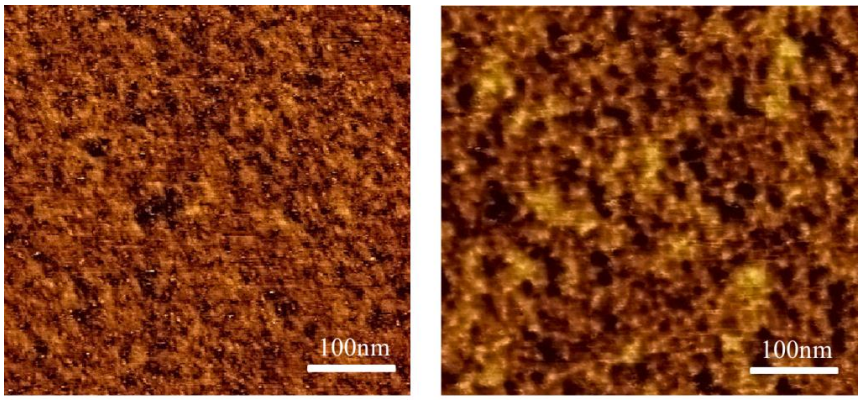


Figure 8. AFM phase mode images on surface of APCN-1 and APCN-3. In the

tapping mode, PDMS shows dark and DMAEMA show light.

In Vitro Drug release Studies. The DMAEMA-based hydrogels and APCNs have been widely explored as a drug carrier.[25,26,52] Herein, a highly water-soluble dye, Rhodamine 6G was used for loading and in vitro release from the prepared APCNs. Table 4 shows the amount of drug loading and encapsulation effciency of the APCNs. The results shows a similar drug loading levels of APCNs, indicating that the drug loading levels is dominated by the swelling ratio (S_w) of the APCNs rather than the hydrophilic (HI) / hydrophobic (HO) composition. The larger S_w of APCNs allows more Rhodamine 6G solution encapsulation, and thus a higher drug loading levels.

Table 4 Drug loading levels and encapsulation effciency of APCNs

sample	weight of samples (g)	drug loading (%)	encapsulation efficiency (%)
APCN-1	0.33	2.2	1.2
APCN-2	0.55	5.3	4.8
APCN-3	0.54	7.1	6.4

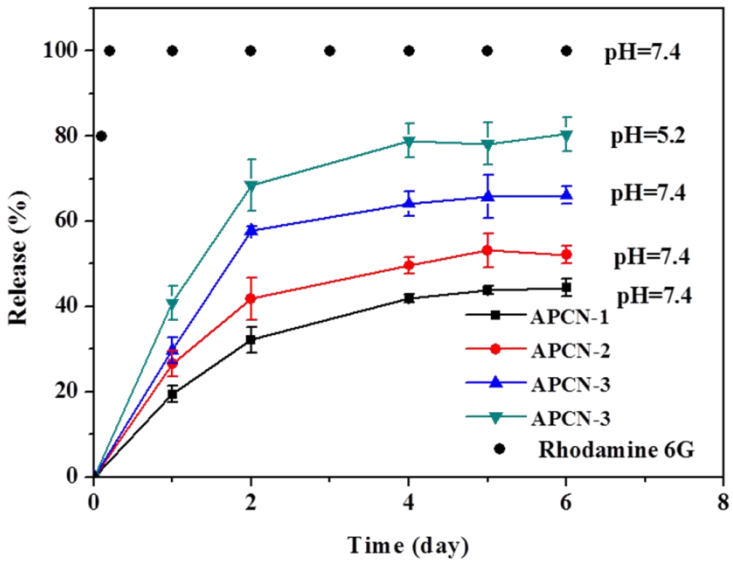


Figure 9. Release kinetics of Rhodamine 6G from loaded APCNs

Figure 9 present the dissolution profile of pure Rhodamine 6G with a concentration of 0.2 g/L and Rhodamine 6G in vitro release profiles from contworks with different pHs. It can be clearly seen that the pure drug is completely released in water in 10 minutes, which accounts for the dissolution procedure of the drugs. But all three contworks are able to control the Rhodamine 6G release. APCN-3 exhibits a relatively faster drug release rate than APCN-1and APCN-2 in water (pH=7.4). Rhodamine 6G release is facilitated by the swelling behavior of conetworks with the diffusion as the driving force. APCN-3 has a high HI content, high S_w in water, which presents a fast drug release profile. And APCN-3 has less cross-linking point than APCN-1 and APCN-2, which also increases the drug release efficiency.

APCN-3 was chosen for a pH-triggered release study. Figure 9 shows the pH-sensitive drug release behavior of APCN-3 in pH 7.4 and pH 5.2 respectively, where APCN-3 in acid buffer (pH=5.2) has a faster drug release profile, which is 15 percent more than in the neutral buffer (pH=7.4). At low pH, the DMAEMA units become protonated, leading to an increase in hydrophilicity of polymer chains, which facilitated drug escape from conetworks. Overall, the result shows that these conetworks respond to pH stimuli to control drug release.

Conclusions

Conclusively, we have described the synthesis of PDMAEMA-involved amphiphilic conetworks through cross-linking of amphiphilic pentablock copolymers via ATRP with well-defined molecular weight and narrow polydispersity. The APCNs

exhibit unique pH-responsive swelling behavior, excellent mechanical properties, outstanding oxygen permeability and phase separation, which can be regulated via precise control of molecular structure and tunable HI/HO composition. The APCNs are suitable for controlled release of Rhodamine 6G, where the release rate can be regulated by varying the HI composition, cross-linking density and the pH of media. The ability of these APCNs to adsorb and desorb solutes in a controlled manner upon triggering the pH in aqueous media, may allow for their potential application as a carrier for controlled release.

Acknowledgments

This work was financially supported by National Science Foundation (NSF51103019, NSF21174027) and National High technology Research and Development Projects (863, 2012AA03A605). Program for New Centure Excellent Talents in University (12X10623).

Notes and References

[a] State Key Laboratory for Modification of Chemical Fibers and Polymer Materials, College of Materials Science and Engineering, Donghua University, 2999 North Renmin Road, songjiang District,Shanghai, 201620, P. R. China.

E-mail: chunjuhe@dhu.edu.cn

1 G. Erdodi and J. P. Kennedy, Amphiphilic Conetworks: Definition, Synthesis, Applications, *Prog. Polym. Sci.*, 2006, **31**, 1-18.

2 P. Papaphilippou, M. Christodoulou, O. M. Marinica, A. Taculescu, L. Vekas, K. Chrissafis and T. Krasia-Christoforou, Multiresponsive Polymer Conetworks Capable of Responding to Changes in pH, Temperature, and Magnetic Field: Synthesis, Characterization, and Evaluation of Their Ability for Controlled Uptake and Release of Solutes, *ACS Appl. Mater. Interfaces*, 2012, **4**, 2139-2147.

3 G. Kali, S. Vavra, K. László and B. Iván, Thermally Responsive Amphiphilic Conetworks and Gels Based on Poly(N-isopropylacrylamide) and Polyisobutylene, *Macromolecules*, 2013, **46**, 5337-5344.

4 C. Zhou, S. Qian, A. Zhang, L. Xu, J. Zhu, Z. Cheng, K. En-Tang, F. Yao and G. D. Fu, A Well-Defined Amphiphilic Polymer Co-network from Precise Control of the End-Functional Groups of Linear RAFT Polymers, *RSC Adv.*, 2014, **4**, 8144-8156.

5 P. C. Nicolson and J. Vogt, Soft Contact Lens Polymers: An Evolution, *Biomaterials*, 2001, **22**, 3273-3283.

6 J. K .Xu, X. S. Li and F. Q. Sun, In Vitro and in Vivo Evaluation of Ketotifen Fumarate-Loaded Silicone Hydrogel Contact Lenses for Ocular Drug Delivery, *Drug Delivery*, 2011, **18**, 150-158.

7 Y. P. Wang, J. A. Finlay, D. E. Betts, T. J. Merkel, J. C. Luft, Callow, J. A. Callow and J. M. DeSimone, Amphiphilic Co-networks with Moisture-induced Surface Segregation for High-erformance Nonfouling Coatings, *Langmuir*, 2011, **27**, 10365-10369.

8 J. Kang, G. Erdodi, J. P. Kennedy, H. Chou, L. Lu and S. Grundfest-Broniatowski,

Toward a Bioartificial Pancreas: Diffusion of Insulin and IgG Across Immunoprotective Membranes with Controlled Hydrophilic Channel Diameters, *Macromol. Biosci.*, 2010, **10**, 369-377.

9 S. Grundfest-Broniatowski, G. Tellioglu, K. S. Rosenthal, J. Kang, G. Erdodi, B. Yalcin, M. Cakmak, J. Drazba, A. Bennett, L. Lu and J. P. Kennedy, A New Bioartificial Pancreas Utilizing Amphiphilic Membranes for the Immunoisolation of Porcine Islets: A Pilot Study in the Canine, *ASAIO J.*, 2009, **55**, 400-405.

10 Y. Sun, J. Collett, N. J. Fullwood, S. M. Neil and S. Rimmer, Culture of Dermal Fibroblasts and Protein Adsorption on Block Conetworks of Poly(butyl methacrylate-*block*-(2,3 propandiol-1-methacrylate-*stat*-ethandiol dimethacrylate)), *Biomaterials*, 2007, **28**, 661-670.

11 B. Iván, J. P. Kennedy and P. W. Mackey, Amphiphilic Networks: Synthesis and Characterization of, and Drug Release from Poly(N,N-dimethylacrylamide)-*l*-polyisobutylene. *ACS Symp. Ser.*, 1991, **469**, 194-202.

12 I. Schoenfeld, S. Dech, B. Ryabenky, B. Daniel, B. Glowacki, R. Ladisch and J. C. Tiller, Investigations on Diffusion Limitations of Biocatalyzed Reactions in Amphiphilic Polymer Conetworks in Organic Solvents, *Biotechnol. Bioeng.*, 2013, **110**, 2333-2342.

13 Y. Yuan, A. K. Zhang, J. Ling, L. H. Yin, Y. Chen and G. D. Fu, Well-defined Biodegradable Amphiphilic Conetworks, *Soft Matter*, 2013, **9**, 6309-6318.

14 S. Meskath, G. Urban and J. Heinze, A New Optochemical Chlorine Gas Sensor Based on the Application of Amphiphilic Co-networks as Matrices, *Sensors and*

Actuators B, 2011, **151**, 327-332.

15 P. M. Imbesi, J. A. Finlay, N. Aldred, M. J. Eller, S. E. Felder, K. A. Pollack, A. T. Lonnecker, J. E. Raymond, M. E. Mackay, E. A. Schweikert, A. S. Clare, J. A. Callow, M. E. Callowc and K. L. Wooley, Targeted Surface Nanocomplexity: Two-dimensional Control over the Composition, Physical Properties and Anti-biofouling Performance of Hyperbranched Fluoropolymer-poly(ethylene glycol) Amphiphilic Crosslinked Networks, *Polym. Chem.*, 2012, **3**, 3121-3131.

16 P. Kurian and J. P. Kennedy, Novel Tricontinuous Membranes for Immunoisolation. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)*, 2002, **43**, 631-632.

17 J. Scherble, B. Iván and R. Mülhaupt, Online Monitoring of Silicone Network Formation by Means of In-situ Mid-infrared Spectroscopy, *Macromol. Chem. Phys.*, 2002, **203**, 1866-1871.

18 K. Süvegh, A. Domján, G. Vankó, B. Iván and A. Vértes, Free Volume and Swelling Dynamics of Poly[2-(dimethylamino)ethyl methacrylate]-*l*-polyisobutylene Amphiphilic Network by Positron Annihilation Investigations, *Macromolecules*, 1998, **31**, 7770-7775.

19 I. Schoenfeld, S. Dech, B. Ryabenky, B. Daniel, B. Glowacki, R. Ladisch and J. C. Tiller, Investigations on Diffusion Limitations of Biocatalyzed Reactions in Amphiphilic Polymer Conetworks in Organic Solvents, *Biotechnol. Bioeng.*, 2013, **110**, 2333-2342.

20 A. S. Lee, A. P. Gast, V. Bultuln and S. P. Armes, Characterizing the Structure of

PH Dependent Polyelectrolyte Block Copolymer Micelles, *Macromolecules*, 1999, **32**, 4302-4310.

21 S. Kikuchi, Y. Chen, K. Fuchise, K. Takada, J. Kitakado, S. Sato, T. Satoh and T. Kakuchi, Thermoresponsive Properties of 3-, 4-, 6-, and 12-armed Star-shaped Poly[2-(dimethylamino)ethyl methacrylate]s Prepared by Core-first Group Transfer Polymerization, *Polym. Chem.*, 2014, **5**, 4701-4709.

22 L. Besnard, M. Protat, F. Malloggi, J. Daillant, F. Cousin, N. Pantoustier, P. Guenoun and P. Perrin, Breaking of the Bancroft Rule for Multiple Emulsions Stabilized by a Single Stimulable Polymer, *Soft Matter.*, 2014, **10**, 7073-7087.

23 T. Traitel, Y. Cohen and J. Kost, Characterization of Glucose-sensitive Insulin Release Systems in Simulated in Vivo Conditions, *Biomaterials*, 2000, **21** , 1679-1687.

24 A. J. Convertine, C. Diab, M. Prieve, A. Paschal, A. S. Hoffman, P. H. Johnson and P. S. Stayton, pH-Responsive Polymeric Micelle Carriers for siRNA Drugs, *Biomacromolecules*, 2010, **11**, 2904-2911.

25 X. J. Zhang, S. Y. Lu, C. M. Gao, C. Chen, X. Zhang and M. Z. Liu, Highly Stable and Degradable Multifunctional Microgel for Self-regulated Insulin Delivery under Physiological Conditions, *Nanoscale*, 2013, **5**, 6498-6506.

26 V. Mishra, S. H. Jung, J. M. Park, H. M. Jeong and H. I. Lee, Triazole-Containing Hydrogels for Time-Dependent Sustained Drug Release, *Macromol.Rapid Commun.*, 2014, **35**, 442-446.

27 Y. L. Lo, G. J. Chen, T. H. Feng, M. H. Lia and L. F. Wang, Synthesis and

Characterization of S-PCL-PDMAEMA for Co-delivery of PDNA and DOX, *RSC Adv.*, 2014, **4**, 11089-11098.

28 X. J. Loh, S. J. Ong, Y. T. Tung and H. T. Choo, Dual Responsive Micelles Based on Poly[(R)-3-hydroxybutyrate] and Poly(2-(di-methylamino)ethyl methacrylate) for Effective Doxorubicin Delivery, Polym. Chem., 2013, 4, 2564-2574.

29 Y. Sui, X. L. Gao, Z. N. Wang and C. J. Gao, Antifouling and Antibacterial Improvement of Surface-functionalized Poly(vinylidene fluoride) Membrane Prepared via Dihydroxyphenylalanine-initiated Atom Transfer Radical Graft Polymerizations, *J. Membr. Sci.*, 2012, **394–395**, 107-119.

30 C. Y. Li, F. J. Xu, and W. T. Yang, Simple Strategy to Functionalize Polymeric Substrates via Surface-Initiated ATRP for Biomedical Application, *Langmuir*, 2013, **29**, 1541-1550

31 M. D. Rikkou, M. Kolokasi, K. Matyjaszewski and C. S. Patrickios, End-Linked Amphiphilic Polymer Conetworks: Synthesis by Sequential Atom Transfer Radical Polymerization and Swelling Characterization, *J. Polym. Sci., Part A: Polym. Chem.*, 2010, **48**, 1878-1886.

32 K. S. Pafiti, Z. Philippou, E. Loizou, L. Porcar, and C. S. Patrickios, End-Linked Poly[2-(dimethylamino)ethyl Methacrylate] Poly(methacrylic acid) Polyampholyte Conetworks: Synthesis by Sequential RAFT Polymerization and Swelling and SANS Characterization, *Macromolecules*, 2011, **44**, 5352-5362.

33 E. Loizou, A. I. Triftaridou, T. K. Georgiou, M. Vamvakaki, and C. S. Patrickios, Cationic Double-Hydrophilic Model Networks: Synthesis, Characterization,

Modeling and Protein Adsorption Studies, *Biomacromolecules*, 2003, **4**, 1150-1160.

34 M. D. Rikkou, E. Loizou, C. S. Patrickios and L. Porcar, Structural Characterization of Amphiphilic Polymer Conetworks End-linked with the Optimal Amount of Cross-linker, *Eur. Polym. J.*, 2010, **46**, 441-449.

35 T. K. Georgiou, C. S. Patrickios, P. W. Groh, B. Iván, Amphiphilic Model Conetworks of Polyisobutylene Methacrylate and 2-(Dimethylamino)ethyl Methacrylate Prepared by the Combination of Quasiliving Carbocationic and Group Transfer Polymerizations, *Macromolecules*, 2007, **40**, 2335-2343.

36 T. K. Georgiou and C. S. Patrickios, Synthesis, Characterization, and DNA Adsorption Studies of Ampholytic Model Conetworks Based on Cross-Linked Star Copolymers, *Biomacromolecules*, 2008, **9**, 574-582.

37 C. S. Patrickios and T. K.Georgiou, Covalent Amphiphilic Polymer Networks, *Curr. Opin. Colloid Interface Sci.*, 2003, **8**, 76-85.

38 G. Kali, S. Vavra, K. Laszlo and B. Iván, Thermally Responsive Amphiphilic Conetworks and Gels Based on Poly(N-isopropylacrylamide) and Polyisobutylene, *Macromolecules*, 2013, **46**, 5337-5344.

39 A. Domján, C. Fodor, S. Kovács, T. Marek, B. Iván and K. Süvegh, Anomalous Swelling Behavior of Poly(*N*-vinylimidazole)-*l*-poly(tetrahydrofuran) Amphiphilic Conetwork in Water Studied by Solid-State NMR and Positron Annihilation Lifetime Spectroscopy, *Macromolecules*, 2012, **45**, 7557-7565.

40 A. I. Triftaridou, D. Kafouris, M. Vamvakaki, T. K. Georgiou, T. C. Krasia, E.

Themistou, N. Hadjiantoniou and C. S. Paktrickios, Three Different Types of Quasi-Model Networks: Synthesis by Group Transfer Polymerization and Characterization, *Polym. Bull.*, 2007, **58**, 185-190.

41 W. J. Zhao, M. Fang, J. P. He, J. Y. Chen, W. Tang and Y. L. Yang, Amphiphilic Polymer Conetworks Prepared by Controlled Radical Polymerization Using a Nitroxide Cross-Linker, *J. Polym. Sci., Part A: Polym. Chem.*, 2010, **48**, 4141-4149.

42 J. F. Xu, M. Qiu, B. M. Ma and C. J. He, "Near Perfect" Amphiphilic Conetwork Based on End-Group Cross-linking of Polydimethylsiloxane Triblock Copolymer via Atom Transfer Radical Polymerization, *ACS Appl. Mater. Interfaces*, 2014, **6**, 15283-15290.

43 R. Karunakaran and J. P. Kennedy, Synthesis, Characterization, and Crosslinking of Methacrylate-telechelic PDMAAm-*b*-PDMS-*b*-PDMAAm Copolymers, *J. Polym. Sci., Part A: Polym. Chem.*, 2007, **45**, 4284-4290.

44 H. S. Abandansari, E. Aghaghafari , M. R. Nabida and H. Niknejad, Preparation of Injectable and Thermoresponsive Hydrogel Based on Penta-block Copolymer with Improved Sol Stability and Mechanical Properties, *Polymer*, 2013, **54**, 1329-1340.

45 K. Matyjaszewski and J. H. Xia, Atom Transfer Radical Polymerization, *Chem. Rev.*, 2001, **101**, 2921-2990.

46 R. N. Keller, H. D. Wycoff and L. E. Marchi, Copper(I) Chloride, *Inorg. Synth.*, 1946, **2**, 1-4.

47 G. Erdodi and J. P. Kennedy, Water-Swollen Highly Oxygen Permeable Membranes: Analytical Technique and Syntheses, *J. Polym. Sci., Part A: Polym. Chem.*, 2005, **43**, 3491-3501.

48 A. Car, P. Baumann, M. Chami, J. T. Duskey, N. Bruns, W. Meier, pH-responsive PDMS-b-PDMAEMA Micelles for Intracellular Anticancer Drug Delivery, *Biomacromolecules*, 2014, **15** , 3235-3245.

49 S. Bas and M. D. Soucek, Synthesis, Characterization and Properties of Amphiphilic Block Copolymers of 2-hydroxyethyl Methacrylate and Polydimethylsiloxane Prepared by Atom Transfer Radical Polymerization, *Polym. J. (Tokyo, Jpn.)*, 2012, **44**, 1087-1097.

50 L. Mespouille, J. M. Raquez, C. W. Frank and P. Dubois, in Controlled/Living Radical Polymerization: Progress in ATRP: Physical and Mechanical Properties of Amphiphilic and Adaptative Polymer Conetworks Produced by Atom Transfer Radical Polymerization, *ACS symposium series*, 2009, **1023**, 19.

51 M. Chhabra, J. M. Prausnitz and C. J. Radke, Polarographic Method for Measuring Oxygen Diffusivity and Solubility in Water-Saturated Polymer Films: Application to Hypertransmissible Soft Contact Lenses, *Ind. Eng. Chem. Res.*, 2008, **47**, 3540-3550.

52 F. J. Xu, E. T. Kang and K. G. Neoh, PH- and Temperature-responsive Hydrogels from Crosslinked Triblock Copolymers Prepared via Consecutive Atom Transfer Radical Polymerizations, *Biomaterials*, 2006, **27**, 2787-2797.