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Synthesis of Stimuli-sensitive Copolymers by RAFT Polymerization: Potential Candidates as Drug Delivery Systems

Marli L.Tebaldi[a]*, Debora Abrantes Leal[a], Sergio R. Montoro[b], Cesar Petzhold[c]

[a]Federal University of Itajubá – UNIFEI, Advanced Campus at Itabira, CEP 35903-087, Itabira, MG, Brazil
[b]Department of Chemical Engineering, School of Engineering of Lorena, University of São Paulo – USP, CEP 12602-810, Lorena, SP, Brazil
[c]Department of Organic Chemistry, Federal University of Rio Grande do Sul – UFRGS, CEP 91501-970, Porto Alegre, RS, Brazil

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Poly(2-(dimethylamino)ethylmethacrylate-*b*-methymethacrylate) (PDMAEMA-*b*-PMMA) poly(2-(dimethylamino)ethylmethacrylate-*b*-vinylcaprolactam-*b*-(2-(dimethylamino)ethyl methacrylate) (PDMAEMA-*b*-PVCL-*b*-PDMAEMA) and poly(vinylcaprolactam-*b*-(2-(dimethylamino) ethylmethacrylate-*b*-vinylcaprolactam) (PVCL-*b*-PDMAEMA-*b*-PVCL) block copolymers were obtained by reversible addition-fragmentation chain transfer (RAFT) polymerization, and the effect of the solution pH on the particle size was investigated. In the case of PDMAEMA-*b*-PMMA, PDMAEMA was first synthesized using 2-cyanoprop-2-yl dithiobenzoate (CPDB) as a chain transfer agent (CTA), which was subsequently used for the RAFT polymerization of MMA. The triblock copolymers were obtained using PDMAEMA or PVCL as macro-CTAs prepared using dibenzyl trithiocarbonate (DBTTC) as a bifunctional RAFT agent. The structure and formation of the copolymers was confirmed through ^{1}H NMR and SEC analysis. The particle size varied considerably depending on the pH of the aqueous solutions of copolymers indicating that these materials could be potential candidates for biomedical applications.

Keywords: *poly(dimethylaminoethyl methacrylate), reversible addition-fragmentation chain transfer (RAFT) polymerization, poly(methylmethacrylate), poly(vinylcaprolactam)*

1. Introduction

Amphiphilic copolymers have been used to fabricate a variety of particles with different characteristics for specific uses, particularly as vehicles for the controlled delivery of therapeutic agents. With regard to these polymers, there is particular interest in polymeric systems that can respond to small changes in the environment conditions, such as pH, temperature, ionic strength and light. These are called "smart" or "stimuli-sensitive" polymers and from a biomedical point of view the most important examples are those that respond to changes in pH and temperature (T)[1].

Temperature-sensitive polymers present amphiphilic characteristic in the chain structure and respond to small changes around the critical temperature, making the chains collapse or expand due to the hydrophilic and hydrophobic interactions in aqueous medium. On the other hand, pH-sensitive polymers are polyelectrolytes which carry in their structure acidic or basic groups and therefore accept or release protons in response to changes in the environmental pH. In addition, some materials can respond to two parameters simultaneously (pH and T), and these have a high potential for application in the biomedical field[2]. Of these polymers, PDMAEMA has attracted much attention due to its dual stimuli-responsive behavior. PDMAEMA is a cationic polymer that undergoes a structural transition below its pKa value and at its phase transition temperature (lower critical solution temperature, LCST), that is, at around 50 °C. By modifying the structure of these polymers it is possible reduce their pKa as well as their LSCT values in order to be compatible with physiological temperature and pH. The incorporation of hydrophobic comonomers into PDMAEMA should provide a decrease in the LCST as well as in the pKa values[3]. On the other hand, PVCL is a thermo-responsive, non-toxic, biocompatible polymer, and its LCST, which is just below human body temperature, can be adjusted with the incorporation of hydrophilic monomers[4]. Due to their important characteristics, there has recently been an increase in studies based on PVCL polymers, especially for biomaterial applications[5]. Several synthetic strategies have been used to obtain homo- and copolymers with defined compositions and versatile functional groups that can to act as coupling sites on the polymeric chains. Other modifications can also be carried out for the preparation of biomedical systems. Living/controlled radical polymerization procedures are suitable methods for obtaining homo- and copolymers with controlled molecular weight distributions and predefined architectures[6]. Of these living polymerization techniques, atom transfer

*e-mail: marlitebaldi@unifei.edu.br

radical polymerization (ATRP)[7] and RAFT[8] are generally considered to be the best strategies to obtain functional polymeric systems for defined applications. Amphiphilic copolymers based on PDMAEMA, such as PMMA-*b*-DMAEMA[3,9], PDMAEMA-*b*-PCL-*b*-PDMAEMA[10], PTFE-*co*-PDMAEMA[11], and PS-*b*-PDMAEMA[12], have been described, with the aim of studying self-assembly behavior at different solution pH values. The LCST of PMMA-*b*-PDMAEMA copolymers synthesized by RAFT was found to be affected by ionic strength, pH and the nature of the ion[3]. A series of copolymers with tunable pH transitions for gene delivery based on DMAEMA were synthesized via RAFT using PDMAEMA as a macro chain transfer agent (MCTA)[13]. Zhu et al.[12] showed that on adjusting certain parameters, such as the solvent, charge density and pH, specific changes in the structure of the aggregations can be obtained for PS-*b*-PDMAEMA copolymers obtained by ATRP. Xiao and others synthesized PMMA-*b*-PDMAEMA by ATRP and investigated the effects of PMMA or PDMAEMA block length on the aggregate formation[9]. However, studies related to new mechanisms of controlled polymerization of VCL are still scarce, due to several factors including the fact that VCL is an unconjugated monomer and its propagating radical is poorly stabilized and, as a consequence, very reactive. Thus, the living/controlled polymerization of VCL still requires optimization. Xanthates and dithiocarbamates are the most suitable CTAs for the RAFT polymerization of VCL[14]. In a previous study we synthesized triblock copolymers of P*t*BA-*b*-PVCL-*b*-P*t*BA obtained by RAFT polymerization using PVCL as a MCTA[4]. Shao et al.[15] synthesized PVCL by RAFT polymerization using trithiocarbonate or dithiocarbamate as CTAs and the former allowed better controlled over the polymerization. In this study, we synthesized new temperature and pH-sensitive PDMAEMA-*b*-PVCL-*b*-PDMAEMA and PVCL-*b*-PDMAEMA-*b*-PVCL triblock copolymers by RAFT polymerization. The effect of pH variations on the particle size and thermo-responsive properties of these copolymers was studied. These polymers demonstrated interesting proprieties since the two monomers are thermo-sensitive, but only DMAEMA is dual sensitive (pH and temperature).

2. Experimental Section

2.1. *Material*

The monomers DMAEMA, MMA and VCL were purchased from Sigma-Aldrich, distilled under reduced pressure and stored under inert atmosphere at –10 °C prior to the polymerization. AIBN (Sigma-Aldrich, 95%) was recrystallized twice from methanol. All other reagents were obtained from Sigma-Aldrich and used without further purification.

2.2. *Characterization*

The copolymer compositions were determined by ^{1}H NMR. The measurements were performed at 25 °C in $CDCl_3$ using a Varian YH 300 spectrometer operating at 300 MHz. The molecular mass and polydispersity (PDI) of the polymers were determined by size exclusion chromatography (SEC) with Styragel columns (10^4, 10^5, 10^6 Å, and linear) thermostated at 30 °C and connected to a Waters 410 differential refractometer using THF as the solvent. The molecular mass was calibrated with polystyrene as the standard.

2.3. *Synthesis of PDMAEMA (MCTA)*

In a typical experiment, DMAEMA (2 g, 12,7 mmol), CPDB (20 mg, 0,09 mmol), AIBN (10 mg, 0,06 mmol) and toluene (2 mL) were placed in a flask and bubbled with Ar for 20 min. The flask was placed in a thermostatic oil bath at 70 °C for 4 h. The final PDMAEMA homopolymer was purified by dissolving the reaction mixture in THF, followed by precipitation in hexane at 0 °C.

2.4. *Synthesis of PDMAEMA-b-PMMA diblock copolymers by RAFT polymerization*

PDMAEMA-*b*-PMMA was prepared applying similar procedure to those employed in the homopolymer preparation. A representative example is described as follows: the MCTA (M_n=7200 g/mol) PDMAEMA-RAFT (1.17 g, 0.16 mmol), MMA (2 g, 20 mmol), AIBN (8 mg, 0.049 mmol) and 3 mL of toluene (70% w/v) were added to a 50 mL flask and bubbled with Ar for 20 min. The polymerization was carried out at 70 °C for 4 h. The copolymer purification procedure was the same as that described for the synthesis of the MCTA.

2.5. *Synthesis of bifunctionalized PDMAEMA and PVCL (MCTAs)*

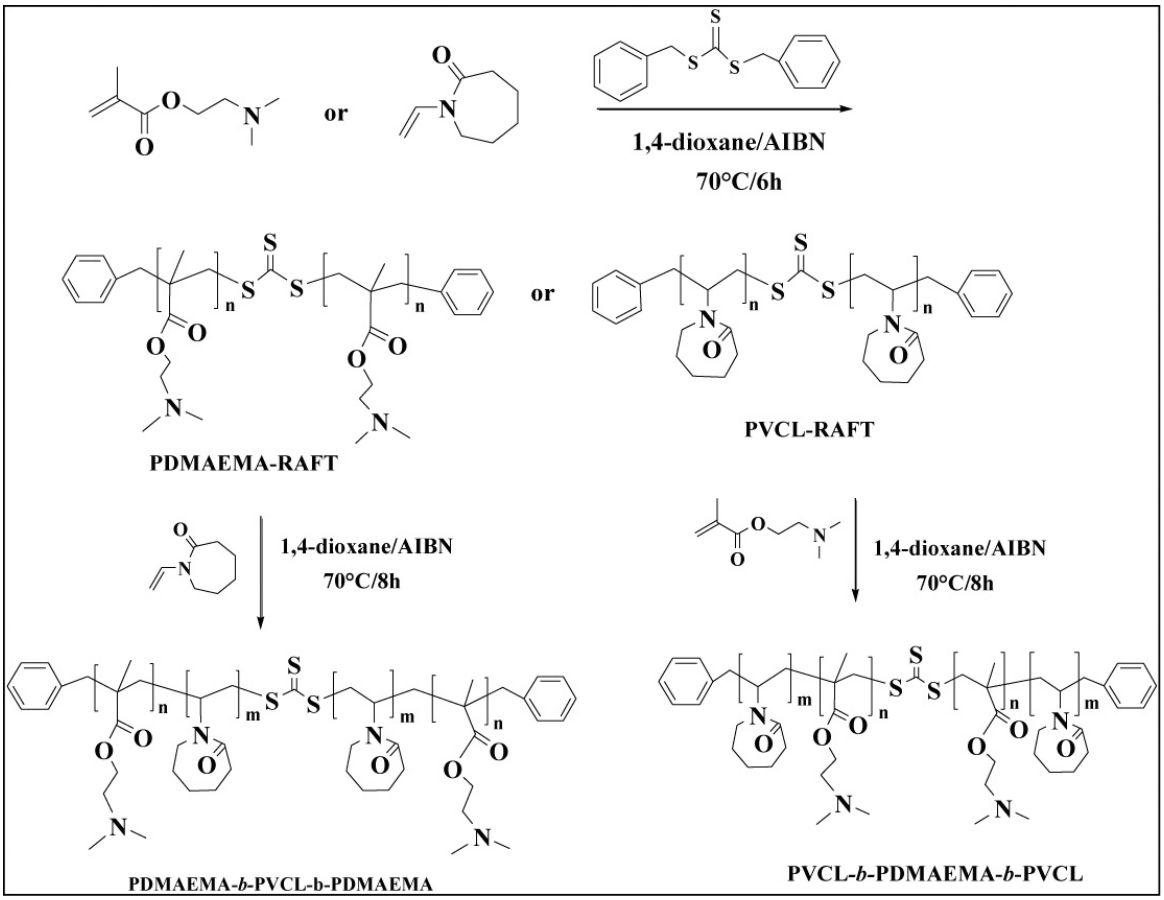
DMAEMA (2 g, 12.7 mmol), DBTTC (21 mg, 0.072 mmol), AIBN (6 mg, 0.037 mmol) and 1,4-dioxane (2 mL) were placed in a flask and bubbled with Ar for 20 min. The flask was placed at 70 °C for 6 h. The final bifunctional CTAs were purified by dissolving the reaction mixture in THF, followed by precipitation in an excess amount of cold hexane. For the synthesis of PVCL the procedure was similar to that employed in the case of PDMAEMA.

2.6. *Synthesis of triblock copolymers*

PDMAEMA and PVCL were used as MCTAs for the polymerization of VCL or DMAEMA in the synthesis of the triblock copolymers (Scheme 1). The procedures for the synthesis and purification of the copolymers were the same as those employed for the MCTAs.

2.7. *Particle size analysis and study of response to pH*

Copolymer solutions were prepared by dissolving 0.02 g of copolymer in 2 mL of THF. This solution was kept under magnetic stirring at room temperature until total dissolution (~ 1 h). The polymer solution was then added to 10 mL of double distilled water drop-wise under magnetic stirring. The THF was removed through 4 h of evaporation at room temperature. The particle size was measured at different pH values (3.5, 6.9 and 10.0) using a particle size analyzer (Malvern Zetasizer Nano, model ZEN 3600). Modification of the pH was carried out by adding a few drops of NaOH



Scheme 1. Synthetic route used to prepare the triblock copolymers PDMAEMA-*b*-PVCL-*b*-PDMAEMA and PVCL-*b*-PDMAEMA-*b*-PVCL via the RAFT process.

(0.1 M) or HCl (0.1 M) solution and controlled with a pH meter. The particle size measurements were carried out in triplicate and the data were reported as the average of the three values.

2.8. *Determination of LCST*

The LCST of the polymer solutions (1 wt% in water) were determined by gently heating the solutions in 20-mL glass tubes immersed in a well-stirred heating bath. The solutions were stirred with a magnetic bar while being heated. The first appearance of turbidity was taken as the LCST (cloud point). The rate of heating was approximately 0.5 °C/min. The measurements were carried out in triplicate and the data were reported as the average of the three values.

3. Results and Discussion

3.1. *RAFT polymerization of PDMAEMA-b-PMMA diblock copolymer*

The PDMAEMA-*b*-PMMA was synthesized and used to compare the effect of the particle size and pH response in different environment with the PDMAEMA-*b*-PVCL-*b*-PDMAEMA triblock. In the preparation of the PDMAEMA-*b*-PMMA, PDMAEMA was firstly synthesized using CPDB as the CTA, toluene as solvent and AIBN as initiator. CPDB was used due to the fact that several previous studies have demonstrated its efficiency as a controlling agent under RAFT conditions, especially for different methacrylates[16-18]. PDMAEMA-RAFT was used as MCTA in the polymerization of MMA to synthesize well-defined PDMAEMA-*b*-PMMA. The synthesis was confirmed by ^{1}H NMR spectroscopy. Figure 1 (left) shows the ^{1}H NMR spectrum of the PDMAEMA-*b*-PMMA ($M_{n,SEC}$ = 24700 g/mol, polydispersity index (PDI)=1.38) used in this study. The molar ratio between PDMAEMA and PMMA repeat units was determined by comparing the integration between the protons in the ethylene groups of PDMAEMA in the region of 4.0-4.2 ppm (peak a) with that in the methyl groups of PMMA in the region of 3.5-3.7 ppm (peak b). The M_n values observed by SEC analysis (Figure 1-right) of the homo- and copolymer were 7200 and 24700 g/mol, respectively, and as consequence the molar ratio of the PDMAEMA to PMMA repeat units in the copolymers was 1/3.8. As can be seen in the Figure 1 (right), the observed curves from SEC analysis of the MCTA and diblock presented a tail in the low molecular mass region, indicating that may have occurred irreversible termination reactions by chain transfer and due to this, the molar ratios of the homo-and copolymers from NMR and SEC are not strictly

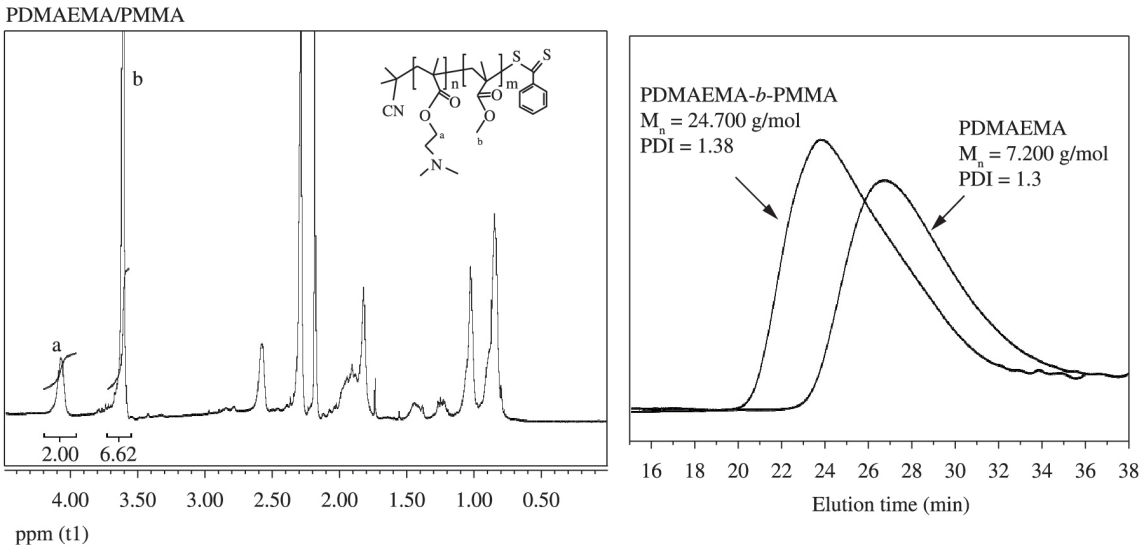


Figure 1. ^{1}H NMR spectrum of the PDMAEMA-*b*-PMMA (left) and SEC traces of PDMAEMA (MCTA) and PDMAEMA-*b*-PMMA diblock copolymer (right).

in agreement. Additionally, the SEC calibration system with standards PS results in relative molecular mass.

3.2. *RAFT polymerization of triblock copolymers*

The controlled polymerization rate (CRP) of unconjugated monomers, like VCL, is not easy to determine because their propagating radicals are highly reactive and consequently unstable. Recently, some studies have been published concerning the controlled polymerization of VCL[4,14-15]. However, to the best of our knowledge, this is the first publication reporting the synthesis of the PDMAEMA-*b*-PVCL-*b*-PDMAEMA and PVCL-*b*-PDMAEMA-*b*-PVCL triblock copolymers. These copolymers could provide a new biocompatible material for application in the biomedical area. PDMAEMA and PVCL were prepared using DBBTC as a bifunctional RAFT agent, with 1,4- dioxane as the solvent and AIBN as initiator. The polymerization occurs with the insertion of monomer molecules into the C–S bond in the trithiocarbonate. PDMAEMA and PVCL were then used as bifunctional MCTAs for the polymerization of VCL and DMAEMA resulting in the triblock copolymers PDMAEMA-*b*-PVCL-*b*-PDMAEMA and PVCL-*b*-PDMAEMA-*b*-PVCL, respectively. The formed triblock have one trithiocarbonate group in the middle of the polymer chain. Figure 2 (left) shows the ^{1}H NMR spectrum obtained from the precipitated copolymer without traces of monomer, which confirms the above synthesis as well as the copolymer composition (triblock 1, Table 1). The molar ratio of the PDMAEMA to PVCL repeat units in the copolymers was 2:1, which was determined by comparing the integration of the protons in the ethylene groups of the PDMAEMA in the region of 4.0-4.2 ppm (peak a) and that of the methylene peaks for the PVCL ring in the α-position in relation to the nitrogen atom at 2.9-3.4 ppm (peak b). This composition seems to be according with the SEC analysis, where the number average of molar mass (M_n) were 13700 and 19200 g/mol for the PDMAEMA and copolymer (PDMAEMA-*b*-PVCL-*b*-PDMAEMA), respectively. SEC curves show tailing to bigger retention times (low molecular mass), which might indicate irreversible termination by transfer chain or also that not all chains of MCTA are active (Figure 2, right).

3.3. *Effect of pH on the mean particle diameter of the copolymers*

The pH-sensitivity of the different copolymers and compositions was evaluated at pH 3.5, 6.9 and 10.0. The averages of the three size measurements are listed in Table 1. The particle size ranged from 82 to 440 nm and increased with an increase in solution pH, for all copolymers.

In acidic solutions the protonation of amine groups occurs and as a consequence the fixed positive charge of the polymeric network leads to stronger electrostatic repulsion[19] and smaller aggregate should be obtained. The particles size at pH 6.9 ranged less, obviously due to copolymers chains are partly protonated. With increasing pH to 10.0, water solubility of the copolymers is lower because in this medium the PDMAEMA is deprotonated and consequently, increasing hydrophobicity, precipitates are formed and bigger particles size are obtained. Copolymers with a higher content of DMAEMA are more protonated and the variation in particle size is more pronounced. In other words, the size particle depends on the composition of the polymer chain, as shown in Table 1. These preliminary tests clearly show the tendency of these polymers to auto-assembled in different environment.

3.4. *Thermo-responsive properties of the copolymers in aqueous solutions*

It is known that the LCST of polymers is dependent on many parameters, including the molecular mass and molecular mass distribution. However, polymers synthesized by controlled radical polymerization techniques exhibit a much sharper LCST transition when compared

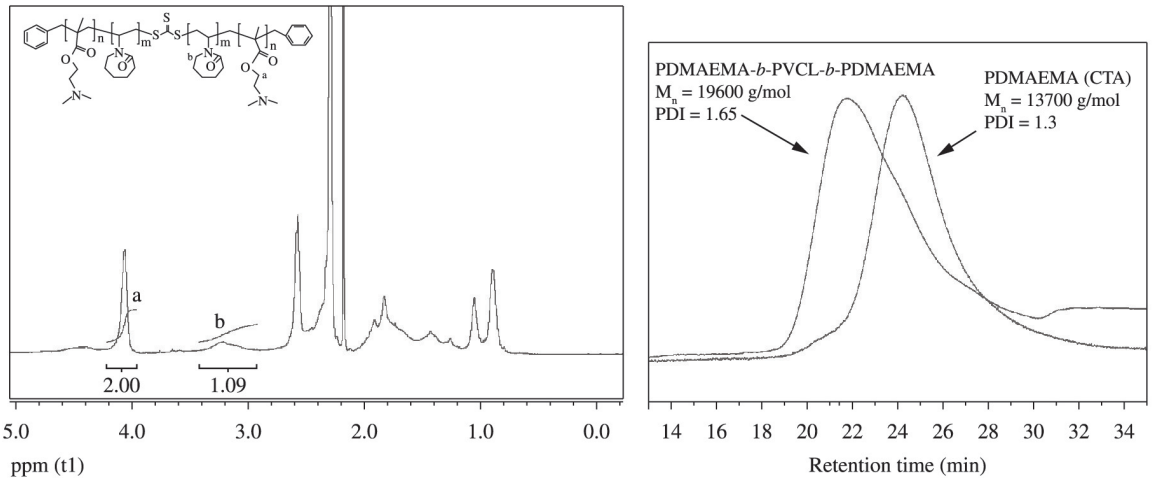


Figure 2. ^{1}H NMR spectrum for the triblock copolymer PDMAEMA-*b*-PVCL-*b*-PDMAEMA (left) and SEC traces of PDMAEMA (MCTA) and PDMAEMA-*b*-PVCL-*b*-PDMAEMA (right).

Table 1. Average particle sizes of copolymers at different aqueous solution pH values.

Sample	$M_{n,SEC}$ (g/mol)	$\overline{M}_w / \overline{M}_n$	PDMAEMA (% mol)	pH = 3.5 size (nm)	pH = 6.9 size (nm)	pH = 10 size (nm)
Diblock[a)]	24700	1.38	20	168	175	320 + P*
Triblock[b)] 1	19600	1.65	62	223	275	440 + P
Triblock[c)] 2	19200	1.9	50	82	145	295 + P
Triblock[c)] 3	11200	1.58	18	105	127	219 + P

PDMAEMA-b-PMMA[a]; PDMAEMA-b-PVCL-b-PDMAEMA[b]; PVCL-b-PDMAEMA-b-PVCL[c]; *P = precipitate in the solution.

Table 2. LCST of homopolymers and different copolymers (1 wt% in water).

Sample	$M_{n,SEC}$ (g/mol)	PDMAEMA (%) mol)	LCST (°C)
PDMAEMA	13700	100	52
PVCL	9000	0	32
Triblock 1	19600	70	38
Triblock 2	19200	50	42
Triblock 3	11200	18	34

with polymers prepared by free radical polymerization. Furthermore, for the copolymers, the LCST is strongly influenced by the hydrophilicity/hydrophobicity balance. When a hydrophilic comonomer is added the LCST increases while on adding a hydrophobic monomer the LCST decreases. PDMAEMA is a hydrophilic polymer and it has an LCST of around 50 °C with a small variation, which is dependent on the molecular mass, while the PVCL homopolymer is a hydrophobic polymer with an LCST of around 32 °C. A proper balance between these two polymers can lead to new materials with characteristics suitable for use as drug carriers. The values for the LCST of 1 wt% aqueous solutions of the homopolymers and copolymers are shown in Table 2. The aqueous solution of pure PDMAEMA exhibited a thermal phase transition at around 52 ºC and it decreased gradually with an increase in the VCL content.

These results clearly indicate that incorporated PVCL units in the PDMAEMA make it more hydrophobic, because decrease number of hydrogen-bonding interactions between the water molecules and copolymers, resulting in a decrease in its phase transition temperature. Thus, it can be noted that by adjusting the copolymer composition it is possible to obtain copolymers with a particular phase transition temperature, for instance, a temperature close the physiological temperature, which makes them desirable candidates for controlled drug delivery systems. The focus of future investigations is to provide a better overview of the observed effects and also to test the obtained polymeric systems as carriers of drugs.

4. Conclusions

Thermal and pH sensitive PDMAEMA-*b*-PVCL-*b*-PDMAEMA and PVCL-*b*-PDMAEMA-*b*-PVCL triblock copolymers were successfully prepared by sequential RAFT polymerization using PDMAEMA and PVCL as MCTAs. PDMAEMA-*b*-PMMA was also synthesized and used for comparison with the triblock copolymer to investigate the effect of pH on the variation in particle size. Preliminary results indicated a significant variation in the particle size according to the solution pH for both copolymers. The triblock PDMAEMA-*b*-PVCL-*b*-PDMAEMA with a greater content of PDMAEMA (around 70%) showed LCST of 38 °C at neutral pH, which is close to the human body temperature. These smart polymers will be evaluated as new carriers in drug-delivery systems in future studies.

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