Korean J. Chem. Eng., **27**(3), 731-740 (2010)
DOI: 10.1007/s11814-010-0216-5

INVITED REVIEW PAPER

Polymeric nanoparticles, micelles and polymersomes from amphiphilic block copolymer

Heui Kyoung Cho*, In Woo Cheong*,†, Jung Min Lee, and Jung Hyun Kim*****

*Department of Applied Chemistry, Kyungpook National University, Daegu 702-701, Korea
**Department of Chemical Engineering, Stanford University, Stanford, CA 94305, United States
***Department of Chemical and Biomolecular Engineering, Yonsei University, Seoul 120-749, Korea
(*Received 7 April 2010 • accepted 20 April 2010*)

Abstract−Block copolymers are made up of blocks of different polymerized monomers. Among the block copolymers, amphiphilic block copolymers can self-assemble to form nano-sized vehicles, such as micelles, nanoparticles, polymersomes, in aqueous or non-aqueous media. This review describes the synthesis, formation, and major applications of amphiphilic block copolymer and corresponding vehicles in order to provide an overview of the current features of functionalized block copolymers for drug delivery applications.

Key words: Amphiphilic, Block Copolymers, Stimuli-responsive, Drug Delivery, Controlled Radical Polymerizations

INTRODUCTION

Copolymers are made by various polymerization techniques from more than two different monomers [1]. Their topology, e.g., block, random, grafting or alternative, is determined by both functional group of monomers and integration techniques. Due to the use of monomers of different nature (mainly different chemical structures), they undergo a micro-domain phase separation arising from the unfavorable entropy of mixing in solution or bulk states [2]. If two different homopolymers are simply blended, they inevitably undergo a macro-domain phase separation. In the case of block copolymers, however, the domain size of the phase separation should be from a few to several hundreds of nanometers due to the chemical bonding between the building blocks in one macromolecule. There have been numerous extensive and intensive research works published because well-defined and periodic self-assembled structures can easily be obtained from the block copolymers [2-7]. Such controllable patterns from block copolymers have attracted much attention for the applications of photonic and electrical devices [8], photolithography [9], porous materials [10], surface modification [11,12], micellization [13-18], drug delivery [19-24], scaffold [25-27], and so on.

Recently, functional block copolymers have attracted a great deal of attention in terms of their typical abilities, i.e., stimuli-responsibility [28-31], drug or protein conjugation [20,32-35], bio-degradability or bio-compatibility [16,36-38], and so on. Although there are several distinguishable review articles on functional block copolymer micelles or nanoparticles [31,39-44], we believe that it is worth providing leading edge techniques in the preparation and application of functional amphiphilic block copolymer and corresponding nanoparticles. Therefore, this review article will cover emerging technologies in amphiphilic block copolymer nanoparticles as well as detailed synthetic skills of functional block copolymers.

†To whom correspondence should be addressed.
E-mail: inwoo@knu.ac.kr

SYNTHESIS OF AMPHIPHILIC BLOCK COPOLYMERS

Block copolymers having amphiphilicity in solution are very similar to surfactants or dispersants. In general, a surfactant is a short-chain molecule having both hydrophilic and hydrophobic units to form micelles or aggregates above CMC. In aqueous solution, surfactant micelles have hydrophobic cores to solubilize hydrophobic guest molecules. Similarly, block copolymers can also form micelles, which are results of the phase separation in the solution state. In the case of block copolymers, however, resultant self-assembled structures are a bit different from that of surfactants due to the macromolecular building blocks. They can form nano-sized aggregates, i.e., nanoparticles, in kinetically 'frozen' state, which is far from the dynamic equilibrium behavior of surfactant micelles [45]. Therefore, block copolymers provide nano-sized vehicles or encapsulants with long-term and high stability for guest molecules to be protected. In addition, they can form various morphologies, such as micelles, nanorods, nanocapsules, and polymersomes [40]. A variety of vehicle shapes are governed by the composition, molecular weight, and block length of amphiphilic block copolymers, and which are manipulated during the synthesis. In the following section, synthetic strategy and methods for various amphiphilic block copolymers are discussed in detail.

Fig. 1 summarizes the synthetic strategies for the formation of diblock or triblock copolymers [46]. Block copolymers can usually be obtained by (a) sequential controlled or living polymerization, (b) simple coupling reaction, (c) using a dual initiator of two different initiating fragments, and (d) the macro-initiators including functionality switching. Detailed synthetic techniques are discussed as follows:

Sequential controlled or living polymerizations can be carried out by anionic (LAP), cationic (LCP), group transfer (GTP), and FRP techniques. Concerning FRP, several detailed information with representative examples are discussed in the following section. For a long period of time, the monomers available in LAP have been

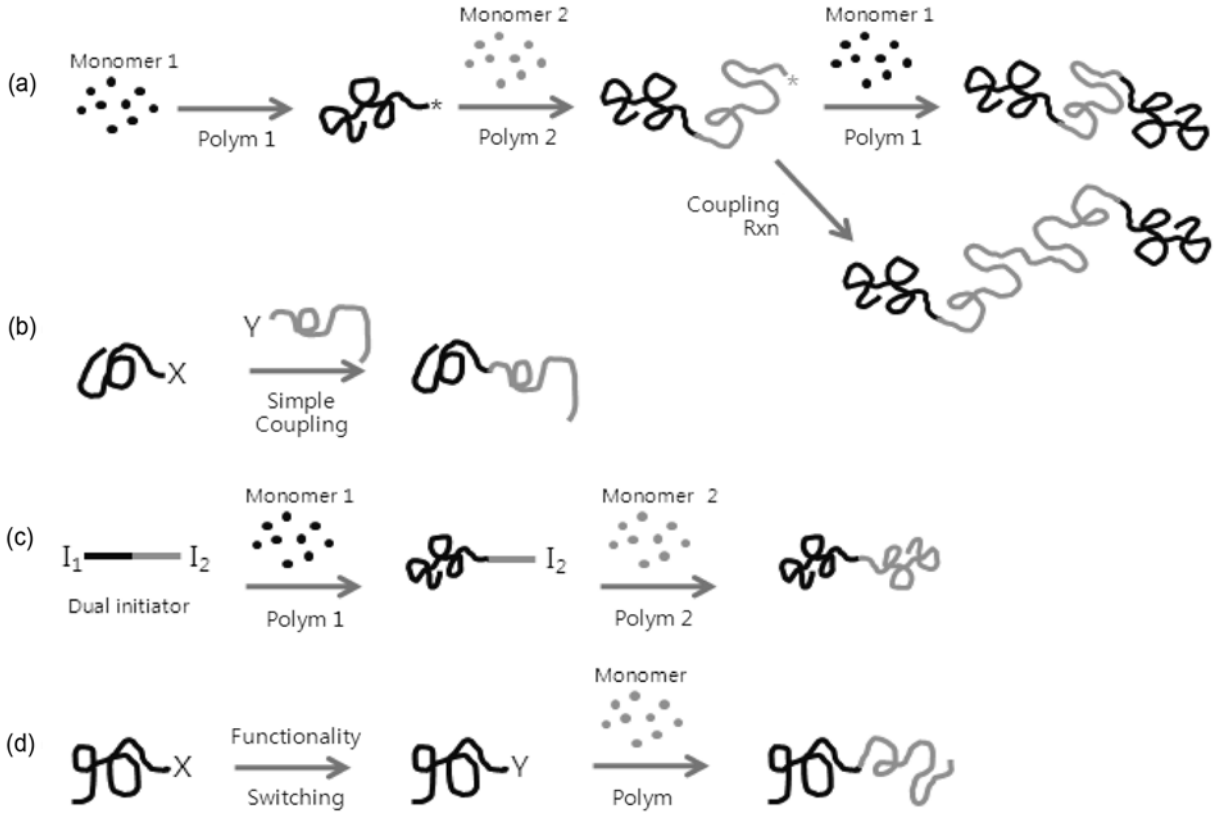

Fig. 1. Possible synthetic strategies for diblock or triblock copolymers: (a) stepwise CLP with different monomers (1 and 2), (b) simple coupling reaction between antagonist macromolecular blocks, (c) the use of dual initiator in sequential CLP, and (d) functionality switching followed by CLP of different propagating mechanism. This scheme was modified from the literature [46].

limited to styrenics and dienics. Acidic or hydroxy-functionalized monomers need protection. In sequential LAP the reactivity of monomers rules block copolymer topology, so the following order of monomer addition is general norm: styrene or dienes>acrylates>siloxanes [46]. For amphiphilic block copolymers, PSt-*b*-PEO or PMMA-*b*-PEO [47,48], and PSt-*b*-PAA [49], PEO block unit is usually prepared anionically after the block formation of vinyl or acrylate monomers. An important class of commercial triblock copolymer can be Poloxamer® or Pluronics® composed of PPO and PEO blocks, and which are generally prepared by sequential LAP. As compared with LAP, LCP is used for the monomers bearing electron donating substituent, such as styrenics, oxazolines, and alkyl vinyl ethers. Both LAP and LCP are significantly affected by the solvent effect governing the interaction of ion-counter ion pair. As compared to LAP or LCP, GTP requires silyl ketene acetal as an initiator with appropriate acid or base catalysts that cleave O-Si bond to form enolate species. It has been reported that GTP produces well-defined (meth)acrylate block copolymers (rather than styrene) with narrow molecular weight distribution [50]. Coupling reaction between the two end groups of different macromolecules is a common synthetic route for step growth polymerizations, like polyurethanes, polyesters, polyamides, and so on. However, the control of molecular weights is significantly affected by the stoichiometric balance between the macromolecules [51]. Thus, a few results are available for amphiphilic block copolymers [52,53]. "Dual" initiators furnish two individual initiation sites of which the mechanism is quite different without any mutual interference. A good example can be PCL-*b*-PSt prepared by ROP/NMP [54] or ROP/ATRP [55,56], in the presence of NMP or ATRP initiator having primary OH group. The use of dual initiator may have an advantage of making block copolymers in a one-pot procedure; however, it cannot be applied to the preparation of amphiphilic block copolymers due to the dissimilar solubility between the two blocks. The use of macro-initiator is a method when the initiation in the second polymerization is carried out by the pre-formed polymer via another mechanism. From one to the other polymerization, the switching of functionality may not be necessary but it can be achieved by *in situ* modification or pre-treatment after the first polymerization [57]. From the bifunctional macro-initiator, ABA or BAB triblock copolymers can be prepared [58-60]. All the examples cannot be dealt with in this article, but a representative technique can be the combination of ROP and ATRP [56,61,62], NMP [63,64] or RAFT [65,66], in which biocompatible or biodegradable block, such as PCL, PLA, PEG (or PEO) can be prepared for bio-medical applications.

As described earlier, the representative preparation technique of block copolymers includes LAP and CLP via cationic, radical and organometallic routes, in which chain transfer and/or termination reactions are very limited. Such a strategy is applied to all kinds of controlled polymerizations in block copolymer fabrications.

Anionic polymerization is an old technique which had been developed by Swarcz in 1956; however, it has widely been used, especially in the industrial manufacturing. Anionic polymerization can achieve

quite a narrow molecular weight distribution (e.g., $M_w/M_n<1.05$), while it needs scrupulous care against any accidental termination reaction due to the presence of impurities. In anionic polymerization, a propagating chain is carbanion formed from the nucleophilic addition to monomers by an initiator [51]. Active anionic species are still "alive" to propagate the second monomer even after consumption of the first monomer. In addition, growing species in LAP rarely lead to bimolecular termination as compared with LRPs. One drawback of LAP might be the narrow choice of monomer and its addition sequence. Therefore, various CRP techniques have been developed in the viewpoint of maintaining living characteristics of growing chains to control the molecular weight distribution.

There have been several results opened to argument in NMP; nevertheless, it seems to have 'living' nature in FRP. It utilizes stable free radicals of nitroxides that are used as persistent counter radicals to trap growing chains in a reversible manner at a certain temperature [67,68]. It is necessary to add excess amounts of NMP agents with respect to the initiator to minimize the number of dead chains [68]. Sometimes, acids can be utilized to reduce the amount of free nitroxide resulting from irreversible termination [69]. Representative NMP agents are TEMPO [67], DEPN [70], and TPAHN [71]. Block copolymers can be prepared by the sequential addition of different monomers or by macroinitiator of alkoxyamine-terminated macromolecules. The representative block copolymer can be the PCL-*b*-PSt prepared with 'dual' hydroxy-substituted alkoxyamine initiator [72]. One drawback of NMP can be a sequence of monomer additions that leads to unreacted monomer or termination of starting block and several attempts to overcome this unexpected lack of reactivity have been unsuccessful. More detailed kinematic feature of NMP is available in the literature [63,64,68,73,74].

ATRP was independently discovered by Sawamoto et al. and Matyjaszewski et al. in 1995 [75-77]. ATRP is very useful in preparing amphiphilic block copolymers but it entails reversible transfer of the halides (e.g., Cl or Br) of transition metal complex between growing and dormant species. For the successful ATRP, scrupulous selection of alkyl halide initiator, catalyst/ligand complex and solvent is necessary. A major drawback of ATRP can be the residual copper halide even after removal process, and which may cause toxicity in bio- or medical applications. An attempt to minimize the copper halide in ATRP was done by using ARGET and ICAR techniques, in which the Cu (I) catalyst is replenished by recycling process. Another similar trial can be SET-LRP. ATRP still has a problem in deactivation of growing species leading to broad molecular weight distribution of block copolymers; however, it has widely been utilized in the preparation of a variety of amphiphilic block copolymers, such as PDMAEMA-*b*-PMMA [78], PSt-*b*-PAA [79], PEG-*b*-PAMA [43], PTMS-*b*-PBA [80]. However, MWD and conversion for specific monomers are still susceptible to the selections of macro-initiator, solvent, and catalyst/ligand in ATRP.

RAFT polymerization is a well-known powerful technique that controls the molecular weight distribution and topology of block copolymers for a variety of monomer classes. The process of RAFT requires conventional procedures like FRP, in which common CTAs are replaced by RAFT agents (usually CPDB or ECMX). Unlike FRP, the presence of oxygen does not matter and the RAFT process itself does not induce substantial retardation. It also has some demerits like typical colors depending on RAFT agent, a need for synthesis of RAFT agent, the hydrolysis of some RAFT agents in water, questionable toxicity of RAFT polymers, and the slow polymerization rate. Among them, toxicity can be a significant problem in drug delivery of bio-medical application assisted by block copolymer nanoparticle, micelle or scaffold; however, this can be overcome by the removal of the end group of RAFT agent through aminolysis or oxidation [81]. Detailed feature and mechanism of RAFT process are well described in the recent literature [17,33,65,81,82]. Through RAFT process, various kinds of amphiphilic block copolymers were synthesized, such as PNaSS-*b*-PNaVB, PBA-*b*-PAMPC [83], PLA-*b*-PNIPAAm-*b*-PLA [66], PNIPAAm-*b*-PAA [84], PNaAMPS-*b*-PNaAMBA [85,86], and so on. Among published RAFT techniques, the fabrication of amphiphilic block copolymers in aqueous media was well summarized in a review article written by York and McCormick, in which various conjugation methods of biological compound to RAFT agent for drug or gene delivery systems are noted [87].

AMPHIPHILIC BLOCK COPOLYMER-BASED VEHICLES

1. Micelles

The self-assembly of amphiphilic block copolymer results in micelles or aggregates, and this is a reversible process driven by solution thermodynamics. The formation of micelle is illustrated in Fig. 2. At a low concentration of block copolymers, they exist as unimers, i.e., individual units in solution. As the concentration increases, the entropy of the solution is decreased due to the unfavorable arrangement or ordering of solvent molecules; while it approaches CMC in which the micellization or aggregation of unimers takes place. The micellization of unimers achieved by hydrophobic interaction increases entropy again. Typical sizes of amphiphilic block copolymer micelles are 5-100 nm and the CMC range of block copolymers is 10^{-7}-10^{-3} M water [88].

The shape or morphology of micelles prepared from amphiphilic block copolymers includes spherical ('core-corona' or 'crew-cut'), rod-like, star-like, vesicles, and so on. The shape varies with the block length ratio and the composition of block copolymers. Zhang et al. demonstrated the effect of block length ratio of PSt-*b*-PAA on the morphological variation of crew-cut micelles in DMF/water solution [89]. The crew-cut type micelles contain long hydrophobic blocks of PSt, so they can be visualized with ease in TEM analysis. On the other hand, core-corona micelles can be obtained when the length of hydrophilic block is longer than that of the hydrophobic block.

Block copolymer micelles can be prepared by several techniques, but most of them are focused on the variations for drug loading. The representative method is a direct dissolution of amphiphilic block copolymer (for marginally water-soluble block copolymers) around CMC and followed by the elevation of temperature or the addition of hydrophobic drugs [90]. The other one might be solvent (e.g., DMF, DMSO, acetone, THF) exchange. In this method, drugs are dissolved in a solvent with the block copolymers (rather water-insoluble), and then water can be added into this solution or vice versa, viz., the solution can be poured into the water. In both cases, the solvent may or may not be miscible with water. In the case of water-immiscible solvent, the O/W emulsion is prepared first in the presence/absence of surfactants and followed by the evapora-

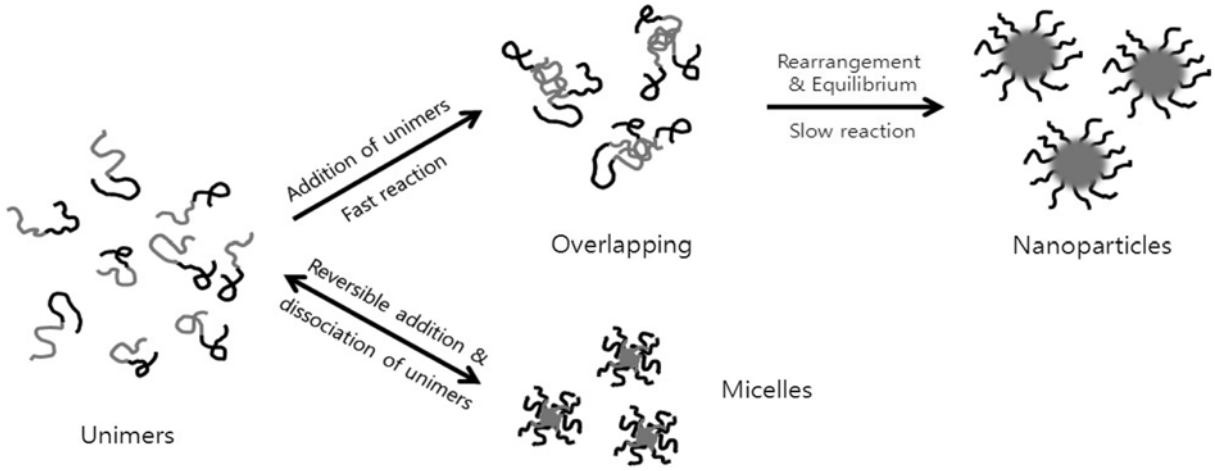

Fig. 2. Nanoparticle formation via self-assembly. The critical size of nanoparticle can be determined by the number of added unimers, and which are inserted though the insertion barrier of steric or electrostatic nature. This scheme was modified from the literature [45].

tion of the solvent. For water-miscible solvent systems, water can be added into the solution or the solution can be dropped into the water. In both cases, the residual solvent can be removed by dialysis or evaporation. The addition or exchange rate of solution-water determines the precipitation rate of block copolymer and subsequently, the final number and size of drug-loaded micelles [90].

The CMC decreases as the portion of hydrophobic block increases. The addition of hydrophobic drugs (or non-polar solvents) also decreases the CMC [91]. On the other hand, the CMC seems not susceptible to the length of hydrophilic block [90]. Therefore, the type or kind of hydrophobic block is very important because it governs solubilization ability for lyophobic drugs as well as the association-dissociation kinetics of block copolymers. In addition, the 'shape' boundary between nanoparticle and micelle seems unclear [15]. In fact, the morphological transition from the micelle to the nanoparticle relies on the molecular weight or the length of hydrophobic unit in the amphiphilic block copolymer.

As mentioned above, the micellization is reversible and which may be unfavorable or rather dangerous in the drug delivery, since the abrupt dilution of micellar solution results in the precipitation of blood-insoluble drugs. In order to avoid disassembly of micelles, a crosslinked core or shell system has been proposed. Rapoport demonstrated a direct core crosslinking technique to prevent the dissolution of Pluronic® micelles against dilution [91]. Wei et al. prepared crosslinked thermo-sensitive micelles by using an acid-catalyzed sol-gel process [18]. Huang demonstrated shell-crosslinked knedel-like structures by using amidation with several di- and multi-amino linkers [49]. Fortunately, we are able to control the dissociation rate of block copolymer micelles by increasing the hydrophobic block length or introducing binding interactions (covalent, ionic, hydrogen-bonding, etc.). In addition, the disassembly rate of block copolymers is much slower than that of short-chain surfactants.

2. Nanoparticles

Besides micelles, amphiphilic block copolymers also form nanoparticles. However, equilibrium dynamics of nanoparticles is different from that of micelles as mentioned earlier. Micellization of block copolymer is based on the self-assembly and thermodynamic aspect of block copolymer unimers around CMC. However, the formation of nanoparticles is 'kinetically' controllable with several factors, such as temperature [14,17], pH level [14,86], electrolytes, and solvent contents [7], etc. It has been known that the CMC of block copolymer should be lower than 10^{-3} wt% and the free energy change should also be higher than 5 kT in the preparation of nanoparticles from block copolymers [45]. Moreover, it would be noted that the molecular weight of lyophobic unit should be longer enough to maintain 'frozen' state of molecular entanglement. After gathering of unimers, the colloidal stability of these nanoparticles is maintained by steric or electrostatic repulsion preventing fusion from Brownian collision. In Fig. 2, the schematic of nanoparticle formation is illustrated.

The nanoparticles prepared from amphiphilic block copolymers can be considered as core/shell particles, in which the core is a sort of lyophobic polymeric matrix for the dissolution or encapsulation of hydrophobic drugs. The shell is a protective layer against coagulation/aggregation and phagocytosis. Depending on the size ratio of core to shell, the morphology of nanoparticles is divided into 'crew-cut' and 'core-corona' types like micelles [15]. Typical size of the nanoparticles ranges from 50 to 200 nm and it varies depending on 'kinetic' control variables as well as the characteristics of block copolymer. Regarding the loading efficiency and/or colloidal stability, nanoparticles seem to be superior to micelles.

Preparation of the nanospheres from amphiphilic block copolymers can be achieved by dissolution in a good solvent, emulsification in water, and followed by removal of the solvent. If the solvent for block copolymer is miscible with water, then nanoprecipitation (dialysis may or may not be used) or emulsification-diffusion (especially for 'partially' water soluble solvents) methods can be utilized [92,93]. Nanoparticles less than 100 nm could be obtained by using this method even for hydrophobic polymers (not amphiphilic block copolymer) as long as adequate surfactants were added [94].

The amphiphilic block copolymers having longer hydrophilic blocks tend to form uniform micelles through the simple direct dissolution; however, the block copolymers having longer hydrophobic blocks are likely to be precipitated in water in the absence of process variable manipulations for nanoparticle formation or nanoencapsulation of drugs. The influence of chain length on morpho-

logical transition from micelle to nanoparticle has been well demonstrated by Riley et al. and Heald et al. [95,96] Zhang et al. demonstrated that various morphologies PSt-*b*-PAA could be obtained by using two different methods, water addition and direct dissolution, in which water contents in water/DMF and polymer concentration were varied [15]. They showed spherical, rod-like, star-like, vesicular, and bilayer structures and morphological transition pattern in two methods were quite different.

3. Polymersomes

Liposomes are well known as nano- or micro-sized spherical vehicles made of phospholipids which self-assemble to form lipid bilayers. This structure has been a model for the investigation of biocell membrane and polymersomes. They can encapsulate hydrophilic drugs and release them in controllable ways. The morphology of polymersomes is very similar to that of liposome and they have been made from amphiphilic block copolymers. It has been known that typical shell thickness (~10 nm) of polymersomes is thicker than that (4-5 nm) of liposome and the appropriate level of hydrophilic part in block copolymer is from 20 to 40 wt% [97]. Due to the high molecular weights of block copolymers, they show better colloidal stability against mechanical shear and osmotic pressure difference.

A conventional method is film rehydration method, in which a volatile solvent is evaporated to make thin and multilayer of block copolymers and they are rehydrated with aqueous solution with vigorous stirring or sonication [40]. Recently, several new techniques, e.g., electroformation [98,99], double emulsion templating [100,101], microfluidic [100,102], and so on, have been developed for the narrower size distribution and the size control of polymersomes [103]. In particular, 'gigantic' polymersomes are gaining increased attention due to their cell-sized compartment, enhanced mechanical stability, and versatile characteristics of block copolymers. Howse reported a size control of polymeric vesicle by using both 'top-down' photolithography and 'bottom-up' dewetting process followed by molecular self-assembly. They could create unilamellar vesicles with a narrow size distribution [104]. A similar work was done by Taylor et al. [105]. They used a PDMS stamp covered with lipids to prepare giant liposome in an A/C current applied ITO glass panel. The detachment of rehydrated liposome was done by ultrasonic energy. Mabrouk et al. studied the formation and viscoelastic property of giant polymersomes of rod-coil block copolymers by using micro pipette aspiration analysis [97]. Shum et al. prepared monodisperse PEG-*b*-PLA polymersomes by making W/O/W emulsion template in a microcapillary fluidic device [100]. They noted that the formation of polymersome was achieved by the dewetting of organic solvent phase (i.e., toluene/chloroform mixture) of acorn-like equilibrium morphology. It has also been reported that inner and outer osmotic pressures should be balanced during the polymersome formation; otherwise, shrinkage or breakup of polymersome occurs. Microfluidic methods seem to produce polymersomes with narrower size distribution as compared with the other techniques. Yang et al. prepared polymersomes from amphiphilic block copolymers bearing the hydrophobic block of a side-on nematic liquid crystal polymer [106]. They investigated the morphology transition from polymersome to tubular micelles with varying the ratio of hydrophilic/hydrophobic blocks. Li et al. prepared polymeric vesicles from Pluronic® L121 (PEO_5-PPO_{68}-PEO_5) triblock copolymers stabilized against aggregation by Pluronic® P85 (PEO_{26}-PPO_{40}-PEO_{26}) micelles, in which the vesicles and micelles were reinforced by IPN structure in the presence of pentaerythritol tetraacrylate [107].

Polymersomes offer encapsulation of water-soluble drugs or nanoparticles like liposomes. They can take up drugs with high loading density as compared with micellar systems. In particular, their mechanical stability and versatility (e.g., stimuli-response, release control, targeting, etc.) can be controllable; therefore, they will gain much interest in drug delivery, biological assay, and cell labeling or imaging in near future.

STIMULI-RESPONSIVE VEHICLES

Over the last few decades, many researchers have been concerned with polymeric vehicles capable of reacting to environmental changes, such as temperature, ionic strength, light, pH level, pressure, and so on, due to the potential application of the stimuli-responsive vehicles in drug delivery system [31,87]. Some of them have already passed several phases of clinical tests. The responses of amphiphilic block copolymers can be sol-gel transition, aggregation, micellization, solubilization, hydrodynamic volume change, cleavage of block units, etc. Especially in drug delivery, the polymeric vehicles are often aimed at specific targeting and controlled drug release. Stimuli-responsive vehicles can be regarded as active targeting systems since drugs are release from the vehicles in response to external or environmental changes. Most of stimuli-responsive block copolymers are about temperature or pH-sensitive systems [108-111]. In the following sections, the recent progress in micelles, nanoparticles, and polymersomes composed of stimuli-responsive block copolymers are reviewed.

1. Temperature-responsive Polymeric Vehicles

The temperature-responsive block copolymer is most extensively studied among micelles, nanoparticles, hydrogels, and other various polymeric vehicles. Several physical changes, e.g., *in situ* micellization/dissolution, sol-gel transition, and drug release can be achieved due to the VPTT, i.e., LCST or UCST of thermo-sensitive blocks. Typical thermo-responsive polymers include PNIPAAm [17-19,33], PDMAEMA [112-114], PMVE [115], and PNVIBA [116]. Representative temperature-sensitive copolymers are PEO- and PNIPAAm-based block copolymers [18,66,110,117]. Pluronic® or Poloxamer® is a typical PEO-based temperature-responsive block copolymer showing sol-gel transitions. Besides the phase transition, PEO plays an important role of 'stealth' for long-term circulation against RES in human body. In the block copolymer synthesis, PEO unit can be introduced in various ways, i.e., as an initiator in ROP or a linker for hydrophobic blocks. Asymmetric PEOs with *a*-methoxy and *N*-amino or hydroxyl groups are commercially available and are used to initiate the polymerization of diblock copolymers [43].

PNIPAAm also has been well-known for VPTT. Cammas et al. prepared PNIPAAm-*b*-PSt block copolymer through simple coupling reaction between NH_2-PNIPAAm and HOOC-PSt blocks and showed reversible thermo-responsive micellization and aggregation behavior around LCST (~32 ºC) of PNIPAAm [19]. Zhou et al. demonstrated complex unimolecular and multimolecular micellization and/or aggregation from the double hydrophilic multiblock copolymers of *N*,*N*-dimethylacrylamide and *N*-isopropylacrylamide [17]. Dayananda et al. prepared pH- and temperature-sensitive block

copolymers of PSM-*b*-PCLA-*b*-PEG-*b*-PCLA-*b*-PSM from ATRP of sulfamethazine methacrylate and ROP of D,L-lactide/ε-caprolactone. They showed the complex pH- and temperature-responsive of the pentablock copolymers. Chu et al. demonstrated the thermo-responsive controlled-release microcapsule by using the LCST of PNIPAAm which was used as a 'gate' material for drug release [118]. Chen et al. prepared thermo-responsive crosslinked polymer vesicles from the self-assembly of PCEMA-*b*-PNIPAAm and subsequent 254 nm UV light-crosslinking reaction of PCEMA shells. The block copolymer was formed by simple coupling reaction between NH_2 and COOH in PNIPAAm and PHEMA blocks, respectively. They demonstrated that they could tune the loading behavior of the polymer vesicles for 4-aminopyridine, as a model drug, with varying temperature under the 278 nm UV light on-off conditions [119].

2. pH-responsive Polymeric Vehicles

Typical example of pH-sensitive block copolymers can be double-hydrophilic (DH) block copolymers. They usually undergo hydrophilic-hydrophobic transition to form micelles or aggregates instantly. Sumerlin demonstrated pH-induced micellization from PNaAMPS-*b*-PNaAMBA copolymers, in which PNaAMPS is pH-insensitive (strong acid salt), while PNaAMBA undergoes hydrophobic aggregation below pH 5.5. They showed the reversible micellization of PNaAMPS-*b*-PNaAMBA could be controlled by manipulating the block length. Boudier investigated micellization behavior of PMAA-*b*-PEO by complexing either PLL or oligochitosan [120]. They demonstrated the strategy for the choice of the partners in the formulation of the DH block copolymer micelles presenting a good colloidal stability in normal human conditions (pH=7.4, 0.9% NaCl) and a pH-responsive behavior for pharmaceutical applications.

Polymeric vesicular systems exhibiting pH sensitivity have been intensively studied in terms of stability, disintegration and controlled release. Du et al. prepared biocompatible and pH-responsive PMPC-*b*-PDPA block copolymers by ATRP [121]. They reported that the stable polymeric vesicles of PMPC-*b*-PDPA could be prepared in physiological pH region. The vesicles were dissociated below pH 6, and which implies that water-soluble drugs or proteins would be released via intracellular routes. Their investigation also suggested that the stability of polymeric vesicles could be controlled by manipulating block length ratio between MPC and PDPA. Adams et al. attempted to prepare polymeric vesicles containing hydrophilic dyes by pH control [122]. The block copolymer used in the preparation was PEO-*b*-PDEAEMA, and which undergoes unimer-micellization transition from low to high pH values due to the deprotonation of DEAEMA block. In their paper, possible mechanism for the formation of block copolymer vesicles was depicted to explain the inefficient encapsulation of the hydrophilic dyes on the 'restructuring' vesicle formation.

3. Other Stimuli-responsive Polymeric Vehicles

As compared with pH- or temperature-responsive block copolymers, light-responsive block copolymers and corresponding micellization/encapsulation/drug release are relatively few, although the use of light as an external stimulus in 'small' molecules has been recognized to be very effective.

In the pioneering work by Jiang et al. [123], ATRP was used to synthesize a light-sensitive diblock copolymer in which PEO was used as a hydrophilic block and a PMA as a hydrophobic block; a pyrene moiety was attached to the side group of the hydrophobic block via the ester bond to produce an amphiphilic block copolymer designated PPy. In aqueous solution, the photosolvolysis of pyrenylmethyl esters under UV light irradiation induced a cleavage of the ester bond between the polymer and the dye, which resulted in a conversion of a hydrophobic PMA into a hydrophilic PMAA leading to micelle dissolution. They observed the irreversible light-induced release of a hydrophobic dye Nile Red from PPy micelles. The cleavage of ester bond was demonstrated by the same group with the similar amphiphilic block copolymer having 2-nitrobenzene moiety [124]. The hydrophilic COOH groups are formed when the cleavage takes place. Most frequently used light-responsive block copolymer can be azobenzene and spirooxazine derivatives. Several articles on the block copolymers having azobenzene moiety were published by Zhao et al. They prepared amphiphilic block copolymers from the methacrylate-based azobenzene-containing side-chain block and P(BA-*co*-AA) block [125,126]. They suggested that the azobenzene moieties with the same substituents on the *para* positions would be recommended, since the azobenzene moiety induces enhanced dipole moment under UV irradiation via *trans* to *cis* configuration transition. In the design of azobenzene-containing block copolymers, the hydrophilicity of hydrophilic blocks and control of block length between hydrophobic blocks having azobenzene and hydrophilic blocks seem to be very critical. Lee et al., synthesized PEO-based block copolymers from spiropyran-containing methacrylate monomer via ATRP [127]. The spiropyran units respond to UV-visible light and undergo a reversible isomerization or interconversion between spiro (closed) and merocyanine (open) forms. They demonstrated a reversible micellization/dissociation and encapsulation/release of coumarin 102 under UV and visible lights irradiation.

For the targeted drug delivery, enzyme, glucose, ionic strength or specific proteins could be a good stimulus which can switch over the physicochemical properties of polymeric vehicles instantly. Kim et al. reported the sugar-responsive polymersome of PEO-*b*-PSBA which showed semi-permeable membrane characteristics. They prepared the polymersome by using the co-assembly of ordinary block copolymer, PEO-*b*-PSt [128]. The PEO-*b*-PSBA was synthesized by ATRP in the presence of PEO macroinitiator. You et al. prepared PEO-*b*-PGEA amphiphilic copolymer by ATRP [129]. The copolymer recognizes lectin proteins, like Concanavalin A, due to the glucose or saccharide moiety in PGEA blocks. The interaction between lectin protein and glucose is strongly affected by the high concentration of the saccharide. Wang et al. demonstrated pH-controlled insulin release by introducing APBA into PEO-*b*-PAA block copolymers, in which APBA exhibits glucose-sensitivity [130]. They used a stepwise ATRP method to prepare PEO-*b*-(PAA-*co*-PAA-APBA) copolymer. First, PEO-*b*-PBA was synthesized by using PEG-Br macroinitiator. Second, the copolymer was hydrolyzed to produce carboxylic acid and followed by the coupling reaction between the hydrolyzed PBA unit (i.e., PAA) and APBA. Napoli et al. prepared the polymersomes containing glucose-oxidase with PEG-*b*-PPS-*b*-PEG triblock copolymers by using episulfide anionic polymerization. The copolymer has sulfide groups and which are transformed to sulfoxide by the enzyme in the presence of glucose [131]. The transformation changes the HLB value of the copolymers and results in the destabilization of the polymersome. Stubenrauch et al. investigated 'dual' stimuli-responsive block copolymers against

pH and ionic strength variations [132]. They prepared block copolymers containing 5,6-bis(ethoxymethyl)-bicyclo[2.2.1]hept-2-ene or endo, exo[2.2.1]bicyclohept-5-ene-2,3-diylbis(phenylmethanone), etc, as hydrophobic blocks, by using ROMP. They prepared the block copolymer micelles and observed hydrodynamic volume changes under pH change and NaCl concentrations. Schilli prepared PNIPAAm-*b*-PAA block copolymers by RAFT and demonstrated 'double' stimuli-responsive micelle system [84]. They showed switchable and reversible micellization by adjusting pH and temperature.

CONCLUSION

The block copolymer vehicle systems include micelles, nanospheres, and polymersomes. All of them have strength and weakness due to their unique morphology and physicochemical properties. The design and synthesis of block polymeric vehicles require much functionality, such as high loading efficiency or level for drugs, stability against environmental changes and instant responsive properties, specific targeting and stealth against RES for prolonged circulation, as well as biocompatibility. For these, well-defined and functionalized block copolymers have been synthesized by using several living/controlled polymerization techniques. Recently, both RAFT and ATRP techniques became the most popular methods in the functionalized block copolymer synthesis in spite of their drawbacks in the applications of drug delivery. Both techniques will be used more frequently in the near future and a variety of research works to overcome such drawbacks have been carried out at the moment. In particular, stimuli-responsive block copolymers will gain much interest in the development of anticancer vectors that enhance the ability to target and modulate drugs.

ACKNOWLEDGEMENT

The authors thank to the financial support (K0006005) from the Fundamental R&D Program for Core Technology of Materials funded by the Ministry of Knowledge Economy, Republic of Korea.

REFERENCES

1. R. N. Young, *Trends Polym. Sci.*, **5**, 4 (1997).
2. V. Abetz and P. F. W. Simon, *Adv. Polym. Sci.*, **189**, 125 (2005).
3. K. Mortensen, *Curr. Opin. Colloid Interface Sci.*, **3**, 12 (1998).
4. S. I. Stupp, *Curr. Opin. Colloid Interface Sci.*, **3**, 20 (1998).
5. H.-A. Klok and S. Lecommandoux, *Adv. Mater.*, **13**, 1217 (2001).
6. A.-V. Ruzette and L. Leibler, *Nat. Mater.*, **4**, 19 (2005).
7. H. Cui, Z. Chen, S. Zhong, K. L. Wooley and D. J. Pochan, *Science*, **317**, 647 (2007).
8. Y. Kang, J. Walish Joseph, T. Gorishnyy and L. Thomas Edwin, *Nat. Mater.*, **6**, 957 (2007).
9. C. Harrison, M. Park, P. Chaikin, R. Register and D. Adamson, *Polym. Mater. Sci. Eng.*, **77**, 406 (1997).
10. L. Hu, J. L. Bartels, J. W. Bartels, K. Maurer and K. D. Moeller, *J. Am. Chem. Soc.*, **131**, 16638 (2009).
11. T. Kasemura, C. Komatu, H. Nishihara, S. Takahashi, Y. Oshibe, H. Ohmura and T. Yamamoto, *J. Adhes.*, **47**, 17 (1994).
12. A. Kidane, G. C. Lantz, S. Jo and K. Park, *J. Biomater. Sci., Polym. Ed.*, **10**, 1089 (1999).
13. T. Rager, W. H. Meyer, G. Wegner, K. Mathauer, W. Machtle, W. Schrof and D. Urban, *Macromol. Chem. Phys.*, **200**, 1681 (1999).
14. S. Li, C. J. Clarke, R. B. Lennox and A. Eisenberg, *Colloids Surf. A*, **133**, 191 (1998).
15. L. Zhang and A. Eisenberg, *Macromolecules*, **32**, 2239 (1999).
16. B. Jeong, Y. H. Bae and S. W. Kim, *Colloids Surf. B*, **16**, 185 (1999).
17. Y. Zhou, K. Jiang, Q. Song and S. Liu, *Langmuir*, **23**, 13076 (2007).
18. H. Wei, D.-Q. Wu, Q. Li, C. Chang, J.-P. Zhou, X.-Z. Zhang and R.-X. Zhuo, *J. Phys. Chem. C*, **112**, 15329 (2008).
19. S. Cammas, K. Suzuki, C. Sone, Y. Sakurai, K. Kataoka and T. Okano, *J. Controlled Release*, **48**, 157 (1997).
20. H. K. Cho, S. Lone, D. D. Kim, J. H. Choi, S. W. Choi, J. H. Cho, J. H. Kim and I. W. Cheong, *Polymer*, **50**, 2357 (2009).
21. H. K. Cho, K. S. Cho, J. H. Cho, S. W. Choi, J. H. Kim and I. W. Cheong, *Colloids Surf. B*, **65**, 61 (2008).
22. K. L. Ulman, G. A. Gornowicz, K. R. Larson and C. L. Lee, *J. Controlled Release*, **10**, 251 (1989).
23. G. S. Kwon and T. Okano, *Pharm. Res.*, **16**, 597 (1999).
24. K. M. Huh, Y. W. Cho and K. Park, *Drug Delivery Technol.*, **3**, 42 (2003).
25. J. Haley, P. Kabiru and Y. Geng, *Mol. BioSyst.*, **6**, 239 (2009).
26. E. M. Kolonko, J. K. Pontrello, S. L. Mangold and L. L. Kiessling, *J. Am. Chem. Soc.*, **131**, 7327 (2009).
27. T. A. Mahmood, V. P. Shastri, C. A. van Blitterswijk, R. Langer and J. Riesle, *J. Biomed. Mater. Res., Part A*, **79A**, 216 (2006).
28. Y. Nakazawa, Y. Kamijo, K. Fujimoto, H. Kawaguchi, Y. Yuguchi, H. Urakawa and K. Kajiwara, *Angew. Makromol. Chem.*, **240**, 187 (1996).
29. C. Pichot, A. Elaissari, D. Duracher, F. Meunier and F. Sauzedde, *Macromol. Symp.*, **175**, 285 (2001).
30. C. He, S. W. Kim and D. S. Lee, *J. Controlled Release*, **127**, 189 (2008).
31. N. Rapoport, *Prog. Polym. Sci.*, **32**, 962 (2007).
32. T. Noh, Y. H. Kook, C. Park, H. Youn, H. Kim, E. T. Oh, E. K. Choi, H. J. Park and C. Kim, *J. Polym. Sci., Part A: Polym. Chem.*, **46**, 7321 (2008).
33. P. De, S. R. Gondi and B. S. Sumerlin, *Biomacromolecules*, **9**, 1064 (2008).
34. X. Hu, S. Liu, X. Chen, G. Mo, Z. Xie and X. Jing, *Biomacromolecules*, **9**, 553 (2008).
35. S. Y. Kim, S. H. Cho, Y. M. Lee and L.-Y. Chu, *Macromol. Res.*, **15**, 646 (2007).
36. J.-Z. Bei, J.-M. Li, Z.-F. Wang, J.-C. Le and S.-G. Wang, *Polym. Adv. Technol.*, **8**, 693 (1997).
37. D. S. Lee, M. S. Shim, S. W. Kim, H. Lee, I. Park and T. Chang, *Macromol. Rapid Commun.*, **22**, 587 (2001).
38. S.-W. Choi, Y. Kim, I. W. Cheong and J.-H. Kim, *Macromol. Rapid Commun.*, **29**, 175 (2008).
39. Y. Zhao, *J. Mater. Chem.*, **19**, 4887 (2009).
40. K. Letchford and H. Burt, *Eur. J. Pharm. Biopharm.*, **65**, 259 (2007).
41. M. A. Hillmyer, *Science*, **317**, 604 (2007).
42. Y. Bae, H. Cabral and K. Kataoka, *Block Copolym. Nanosci.*, 73 (2006).
43. G. Gaucher, M.-H. Dufresne, V. P. Sant, N. Kang, D. Maysinger and J.-C. Leroux, *J. Controlled Release*, **109**, 169 (2005).
44. K. Kataoka, G. S. Kwon, M. Yokoyama, T. Okano and Y. Sakurai, *J. Controlled Release*, **24**, 119 (1993).

45. K. Johnson Brian and K. Prud'homme Robert, *Phys. Rev. Lett.*, **91**, 118302 (2003).
46. M. Lazzari, G. Liu and S. Lecommandoux, *Block copolymers in nanoscience*, Wiley-VCH, Weinheim (2006).
47. J. Huang, X. Huang and S. Zhang, *Macromolecules*, **28**, 4421 (1995).
48. X. Huang, S. Chen and J. Huang, *J. Polym. Sci., Part A: Polym. Chem.*, **37**, 825 (1999).
49. H. Huang, T. Kowalewski, E. E. Remsen, R. Gertzmann and K. L. Wooley, *J. Am. Chem. Soc.*, **119**, 11653 (1997).
50. C. S. Patrickios, W. R. Hertler, N. L. Abbott and T. A. Hatton, *Macromolecules*, **27**, 930 (1994).
51. G. Odian, *Principles of polymerization*, Third Ed., Wiley-Interscience, New York (1991).
52. Y. J. Kim, Y. K. Sung, A. Z. Piao, D. W. Gringer, T. Okano and S. W. Kim, *J. Appl. Polym. Sci.*, **54**, 1863 (1994).
53. S. Beinat, M. Schappacher and A. Deffieux, *Macromolecules*, **29**, 6737 (1996).
54. C. J. Hawker, J. L. Hedrick, E. E. Malmstroem, M. Trollss, D. Mecerreyes, G. Moineau, P. Dubois and R. Jerome, *Macromolecules*, **31**, 213 (1998).
55. K. V. Bernaerts, E. H. Schacht, E. J. Goethals and F. E. Du Prez, *J. Polym. Sci., Part A: Polym. Chem.*, **41**, 3206 (2003).
56. D. Mecerreyes, G. Moineau, P. Dubois, R. Jerome, J. L. Hedrick, C. J. Hawker, E. E. Malmstrom and M. Trollsas, *Angew. Chem.*, **37**, 1274 (1998).
57. S. Angot, D. Taton and Y. Gnanou, *Macromolecules*, **33**, 5418 (2000).
58. F. Bandermann, H. D. Speikamp and L. Weigel, *Makromol. Chem.*, **186**, 2017 (1985).
59. H. S. Yu, W. J. Choi, K. T. Lim and S. K. Choi, *Macromolecules*, **21**, 2893 (1988).
60. G. Hild and J.-P. Lamps, *Polymer*, **39**, 2637 (1998).
61. F. F. Wolf, N. Friedemann and H. Frey, *Macromolecules*, **42**, 5622 (2009).
62. Y. Zhao, X. Shuai, C. Chen and F. Xi, *Chem. Commun.*, 1608 (2004).
63. Y. Zhang, M. Pan, C. Liu and J. Huang, *J. Polym. Sci., Part A: Polym. Chem.*, **46**, 2624 (2008).
64. O. Altintas, A. L. Demirel, G. Hizal and U. Tunca, *J. Polym. Sci., Part A: Polym. Chem.*, **46**, 5916 (2008).
65. A. O. Saeed, S. Dey, S. M. Howdle, K. J. Thurecht and C. Alexander, *J. Mater. Chem.*, **19**, 4529 (2009).
66. Y. You, C. Hong, W. Wang, W. Lu and C. Pan, *Macromolecules*, **37**, 9761 (2004).
67. G. Moad, E. Rizzardo and D. H. Solomon, *Macromolecules*, **15**, 909 (1982).
68. C. J. Hawker, A. W. Bosman and E. Harth, *Chem. Rev.*, **101**, 3661 (2001).
69. B. Keoshkerian, M. Georges, M. Quinlan, R. Veregin and B. Goodbrand, *Macromolecules*, **31**, 7559 (1998).
70. D. Benoit, S. Grimaldi, S. Robin, J.-P. Finet, P. Tordo and Y. Gnanou, *J. Am. Chem. Soc.*, **122**, 5929 (2000).
71. N. L. Hill and R. Braslau, *J. Polym. Sci. A*, **45**, 2341 (2007).
72. A. P. Smith and C. L. Fraser, *Macromolecules*, **35**, 594 (2002).
73. K. Ohno, Y. Izu, S. Yamamoto, T. Miyamoto and T. Fukuda, *Macromol. Chem. Phys.*, **200**, 1619 (1999).
74. M. R. Korn and M. R. Gagne, *Polym. Mater. Sci. Eng.*, **84**, 611 (2001).
75. *Advances in Free-Radical Polymerization*, K. Matyjaszewski, Ed., A.C.S., Washington D.C., 685 (1998).
76. K. Matyjaszewski, *ACS Symp. Series*, **685**, 2 (1998).
77. K. Matyjaszewski, *Macromolecules*, **31**, 4710 (1998).
78. X. Zhang and K. Matyjaszewski, *Macromolecules*, **32**, 1763 (1999).
79. C. Burguiere, C. Chassenieux and B. Charleux, *Polymer*, **44**, 509 (2003).
80. A. Muhlebach, S. G. Gaynor and K. Matyjaszewski, *Macromolecules*, **31**, 6046 (1998).
81. C. Barner-Kowollik and S. Perrier, *J. Polym. Sci., Part A: Polym. Chem.* , **46**, 5715 (2008).
82. Z. Jia, L. Wong, T. P. Davis and V. Bulmus, *Biomacromolecules*, **9**, 3106 (2008).
83. H. Stenzel Martina, C. Barner-Kowollik, P. Davis Thomas and M. Dalton Helen, *Macromol. Biosci.*, **4**, 445 (2004).
84. C. M. Schilli, M. Zhang, E. Rizzardo, S. H. Thang, Y. K. Chong, K. Edwards, G. Karlsson and A. H. E. Mueller, *Macromolecules*, **37**, 7861 (2004).
85. B. S. Sumerlin, M. S. Donovan, Y. Mitsukami, A. B. Lowe and C. L. McCormick, *Macromolecules*, **34**, 6561 (2001).
86. B. S. Sumerlin, A. B. Lowe, D. B. Thomas and C. L. McCormick, *Macromolecules*, **36**, 5982 (2003).
87. A. W. York, S. E. Kirkland and C. L. McCormick, *Adv. Drug Delivery Rev.*, **60**, 1018 (2008).
88. G. Riess, *Prog. Polym. Sci.*, **28**, 1107 (2003).
89. L. Zhang and A. Eisenberg, *J. Am. Chem. Soc.*, **118**, 3168 (1996).
90. C. Allen, D. Maysinger and A. Eisenberg, *Colloids Surf. B*, **16**, 3 (1999).
91. N. Rapoport, *Colloids Surf. B*, **16**, 93 (1999).
92. Y. M. Oh, T. K. Jung, S. C. Chi and B. C. Shin, *J. Korean Chem. Soc.*, **47**, 601 (2003).
93. M. Sasatsu, H. Onishi and Y. Machida, *Int. J. Pharm.*, **294**, 233 (2005).
94. S.-W. Choi, W.-S. Kim and J.-H. Kim, *Methods Mol. Biol.*, **303**, 121 (2005).
95. T. Riley, S. Stolnik, C. R. Heald, C. D. Xiong, M. C. Garnett, L. Illum, S. S. Davis, S. C. Purkiss, R. J. Barlow and P. R. Gellert, *Langmuir*, **17**, 3168 (2001).
96. C. R. Heald, S. Stolnik, K. S. Kujawinski, C. D. Matteis, M. C. Garnett, L. Illum, S. S. Davis, S. C. Purkiss, R. J. Barlow and P. R. Gellert, *Langmuir*, **18**, 3669 (2002).
97. E. Mabrouk, D. Cuvelier, L.-L. Pontani, B. Xu, D. Levy, P. Keller, F. Brochard-Wyart, P. Nassoy and M.-H. Li, *Soft Matt.*, **5**, 1870 (2009).
98. B. M. Discher, Y.-Y. Won, D. S. Ege, J. C. M. Lee, F. S. Bates, D. E. Discher and D. A. Hammer, *Science*, **284**, 1143 (1999).
99. L. Theogarajan, S. Desai, M. Baldo and C. Scholz, *Polym. Int.*, **57**, 660 (2008).
100. H. C. Shum, J.-W. Kim and D. A. Weitz, *J. Am. Chem. Soc.*, **130**, 9543 (2008).
101. R. C. Hayward, A. S. Utada, N. Dan and D. A. Weitz, *Langmuir*, **22**, 4457 (2006).
102. L. Liu, J.-P. Yang, X.-J. Ju, R. Xie, L. Yang, B. Liang and L.-Y. Chu, *J. Colloid Interface Sci.*, **336**, 100 (2009).
103. J. R. Howse, R. A. L. Jones, G. Battaglia, R. E. Ducker, G. J. Leggett and A. J. Ryan, *Nat. Mater.*, **8**, 507 (2009).
104. J. R. Howse, R. A. L. Jones, G. Battaglia, R. E. Ducker, G. J. Leg-

gett and A. J. Ryan, *Nature*, **8**, 507 (2009).
105. P. Taylor, C. Xu, P. D. I. Fletcher and V. N. Paunov, *Chem. Commun.*, 1732 (2003).
106. J. Yang, R. Pinol, F. Gubellini, D. Levy, P.-A. Albouy, P. Keller and M.-H. Li, *Langmuir*, **22**, 7907 (2006).
107. F. Li, L. H. J. d. Haan, A. T. M. Marcelis, F. A. M. Leermakers, M. A. C. Stuartb and E. J. R. Sudholter, *Soft Matt.*, **5**, 4042 (2009).
108. T. Terada, T. Inaba, H. Kitano, Y. Maeda and N. Tsukida, *Macromol. Chem. Phys.*, **195**, 3261 (1994).
109. G. Chen and A. S. Hoffman, *Macromol. Chem. Phys.*, **196**, 1251 (1995).
110. G. Li, X. Yang, B. Wang, J. Wang and X. Yang, *Polymer*, **49**, 3436 (2008).
111. B.-S. Kim, H.-i. Lee, Y. Min, Z. Poon and P. T. Hammond, *Chem. Commun.*, 4194 (2009).
112. M. A. Ward and T. K. Georgiou, *J. Polym. Sci., Part A: Polym. Chem.*, **48**, 775 (2010).
113. J. Li, J. Ren, Y. Cao and W. Yuan, *Polymer*, **51**, 1301 (2010).
114. D. Tong, J. Yao, H. Li and S. Han, *J. Appl. Polym. Sci.*, **102**, 3552 (2006).
115. K. F. Arndt, T. Schmidt and R. Reichelt, *Polymer*, **42**, 6785 (2001).
116. K. Yamamoto, T. Serizawa, Y. Muraoka and M. Akashi, *J. Polym. Sci. A*, **38**, 3674 (2000).
117. H.-H. Lin and Y.-L. Cheng, *Macromolecules*, **34**, 3710 (2001).
118. L. Y. Chu, S. H. Park, T. Yamaguchi and S. I. Nakao, *J. Membr. Sci.*, **192**, 27 (2001).
119. X. D. Xiangrong Chen, Zhaohui Zheng and Yuxing Peng, *New J. Chem.*, **30**, 577 (2006).
120. A. Boudier, A. Aubert-Pouëssel, C. Gérardin, J.-M. Devoisselle and S. Bégu, *Int. J. Pharm.*, **379**, 212 (2009).
121. J. Du, Y. Tang, A. L. Lewis and S. P. Armes, *J. Am. Chem. Soc.*, **127**, 17982 (2005).
122. D. J. Adams, S. Adams, D. Atkins, M. F. Butler and S. Furzeland, *J. Controlled Release*, **128**, 168 (2008).
123. J. Jiang, X. Tong and Y. Zhao, *J. Am. Chem. Soc.*, **127**, 8290 (2005).
124. J. Jiang, X. Tong, D. Morris and Y. Zhao, *Macromolecules*, **39**, 4633 (2006).
125. Y. Zhao and J. He, *Soft Matt.*, **5**, 2686 (2009).
126. X. Tong, G. Wang, A. Soldera and Y. Zhao, *J. Phys. Chem. B*, **109**, 20281 (2005).
127. H.-I. Lee, W. Wu, J. K. Oh, L. Mueller, G. Sherwood, L. Peteanu, T. Kowalewski and K. Matyjaszewski, *Angew. Chem., Int. Ed.*, **46**, 2453 (2007).
128. K. T. Kim, J. J. L. M. Cornelissen, R. J. M. Nolte and J. C. M. van Hest, *PMSE Prepr.*, **101**, 1115 (2009).
129. L.-C. You, F.-Z. Lu, Z.-C. Li, W. Zhang and F.-M. Li, *Macromolecules*, **36**, 1 (2003).
130. B. Wang, R. Ma, G. Liu, Y. Li, X. Liu, Y. An and L. Shi, *Langmuir*, **25**, 12522 (2009).
131. A. Napoli, M. J. Boerakker, N. Tirelli, R. J. M. Nolte, N. A. J. M. Sommerdijk and J. A. Hubbell, *Langmuir*, **20**, 3487 (2004).
132. K. Stubenrauch, I. Voets, G. Fritz-Popovski and G. Trimmel, *J. Polym. Sci., Part A: Polym. Chem.*, **47**, 1178 (2009).

ABBREVIATIONS

ARGET : activators regenerated by electron transfer
APBA : 3-aminophenylboronic acid
ATRP : atom transfer radical polymerization
bcc : body-centered cubic
CLP : controlled living polymerization
CMC : critical micelle concentration
CPDB : cyanoisopropyldithiobenzoate
CTA : chain transfer agent
DEPN : *N-tert*-butyl-*N*-[1-diethylphophono-(2,2-dimethylpropyl)] nitroxide
DMF : dimethylformamide
DMSO : dimethylsulfoxide
ECMX : O-ethyl-S-cyanomethyl xanthate
FRP : free-radical polymerization
GTP : group transfer polymerization
ICAR : initiators for continuous activator regeneration
LAP : living anionic polymerization
LCP : living cationic polymerization
LCST : lower critical solution temperature
LRP : living radical polymerization
NMP : nitroxide-mediated polymerization
PAA : poly (acrylic acid)
PAMA : poly (alkyl(meth)acrylate)
PAMPC : poly (2-acryloyloxyethyl phosphorylcholine)
PBA : poly (butyl acrylate)
PCEMA : poly (2-cinnamoylethyl methacrylate)
PCL : poly (*e*-caprolactone)
PCLA : poly (lactide-*co*-caprolctone)
PDEAEMA : poly (2-diethylaminoethyl methacrylate)
PDMA : poly (*N*,*N*-dimethylacrylamide)
PDMAEMA : poly (2-dimethylaminoethyl methacrylate)
PDMS : poly (dimethylsiloxane)
PDPA : poly (2-diisopropylaminoethyl methacrylate)
PEG : poly (ethyl glycol)
PEO : poly (ethylene oxide)
PGEA : poly (2-glucosyloxyethyl acrylate)
PHEMA : poly (2-hydroxyethyl methacrylate)
PLA : poly (lactic acid)
PLLA : poly-L-lysine
PMA : poly (methacrylate)
PMAA : poly (methacrylic acid)
PMMA : poly (methyl methacrylate)
PMPC : poly (2-methacryloyloxyethyl phosphorylcholine)
PMVE : poly (methyl vinyl ether)
PNaAMBA : poly (sodium 3-acrylamido-3-methylbutanoate)
PNaAMPS : poly (sodium 2-acrylamido-2-methylpropanesulfonate)
PNaSS : poly (sodium 4-styrenesulfonate)
PNaVB : poly (sodium 4-vinylbenzoate)
PNIPAAm : poly (*N*-isopropyl acrylamide)
PNVIBA : poly (*N*-vinylisobutyramide)
PPO : poly (propylethylene oxide)
PPS : poly (propylene sulfide)
PSBA : poly (styrene boronic acid)
PSM : poly (sulfamethazine methacrylate)
PSt : poly (styrene)
PTMS : poly (2-trimethylsilyloxyethyl acrylate)
RAFT : reversible addition fragmentation chain transfer
RES : reticuloendothelial system

ROMP : ring opening metathesis polymerization
SET-LRP: single-electron transfer living radical polymerization
TEMPO : tetramethyl piperidyl-*N*-1-oxyl
THF : tetrahydrofuran
TPAHN : *tert*-butyl-2-methyl-1-phenoxy nitroxide
UCST : upper critical solution temperature
VPTT : volume phase transition temperature
W/O/W : water-in-oil-in-water