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# Schizophrenic thermoresponsive block copolymer micelles based on LCST and UCST behavior in ethanol–water mixtures

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ABSTRACT

The development of responsive and multiresponsive polymers is gaining interest as they enable the development of more and more complex responsive materials. In this contribution, the synthesis and solubility behavior of well-defined poly(methyl acrylate) (PMA) and poly(diethylene glycol ethyl ether acrylate) (PDEGEA) homopolymers as well as PMA-*block*-PDEGEA block copolymers is reported. At first, a solubility screening of the homopolymers in ethanol–water solvent mixtures was performed in a high-throughput experimentation (HTE) manner using parallel turbidimetry, which revealed that in 35 wt% ethanol PMA undergoes an upper critical solution temperature (UCST) phase transition while PDEGEA undergoes a lower critical solution temperature phase transition in this solvent mixture. Moreover, the thermoresponsive self-assembly of PMA-*b*-PDEGEA block copolymers in water and ethanol were investigated by turbidimetry and DLS revealing UCST-induced disassembly of the micelles in ethanol and LCST-induced clustering of the micelles in water. Finally schizophrenic behavior of the PMA-*b*-PDEGEA block copolymers in 35 wt% ethanol is demonstrated.



## 1. Introduction

Thermoresponsive polymers have attracted significant interest due to their potential applications in drug delivery, homogeneous catalysis, biomimetic materials, and cosmetics. Polymeric micelles are mostly prepared via self-assembly of amphiphilic block copolymers and the incorporation of thermoresponsive polymer blocks leads to responsive micelles [1–8]. The preparation of such well-defined amphiphilic block copolymers is strongly facilitated by the important advances that have been made in living and controlled polymerization techniques in the last few decades [9–14]. These polymerization techniques, including anionic, controlled radical, group transfer, and metathesis polymerization, have all been successfully used to prepare well-defined block copolymers.

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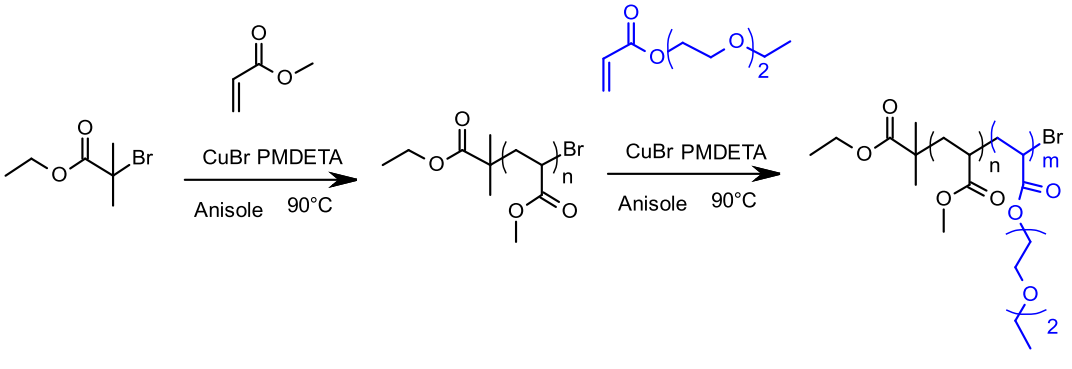
Thermoresponsive polymer solubility transitions can be basically divided in two types; lower critical solution temperature (LCST) behavior and upper critical solution temperature (UCST) behavior. From the literature perspective, LCST is most commonly studied since all water-soluble polymers with intermediate hydrophilicity exhibit a LCST transition, including a wide range of homopolymers and almost unlimited number of different copolymers [15–21]. The LCST phase transition has also been exploited for a wide range of applications often in the biomedical field [17,22], including drug delivery [15,23], switchable surfaces for cell growth [24,25] and actuators for microfluidic devices [26,27], whereby the transition temperature can be easily tuned by copolymerization or by adding additives like salts or buffers [28–31]. In contrast to the vast amount of literature on LCST polymers, much less studies are reported involving UCST polymers since a UCST phase transition is not commonly observed in aqueous polymer solutions. From a thermodynamic perspective, temperature induced solubility phase transitions are related to both polymer–polymer and polymer–solvent interactions. In water the polymer–solvent interactions mainly depend on hydrogen bonding between water and the polymer as well as polymer–polymer interactions. Heating an aqueous polymer solution will decrease the attractive hydrogen bonding polymer–water interactions while the loss of entropy due to fixation of water molecules increases. Eventually, this leads to entropy driven dehydration of the polymer chains upon heating, i.e. LCST behavior. Since UCST behavior is the reverse phenomenon, it rarely occurs in water and specific polymers need to be designed with strong attractive forces at low temperature while being strongly hydrophilic to avoid the occurrence of LCST behavior upon heating too, or at least make sure the LCST phase transition occurs at higher temperatures than the UCST phase transition [32–35]. Alternatively, the solvent can be changed from water to alcohol/water mixtures that show non-ideal mixing behavior, accompanied with significant decrease in solvent polarity upon heating also leading to a UCST type phase behavior [36,37]. There are several polymer classes that are studied for their UCST behavior in water like poly(vinyl methyl ether)s [38], *N*-acryloylglycinamide (NAGA) homopolymer and copolymers from NAGA and *N*-acetylacrylamide (NAcAAm) [32,35], poly(*p*-dioxanone)-grafted poly(vinyl alcohol) copolymers [39], proline based systems [40] and homopolymers of *N*-acryloylasparaginamide [34]. UCST behavior in water–alcohol solvent mixtures has been reported for, e.g., poly(2-oxazoline)s [41–43], poly(methyl methacrylate) [44–46], poly(methyl acrylate) [47], poly(oligoethyleneglycol (meth)acrylate) [46] and a polyampholyte [48]. Furthermore, polymer UCST behavior has been observed in water–DMSO mixtures [49] or in ionic liquids [50] too. From the application perspective, there are only few examples involving UCST polymers utilization for nanoparticles [51], nanocomposites [52] and nanogels [53].

The occurrence of LCST and UCST behavior in different polymer systems prompted scientists to combine both within a single material. In case of block copolymers, such dual responsive systems that can form micelles or reversed micelles at different conditions are known as 'schizophrenic' block copolymers [54]. Combining both LCST and UCST thermoresponsive behavior into one block copolymer enables inversion of core and corona by simply changing the temperature and has mostly been achieved with polybetaines [55–58] or polysulfobetaine [59–61] as UCST polymer [62–65]. For example, a non-ionic LCST polymer based on *N*-isopropylacrylamide (NIPA) and a polybetaine UCST polymer based on 3-[*N*-(3-methacrylamidopropyl)-*N*,*N*-dimethyl]ammoniopropane sulfonate was reported to yield schizophrenic block copolymers after fine tuning of the block length [66]. Only very recently, we reported a schizophrenic block copolymer that could be switched between three states based on the combined UCST and LCST behavior of poly(dimethylaminoethyl methacrylate) in presence of hexacyanocobalt(III) trivalent anions [67–69].

In the current contribution, we aimed to introduce both LCST and UCST behavior within a non-ionic amphiphilic block copolymer leading to both thermoresponsive as well as schizophrenic micelles, depending on the utilized solvent mixture. Poly(methyl acrylate) (PMA) was chosen as UCST block based on our recent report that it shows UCST behavior in ethanol–water solvent mixtures [47]. Poly(diethylene glycol ethyl ether acrylate) (PDEGEA) was chosen as LCST segment since it shows LCST behavior in water and expectedly also in ethanol–water solvent mixtures with low ethanol content [70]. At first, the LCST and UCST behaviors of PMA and PDEGEA homopolymers




**Scheme 1.** Schematic representation of the synthesis of PMA macroinitiators and PMA-*b*-PDEGEA block copolymers via ATRP.

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