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Thermoresponsive poly(oligo ethylene glycol acrylates)

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ABSTRACT

Thermoresponsive polymers have been the subject of numerous publications and research topics in the last few decades mostly driven by their easily controllable temperature stimulus and high potential for in vitro and in vivo applications. P(NIPAAm) is the most studied amongst these polymers, but recently other types of polymers are increasingly being investigated for their thermoresponsive behavior. In particular, polymers bearing a short oligo ethylene glycol (OEG) side chain have been shown to combine the biocompatibility of polyethylene glycol (PEG) with a versatile and controllable LCST behavior. These polymers can be synthesized via controlled radical polymerization techniques from various monomers consisting of an OEG chain and a polymerizable group like a (meth)acrylate, styrene or acrylamide. OEG acrylates offer significant advantages over, e.g., OEG methacrylates as the lower hydrophilicity of the backbone facilitates thermoresponsive behavior with smaller, more defined side chains. Furthermore, PEG acrylates can be polymerized using all major controlled radical polymerization techniques, unlike OEG methacrylates. This review will focus on OEG acrylate based (co)polymers and will provide a comprehensive overview of their reported thermoresponsive properties. The combination and comparison of this data will not only highlight the potential of these monomers, but will also serve as a starting point for future studies.

Abbreviations: AA, acrylic acid; AIBN, azobisisobutyronitrile; AMHS, aminoethyl methacrylate hydrochloride; Amor, *N*-acryloyl-morpholine; ATRP, atom-transfer radical polymerization; BB, blocbuilder®; BSPA, 3-(benzylsulfanylthiocarbonylsulfanyl)propionic acid; CBDB, 2-cyano-2-butyl dithiobenzoate; CBI, cholesteryl-2-bromoisobutyrate; CTA1, 1,2-*bis*-(4-(*t*-butoxy-carbonyl)benzyl sulfanylthiocarbonyl sylfanyl) ethane; CTA2, 4-butylsulfanyl-thiocarbonyl-sulfanylmethyl-benzoic acid; CTA3, 1,1,1-*tris*(3-(4-(tert-butoxycarbonyl)-benzylsulfanyl-thiocarbonyl-sulfanyl-propanoyl-oxy))-ethane; CTA4, 2-[[(dodecylthio)thioxomethyl]thio]-2-methyl propanoic acid; CTA5, S,S′-bis(α,α′-dimethylacetic acid) trithiocarbonate; *Đ*, dispersity; DBTTC, dibenzyltrithiocarbonate; DCPA, 2-[(dodecylsulfanylcarbonylthiolsulfanyl) propionic acid]; DEA, 2-(1,3-dioxan-2-yloxy)ethyl acrylate; DLS, dynamic light scattering; DMA, *N*,*N*-dimethylacrylamide; DMDEA, 2-(5,5-dimethyl-1,3-dioxan-2-yloxy)ethyl acrylate; 4-DMNMA, 2-(6-(dimethylamino)-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)ethyl methacrylate; DMP, 2-dodecylsulfanylthiocarbonylsulfanyl-2-methyl-propionic acid; DP, degree of polymerization; EBiB, ethyl 2-bromoisobutyrate; EBP, ethyl 2-bromopropionate; eDEGA, di(ethylene glycol) ethyl ether acrylate; EGFP, enhanced green fluorescent protein; eTEGA, tri(ethylene glycol) ethyl ether acrylate; F_M, fraction of monomer M incorporated in the polymer; f_M, fraction of monomer M in the polymerization mixture; FRP, free radical polymerization; GC, gas chromatography; GOx, glucose oxidase; HEA, hydroxyethyl acrylate; HPA, hydroxypropyl acrylate; LCST, lower critical solution temperature; MALDI, matrix assisted laser desorption/ionization; MBP, methyl 2-bromopropionate; MBSP, 4-methoxybenzylsulfanylthiocarbonylsulfanylpropane; mDEGA, di(ethylene glycol) methyl ether acrylate; mDEGMA, di(ethylene glycol) methyl ether methacrylate; M_n, number average molecular weight; mEGA, ethylene glycol methyl ether acrylate; mOEGA, oligo(ethylene glycol) methyl ether acrylate; mOEGMA, oligo(ethylene glycol) methyl ether methacrylate; mTEGA, tri(ethylene glycol) methyl ether acrylate; NBA, nitrobenzyl acrylate; NMP, nitroxide mediated polymerization; OEG, oligo(ethylene glycol); OEGA, oligo(ethylene glycol) acrylate; PBS, phosphate buffer solution; PEG, poly(ethylene glycol); PNIPAAm, poly(*N*,*N*-dimethylacrylamide); SPNP, superparamgnetic nanoparticle; RAFT, reversible addition-fragmentation chain-transfer polymerization; SEC, size exclusion chromatography; SG1, *N*-*tert*-butyl-*N*-(1′-diethylphosphono-2.2′-dimethylpropyl)-nitroxide; T_{cp}, cloud point temperature; TEGSt, 4-vinylbenzyl methoxytris(oxyethylene) ether; TFA, trifluoroacetic acid; TGA, thermogravimetric analysis; TPANO, 2,2,5-trimethyl-4-phenyl-3-azahexane-3-nitroxide; TPPA, 2,2,5-trimethyl-3-(2-phenylethoxy)-4-phenyl-3-azahexane; UCST, upper critical solution temperature.

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Contents

1. Introduction

The field of stimuli-responsive polymers and polymeric materials, that change their physical properties in response to external stimuli, has considerably expanded in the last few decades. The most common stimuli include temperature, pH, electromagnetic radiation and small molecules like glucose, which can trigger a variety of responses such as a color change, a change in shape or a phase transition, all of which have been reported and reviewed extensively [1–7]. Thermosensitive polymers are amongst the most widely investigated responsive polymers due to their potential biomedical applications and easy to control stimulus. A temperature response can be achieved via a number of mechanisms including liquid crystal elastomer transitions [8,9] and solid state transitions in shape memory materials [10,11], although a solution phase transition around a certain temperature is the most widely used (Fig. 1, left). This temperature is referred to as a lower critical solution temperature (LCST) if the polymer becomes insoluble upon heating or upper critical solution temperature (UCST) if it becomes soluble upon heating [1,3,12]. Of all known thermoresponsive polymers, poly(*N*-isopropylacrylamide) (PNIPAAm) is generally considered to be the gold standard (Fig. 1, right). Its LCST around body temperature (≈32 °C) in water together with a low concentration and pH dependency make it a prime candidate for in vivo biomedical applications [13].

An emerging class of thermoresponsive polymers that may compete with or even surpass PNIPAAm are polymers bearing short oligo ethylene glycol (OEG) side chains [14]. Such polymers are easily accessible via polymerization of OEG macromonomers that consist of an asymmetrical OEG chain functionalized with both a polymerizable group, e.g., acrylate, methacrylate or styrene, and a methyl ether, ethyl ether or hydroxy-group. Polymerization of these monomers provides direct access to previously inaccessible poly(ethylene glycol) (PEG) architectures like comb/graft copolymers or even PEG networks using, e.g., controlled radical polymerization techniques, expanding the possibilities far beyond linear PEG [15]. The resulting polymers are predominantly built up of OEG units, making them highly biocompatible similar to linear PEG [16–20]. These new architectural possibilities, however, introduce a specific combination of α and ω end-groups related to the chosen CRP technique and controlling agent, which significantly influences the polymer cytotoxicity as shown by Maynard and coworkers in 2009 [21]. Careful control of the hydrophilic/hydrophobic balance of such polymers by considerate monomer design allows a versatile and predictably tuneable thermoresponsive behavior.

Upon heating an LCST polymer solution, phase separation will occur at the cloud point temperature (T_{cp}), which is accompanied by the formation of phase separated, high polymer concentration droplets, leading to clouding of the solution. At the T_{cp}, the enthalpic gain due to hydrogen bonding of water molecules to the polymer can no longer compensate the entropic loss, leading to a Gibbs free energy equal to zero indicating that water acts as theta solvent at this temperature. Increasing the hydrophilicity of the polymer will therefore increase the enthalpic gain and increase the T_{cp}, i.e. the point where the enthalpic gain just compensates for the entropic loss, whereas increasing the hydrophobicity will decrease the cloud point. This means that the hydrophilic/hydrophobic balance of the polymer determines the cloud point, which in turn can be controlled by the identity of monomer i.e. type of backbone, side chain length and end-group [22]. The most common types of backbone are acrylates or methacrylates [16,17,23–31] and in a few cases styrenics

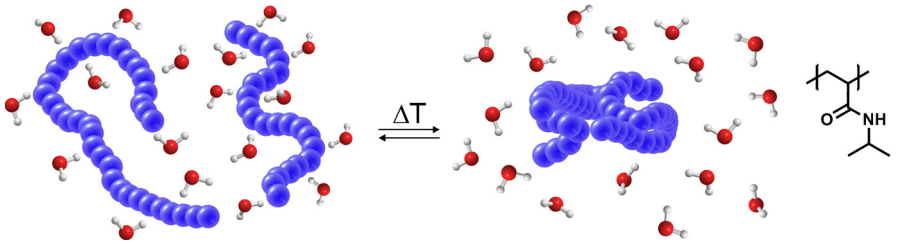

Fig. 1. Left Schematic representation of a polymer phase transition in aqueous solution from a completely dissolved homogeneous state to a two-phase demixed system comprising a high polymer concentration phase and a low polymer concentration aqueous phase. Even though the collapsed polymer chains in the high concentrated phase are still partially hydrated, these water molecules are not shown in the picture for simplicity. The scheme shows an LCST transition if $\Delta T > 0$ and an UCST if $\Delta T < 0$. Right: the chemical structure of PNIPAAm.

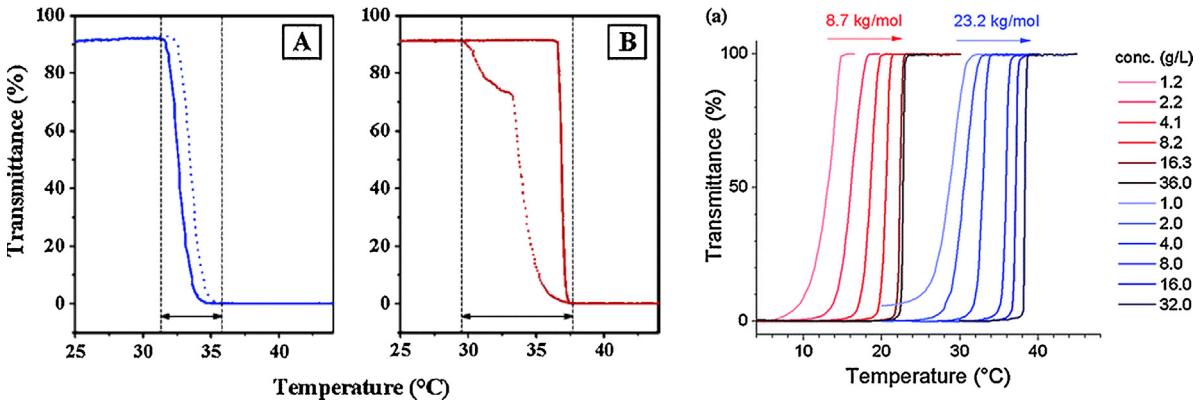

Fig. 2. Comparison of the LCST behavior between equal length P(mDEGMA$_{95}$-*co*-mOEGMA$_5$) (blue) and PNIPAAm (red) in aqueous solution (3 wt%) [14], Copyright 2006. Reproduced with permission from the American Chemical Society. Right: UCST behavior of P(mOEGMA) in isopropanol and its M_n and polymer concentration dependency [19]. Copyright 2011. Reproduced with permission from the Royal Society of Chemistry. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

[32–35], vinyl ethers [36–39], (meth)acrylamides [20] or other less common polymers such as polycarbonates [40], poly-L-cysteines [41] or poly(isocyanide)s [42–44]. Side chain end-groups are mostly limited to hydroxyl-, methyl or ethyl groups. Beside the monomer, other polymer characteristics like molecular weight, dispersity $Đ$ and α and ω end-groups can cause significant changes in T_{cp} [45]. Finally, environmental factors like polymer concentration in (aqueous) solution and the presence and concentration of ions also can strongly influence T_{cp} [46].

Of all the types of ethylene glycol based macromonomers, the OEG methacrylates (OEGMA) have been most extensively studied, reported and reviewed by various groups [16,17,23–29]. Thermoresponsive OEGMA homopolymers, prepared by living anionic polymerization, were first reported by Ishizone in 2003[24], but this class of LCST polymers were only widely recognized after the work of Lutz in 2006 where he demonstrated the tunability of the T_{cp} by copolymerization of short and long OEGMA monomers using atom transfer radical polymerization [47]. Shortly after, Lutz compared the thermoresponsive properties of an OEGMA copolymer to PNIPAAm openly suggesting that these types of copolymers posses the potential to surpass the "gold standard" (Fig. 2, left). This statement is directed by the tunability of the T_{cp}, the limited hysteresis between heating and cooling curves and the similar level of biocompatibility as linear PEG [14]. More recently these types of polymers have also been reported to exhibit UCST behavior in aliphatic alcohol/water mixtures with similar versatility and controllability (Fig. 2, right) [19,48].

While methacrylates are less prone to hydrolysis by their more hydrophobic backbone [17,49], that same backbone greatly limits the use of small defined side groups. In order to create the delicate hydrophilic/hydrophobic balance required for LCST behavior, most publications use the longer OEGMA chains containing 8–9 ethylene glycol repeat units [17,46,47,50–53], and only a handful of studies report the combination of the 'shorter' defined OEGMAs, such as mDEGMA and mTEGMA [54,55]. The utilization of longer OEG side chains results, however, in ill-defined graft copolymer structures with a chain length distribution in the side chains, somehow conflicting the use of controlled radical polymerization (CRP) methods, graphically represented in Fig. 3 for a mDEGA-mOEGA statistical copolymer. Furthermore, OEGMA monomers cannot be polymerized with all of the three most popular CRP methods since nitroxide mediated polymerization (NMP) of OEGMA is not possible without adding small amounts of styrenic comonomers [56,57].

The less hydrophobic acrylate backbone opens up a new range of possible thermosensitive monomers including smaller defined mono-, di- and triethylene glycol chains, which are either commercially available or can be synthesized using the available oligoethylene glycol mono ether. End-group functionalization of polyacrylates is also considered to be easier compared to the polymethacrylate analogs [58]. Furthermore, acrylates can also be polymerized by NMP, albeit backbiting and branching can be more pronounced for acrylates compared to methacrylates, especially at elevated temperature (>80 °C) required for NMP [59]. Nonetheless, well-defined poly(oligo ethylene glycol acrylate)s (POEGA)s have a less hydrophobic backbone compared to POEGMAs facilitating access to the required hydrophilic/hydrophobic balance for thermoresponsive behavior with a wide variety of short defined side chains. Despite these advantages of POEGAs, they are significantly less represented in scientific literature than POEGMAs. The aim of this review is, therefore, to discuss the literature on POEGAs and to provide a comprehensive overview of their thermoresponsive properties to illustrate their highly beneficial properties.

The versatility of thermoresponsive POEGAs is shown in Fig. 4 depicting a number of different, easily available monomer structures and the average T_{cp} of the corresponding homopolymers. The used abbreviations of OEG(M)As in the current literature are not consistent, which may cause confusion. Mono(ethylene glycol) methyl ether acrylate for example is occasionally abbreviated as MEA [60,61,62,63,64], EGMEA [65] or MOEA [66] and TEGMA could be interpreted as both triethylene glycol methyl ether acrylate [33,67–69] or triethylene glycol methyl ether methacrylate [24,70]. To prevent any confusion in this

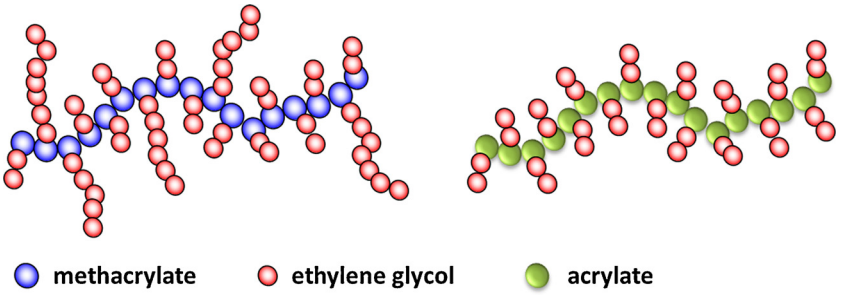

Fig. 3. Graphic representation of the difference in side length distribution through the comparison of the commonly studied thermoresponsive P(mDEGMA-co-mOEGMA) copolymers with P(mDEGA) with defined short side-chains.

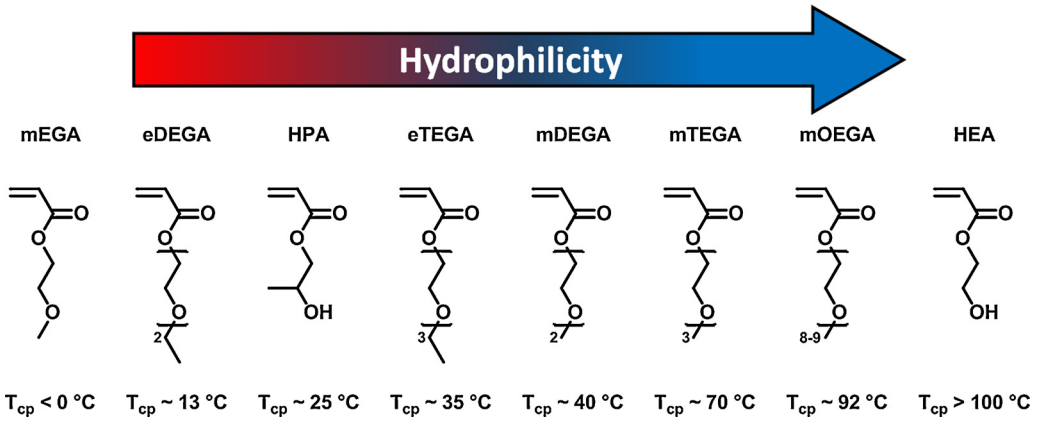

Fig. 4. Overview of the selected OEGA monomers that will be discussed in this review and their abbreviations, arranged according to increased hydrophilicity, with average cloud point temperatures (T_{cp}) of the corresponding homopolymer.

review all monomers will be named following the same easy systematic scheme: the central part of the abbreviation consists of the number of ethylene glycol units in the monomer and will be generally written as XEG where EG means (mono)ethylene glycol, DEG diethylene glycol, TEG triethylene glycol, etc. The type of backbone will be abbreviated as follows: A for acrylates and MA for methacrylates. The end-group of the ethylene glycol side chain will be annotated by a letter preceding the abbreviation: m for methyl, e for ethyl and H for hydrogen. The only exceptions are hydroxyethylacrylate and hydroxypropylacrylate, which are generally known as HEA and HPA, respectively.

2. Thermoresponsive OEGA homopolymers

This chapter will focus on thermoresponsive OEGA homopolymers and will discuss the reported T_{cp}s. All homopolymers will be described according to increasing monomer hydrophilicity starting from mEGA (Fig. 4). The table at the end of the chapter summarizes all the discussed OEGA homopolymers and contains all the given data on the polymer characteristics for an easy comparison of T_{cp}s (Table 1). All the T_{cp}s were measured in aqueous solutions unless mentioned otherwise. Since the monomer structure is the main influencing factor, differences in reported T_{cp}s for a certain POEGA are rather small and caused by differences in molecular weight, polymer end-group or polymer concentration, for example.

mEGA is the most hydrophobic OEGA monomer and therefore has the lowest T_{cp}. The only reported T_{cp} of P(mEGA) was published by Moeller and co-workers in 2012. The homopolymer was synthesized using NMP with Blocbuilder® (BB) as controlling agent. This species is an alkoxyamine that homolytically cleaves into an isobutyric acid radical and the stable nitroxide radical *N*-*tert*-butyl-*N*-(1′-diethylphosphono-2.2′-dimethylpropyl)-nitroxide (SG-1) at mildly elevated temperatures (>30 °C). The use of a 1/0.1 BB/SG-1 ratio allowed for the controlled synthesis of P(mEGA) with a T_{cp} of 5 °C (0.5 wt%) [61]. The same group also reported a $T_{cp} < 0$ (0.5 wt%) for P(mEGA), synthesized via RAFT using dibenzyl trithiocarbonate (DBTTC) as chain transfer agent [64]. This difference in T_{cp} can be ascribed to the higher hydrophobicity of the two benzyl end-groups of the latter polymer, decreasing the (already) very low T_{cp} of the comparable P(mEGA) prepared via NMP to a value below 0 °C.

The thermoresponsive properties of P(eDEGA) were first reported by Lutz and co-workers in 2007 as proof of the possible thermoresponsivity of POEGA. P(eDEGA) was synthesized via atom transfer radical polymerization (ATRP) (M_n = 17,500 g/mol, $Đ$ = 1.66) and showed a T_{cp} of 9 °C (0.3 wt%). A few years later, Davis and co-workers reported a higher T_{cp} of 15 °C (0.2 wt%) for a P(eDEGA)

Table 1
Overview of all the reported cloud points (T_{cp}) in aqueous solution of oligo ethylene glycol acrylate homopolymers and relevant data with regard to polymer structure and T_{cp} determination.

Homopolymer	Wt%[c]	T_{cp} (°C)	M_n (g/mol)	$Đ$	Polym. tech.	Remarks	Ref.
P(mEGA)	0.5	5	5800[f]	1.28	NMP	BB/SG-1	[61]
P(eDEGA$_{95}$)[a]	0.3	≈9	17,500[g]	1.66	ATRP	MBP, CuBr/Bipy	[90]
P(eDEGA$_{62}$)[a]	0.1	10	11,600[f]	1.41	RAFT	DMP/AIBN	[76]
P(eDEGA$_{93}$)[a]	0.5	16.5	16,600[f]	2.1	FRP	AIBN	[75]
P(eDEGA$_{73}$)[a]	0.5	13.2	9900[f]	1.3	NMP	BB/SG-1	[75]
P(eDEGA$_{162}$)[a]	0.2	15	21,500[h]	1.23	RAFT	BSPA/AIBN	[71,91]
P(HPA)	10	16	n.d.	n.d.	n.d.	n.d.	[78]
P(HPA)	0.25–1.5	33.3–18.3	11,100[i]	1.21	NMP	BB/SG-1	[79]
P(HPA)	0.25–2.0	31.8–19.2[d]	9100[f]	1.19	NMP	BB/SG-1	[80]
P(HPA)	0.2	29.5	6500[j]	n.d.	FRP	AIBN	[82]
P(HPA$_{75}$)[a]	0.5	31.7	11,200[f]	3.2	FRP	AIBN	[75]
P(HPA$_{75}$)[a]	0.5	28.7	9000[f]	1.4	NMP	BB/SG-1	[75]
P(HPA$_{38-98}$)[a]	0.5	63–37	2800–9100[k]	1.08–1.15	RAFT	CTA4/AIBN, pH = 6.5	[81]
P(HPA$_{29-98}$)[a]	0.5	61–32	2000–5900[k]	1.18–1.28	RAFT	CTA5/AIBN, pH = 2	[81]
P(eTEGA)	0.1	34	8000[l]	2.3	ATRP	EBP, CuBr/PMDETA	[84]
P(eTEGA$_{74}$)[a]	0.2	36	14,500[g]	1.16	ATRP	EBiB, CuBr/PMDETA	[83]
P(eTEGA)	0.1	35–39	7000–40,000[m]	1.2–2.3	ATRP, RAFT & AP	EBP, CuBr/PMDETA; CBDB/AIBN, LDA/LiCl	[85]
P(mDEGA$_{28-513}$)[a]	0.3	9.0–41.2	4500–36,400[n]	1.20–1.47	RAFT	CTA1/AIBN, 2 symmetrical *tert*-butyl benzoate end-groups	[86]
P(mDEGA$_{28-513}$)[a]	0.3	16.8–42.0	n.d.[o]	n.d.	RAFT	CTA1/AIBN, post modified to 2 symmetrical benzoic acid end-groups	[86]
P(mDEGA$_{24-337}$)[a]	0.3	18.0–41.8	2500–35,200[n]	1.25–1.44	RAFT	CTA2/AIBN, benzoic acid and butyl end-group	[86]
P(mDEGA)	0.1	38	9700[h]	1.7	RAFT	MBSP/AIBN	[87]
P(mDEGA$_{76}$)[a]	0.05–1	46–38[e]	9200[g]	1.14	NMP	TPPA/TPANO	[33]
P(mDEGA)	0.5	36.5–42[e]	8400–16,000[g]	n.d.	NMP	TPPA/TPANO	[33]
P(mDEGA)	0.5	44.5–46[e]	8200–15,800[g]	n.d.	NMP	TPPA/TPANO, after removal of nitroxide group by reduction with ascorbic acid	[33]
P(mDEGA)	0.5	45	51,000[p]	3.4	FRP	AIBN	[89]
P(mTEGA$_{52}$)[a]	0.05–1	75–56[e]	7800[g]	1.18	NMP	TPPA/TPANO	[33]
P(mTEGA)	0.5	56–61[e]	6700–12,400[g]	n.d.	NMP	TPPA/TPANO	[33]
P(mOEGA)[b]	0.2	92–94	12,300–24,400[h]	1.18–1.25	RAFT	BSPA/AIBN	[71,91]

[a]Units calculated using ^{1}H NMR spectroscopy; [b]M_n = 454 g/mol, 8–9 units; [c]All values for concentration were calculated into wt%, e.g., 5 mg/ml = 0.5 wt%; [d]Calculated from exponential fit of the experimental data; [e]Estimated from graph. M_n (g/mol) and $Đ$ were calculated via SEC, given as a range between min. and max. values; [f]DMF (LiBr) vs. PMMA standards; [g]THF vs. PS standards; [h]DMA (LiBr) vs. PS standards; [i]DMA (LiCl) vs. PMMA standards; [j]THF; [k]THF (BHT) vs. PMMA standards; [l]n.d. vs. PS standards; [m]THF with MALLS; [n]THF vs. PS standards; [o]Same values of the pre-modified polymer (see previous table entry); [p]$CHCl_3$ vs. PEG standards.

containing a benzyl/carboxylic acid end-group combination synthesized by reversible addition-fragmentation chain transfer (RAFT) polymerization [71]. Moeller and co-workers used eDEGA as model monomer for the optimization of lipase-catalyzed transacylation of methyl (meth)acrylate with mono-alcohols, diols or triols for the synthesis of functional (meth)acrylate monomers [72,73]. These monomers were then (co)polymerized via free radical polymerization (FRP) and NMP to investigate their thermoresponsive properties. Beside the obvious differences in M_n and $Đ$, the T_{cp} decreased by 3 °C from 16.5 °C for FRP (AIBN) to 13.2 °C (0.5 wt%) for NMP (BB/SG-1), ascribed to the more hydrophobic SG-1 end-group [74,75]. Recently, Sumerlin reported P(eDEGA) via RAFT using 2-dodecylsulfanyl thiocarbonylsulfanyl-2-methyl-propionic acid (DMP) yielding a T_{cp} of 10 °C, confirming the pre-existing range [76].

HPA is perhaps the most unique OEGA monomer since it results in rather hydrophobic polymers while containing a hydroxyl group. Furthermore, it is actually sold and used as a mixture of isomers, making every homopolymer a statistical copolymer. The isomeric mixture contains approximately 75% 2-hydroxypropyl acrylate (2-HPA, Fig. 4) and 25% 1-methyl-2-hydroxyethyl acrylate (1-MeHPA) as a result of its synthesis through the ring opening of propylene oxide with acrylic acid (AA) [77]. The first report of the thermoresponsive properties of P(HPA) was published by Taylor and Cerankowski in 1975 during their investigation of new polymer films with temperature dependent permeability [78]. They reported a T_{cp} of 16 °C (10 wt%), which is up to this date still the lowest T_{cp} reported for P(HPA) in scientific literature. Schubert and co-workers investigated the thermoresponsive properties of P(HPA) in further detail by evaluating the dependency of the T_{cp} on the polymer concentration [79]. P(HPA), synthesized via NMP (BB/SG-1, M_n = 11,100 g/mol, $Đ$ = 1.21), showed T_{cp}s ranging from 33.3 °C (0.25 wt%) to 18.3 °C (1.5 wt%). Beside this common inverse dependency between T_{cp} and polymer concentration, they could also observe an increasingly large hysteresis and width of the transition with increasing concentration (Fig. 5). This T_{cp} range and dependency was confirmed one year

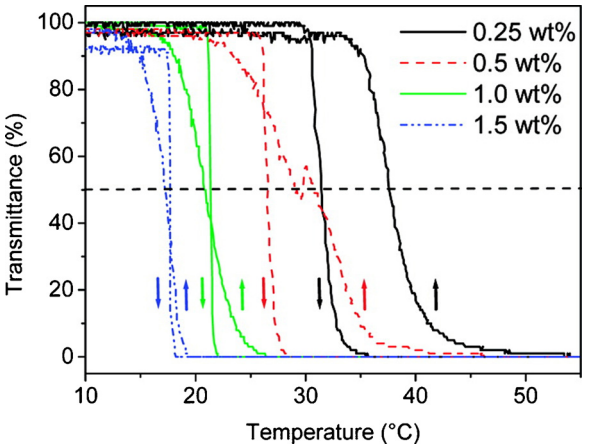

Fig. 5. Transmittance as a function of temperature at a heating and cooling rates of 1 K/min for P(HPA) at different polymer concentrations in aqueous solution, determined by turbidity measurements at 600 nm (the modulation imposed on the curves represents fluctuations in the turbidity measurements determined at discrete intervals) [79].

later by Moeller and co-workers who also synthesized P(HPA) via NMP (BB/SG-1) and reported T_{cp}s ranging from 31.8 °C (0.25 wt%) to 19.2 °C (2.0 wt%). The kinetics of the homopolymerization of HPA were further investigated by ^{1}H NMR spectroscopy allowing to distinguish between the two isomers and to study their reactivity separately. It was reported that the minor HPA isomer, 1-MeHPA, had a slightly lower reactivity compared to 2-HPA. The lower reactivity was proposed to be caused by the sterically more hindered radical and/or the increased radical stabilization through the secondary carbon attached to the ester [80]. A year later, the same group reported the successful synthesis of HPA as a mixture of isomers via the lipase-catalyzed transacylation of methyl acrylate with 1,2-propanediol similar to the synthesis of eDEGA [72]. The polymerization of the synthesized monomer via FRP (AIBN) and NMP (BB/SG-1) revealed a T_{cp} (0.5 wt%) of 31.7 °C and 28.7 °C, respectively, coinciding with the trend for P(eDEGA). This decrease in T_{cp} can again be attributed to the effect of the hydrophobic SG-1 end-group [74,75]. In the same year, Tirelli et al. used RAFT to synthesize P(HPA) of varying length with on one or both polymer chain ends a carboxylic acid group. These very hydrophilic end-groups cause a dramatic increase in T_{cp} especially for the shorter polymers. They report T_{cp}s ranging from 63 to 37 °C (0.5 wt%, pH = 6.5) for P(HPA) with a single COOH end-group and a DP from 38 to 98. Similar dependency was obtained for P(HPA) with COOH end-groups on both ends, showing lower T_{cp} values from 61 to 32 °C (0.5 wt%, pH = 2) with a DP from 29 to 98. For these latter polymers no thermoresponsivity was observed at neutral pH. Only in a sufficiently acidic environment (pH = 2), i.e. upon protonation of the acid groups, polymer phase separation was observed, suggesting that the very hydrophilic carboxylate end-groups render the polymer too hydrophilic, resulting in the loss of LCST behavior [81]. Wang and co-workers also reported a T_{cp} of 29.5 °C (0.2 wt%) for P(HPA) in their search for two temperature responsive homopolymers for layer-by-layer assembly at neutral pH through hydrogen bonding [82].

The amount of scientific publications reporting thermoresponsive P(eTEGA) can be brought down to a few papers. Zhao and co-workers reported in 2008 a T_{cp} of 36 °C (0.2 wt%) for P(eTEGA) obtained via ATRP resulting in butyl and bromide end-groups [83]. A year later, Tsvetanov and co-workers reported a similar result for a P(eTEGA) prepared by ATRP initiated by ethyl 2-bromopropionate (EBP) resulting in a T_{cp} of 34 °C (0.1 wt%) [84]. In 2011 Rangelov and co-workers investigated the influence of the molecular weight on the T_{cp} by homopolymerizing eTEGA using ATRP initiated by EBP (CuBr/PMDETA), RAFT controlled by 2-cyano-2-butyl dithiobenzoate (CBDB/AIBN) and anionic polymerization (AP) employing LDA/LiCl as initiator. These methods allowed for the synthesis of P(eTEGA) with M_ns spanning from 7000 to 40,000 g/mol (THF-SEC). Turbidity measurements (0.1 wt%) revealed T_{cp}s between 35 and 39 °C but without a noticeable trend in function of the molecular weight. The authors ascribe this insensitivity of the T_{cp} to the molecular weight as an inherent property of eTEGA, whereas the influence of the large polymer size and different polymerization techniques, and thus end-groups, are neglected which could obscure a possible trend [85].

The mDEGA monomer has the largest reported T_{cp} range of all OEGA monomers. The first to report the thermoresponsive properties of P(mDEGA) were Zhao and co-workers in 2006 who also investigated the effect of molecular weight, end-group and polymer concentration. P(mDEGA) was synthesized via NMP using 2,2,5-trimethyl-3-(2-phenylethoxy)-4-phenyl-3-azahexane/2,2,5-trimethyl-4-phenyl-3-azahexane-3-nitroxide (TPPA/TPANO) and revealed a T_{cp} of 38 °C (0.5 wt%). Further investigations demonstrated that the T_{cp} was inversely dependent on the polymer concentration and ranging from 46 °C (0.05 wt%) to 36 °C (5 wt%). This effect is shown to be dominant up to 1 wt% while the T_{cp} only decreases another 2 °C following a subsequent 4 wt% increase (Fig. 6, left). They also reported a strong dependency between the T_{cp} and the M_n of the polymer, allowing an increase from 36.5 to 42 °C (0.5 wt%) when doubling the M_n. This effect is again more dominant in smaller polymers and reaches a plateau at higher M_n indicating that it is caused by the hydrophobic end-groups. Finally they investigated the effect of the hydrophobic TPANO end-group by removing it using ascorbic acid. The decrease in hydrophobicity resulted in the anticipated increase of T_{cp}, which was more important for the smaller polymers. This increased hydrophilicity also seemed to minimize the dependency of the M_n to a 1.5 °C difference for the polymer without the TPANO end-group when the M_n is doubled [33]. This extensive investigation was partially repeated by Laschewsky and co-worker, but using RAFT polymerization with various transfer agents to investigate the effect of chain length and polymer end-group on the T_{cp}. By careful design of these chain transfer agents, polymers were created with two *tert*-butyl benzoate end-groups, two benzoic acid end-groups and a benzoic acid/butyl end-group combination. Results show a strong dependency of the T_{cp} on the M_n, especially for relatively small polymers (DP < 100) and an end-group dependency

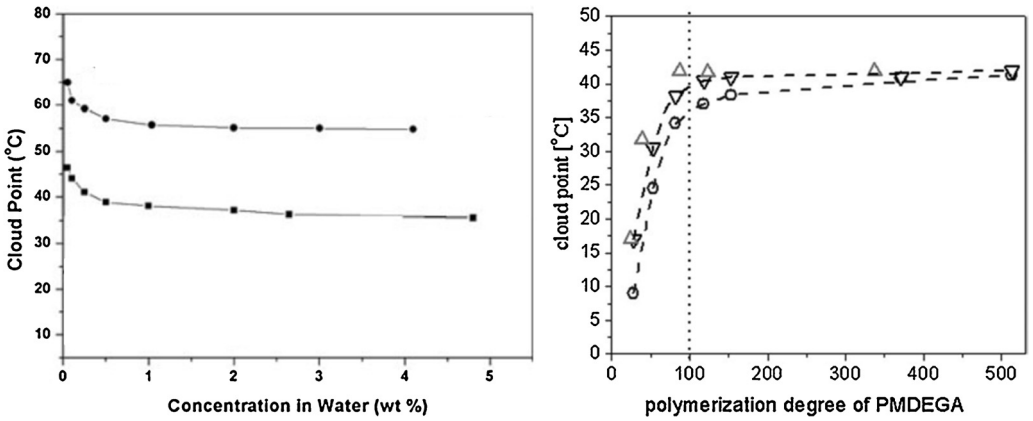

Fig. 6. Left Concentration effect on the T_{cp} for (■) P(mDEGA) (M_n = 9200 g/mol, $Đ$ = 1.14) and (●) P(mTEGA) (M_n = 7800 g/mol, $Đ$ = 1.18) in water [33]. Right: molecular weight effect on the T_{cp} with (○) *tert*-butyl benzoate end-groups, (▽) benzoic acid end-groups, (△) benzoic acid/n-butyl end-groups [86].

on the T_{cp} similar to the results from Zhao. The polymers with the more hydrophobic *tert*-butyl benzoate end-groups showed T_{cp}s ranging from 9.0 to 41.2 °C (0.3 wt%) for polymers with 28–513 units. Post-modification of the end-groups into the more hydrophilic benzoic acid groups causes an increase in T_{cp}, ranging from 16.8 to 42.0 °C (0.3 wt%) for polymers with 28–513 units. This increase is again bigger for the smaller polymers. The asymmetrical polymer, however, shows T_{cp}s ranging from 18.0 to 41.8 °C (0.3 wt%) with lengths ranging from 24 to 337 units, which is higher than for the other polymers (Fig. 6, right). These unexplained final T_{cp} results are not only surprisingly high, but also seem to reach a plateau value of 41.6 °C after just 80 units [86]. In 2011, Laschewsky and co-workers reported a T_{cp} of 38 °C (0.1 wt%) for P(mDEGA) (M_n = 9700 g/mol, $Đ$ = 1.7), synthesized via RAFT using 4-methoxybenzylsulfanylthiocarbonylsulfanylpropane (MBSP) as CTA. These homopolymers were later spin coated on a silicon surface in order to investigate the thermoresponsive transition from the swollen to the collapsed state for P(mDEGA) thin films [87,88]. In between these two thorough investigations, Kubota and co-workers used confocal microraman and infrared spectroscopy to investigate the phase separation of a P(mDEGA). During the LCST transition, the hydrogen bonds between water and the polymer are broken and the water is expelled from the precipitated polymer. This reduces the effect of the water on the vibrational stretch energy of the carbonyl bond in the polymer which can be quantified using these two spectroscopy techniques as a blue shift of the carbonyl stretch energy. Using this methodology, they calculated a T_{cp} of 45 °C (0.5 wt%) [89].

The only report on the thermoresponsive properties of P(mTEGA) is published by Zhao and co-workers in 2006. Similar to the investigation of P(mDEGA), they investigated both the T_{cp} dependency on polymer concentration and molecular weight. P(mTEGA) synthesized via NMP (TPPA/TPANO) showed a range of T_{cp}s from 75 °C (0.05 wt%) to 56 °C (1 wt%), showing similar inverse dependency and weakening of this effect beyond 1 wt% as discussed before for P(mDEGA) (Fig. 6, left). The molecular weight dependency was also found to be very similar, since an increase in T_{cp} was reported from 46 to 61 °C (0.5 wt%) when M_n was almost doubled [33].

Finally, mOEGA can be considered to be the most hydrophilic mOEGA monomer that still has a reported T_{cp} as homopolymer. The side chain of this monomer needs to be defined by an average M_n since the length is not strictly defined to a single length leading to ill-defined side chain distributions. The most used and commercially available mOEGA monomer has a M_n of 454 g/mol, i.e. 8.4 EG units on average. The only reported T_{cp} for P(mOEGA) was published by Davis and co-workers in 2009 employing RAFT using 3-(benzylsulfanylthiocarbonylsulfanyl)propionic acid (BSPA) resulting in a T_{cp} of 92 °C (0.2 wt%) [71].

3. Thermoresponsive OEGA copolymers

This chapter will focus on the thermoresponsive properties of copolymers containing only OEGA based monomers. Combining two different OEGA monomers allows accurate fine tuning of the copolymer T_{cp} to anywhere in between the T_{cp}s of the responsive homopolymers by controlling the monomer ratio. All copolymers will be described according to increasing monomer hydrophilicity of the most hydrophobic monomer starting from mEGA (Fig. 4) and all data relevant for an easy and direct comparison can be found in Table 2. This chapter will emphasize the versatility of these monomers by showing that the T_{cp}s can be varied in between 0 °C and 100 °C.

P(mEGA) has been shown to have the lowest T_{cp} as homopolymer, i.e. it is the most hydrophobic OEGA monomer, therefore combining it with very hydrophilic monomers will open up a wide range of T_{cp}s. Hydroxyethyl acrylate (HEA) is considered to be the most hydrophilic OEGA monomer resulting in fully water soluble homopolymers. The copolymerization of these two OEGA monomers allows fine tuning of the T_{cp} in between roughly 10 °C and 100 °C, making this a very interesting combination. Moeller and co-workers have thoroughly investigated the thermoresponsive properties of P(mEGA-*co*-HEA) prepared by RAFT polymerization using dibenzyltrithiocarbonate (DBTTC), introducing two hydrophobic benzyl end-groups.

Table 2
Overview of all the reported cloud points (T_{cp}) in aqueous solution of copolymers containing only OEGA monomers and relevant data with regard to polymer structure and T_{cp} determination.

Copolymer	X (%)	Wt%[e]	T_{cp} (°C)	M_n (g/mol)	$Đ$	Polym. tech.	Remarks	Ref.
P(mEGA$_x$-*co*-HEA$_{100-x}$)	88–20[b]	0.5	5.7–56.8	6800–11,900[g]	1.3–1.4	RAFT	DBTTC/AIBN	[64]
P(mEGA$_x$-*co*-HEA$_{100-x}$)	30–20[b]	0.5	6.0–9.5	2400–3100[g]	1.3–1.3	RAFT	DBTTC/AIBN	[64]
P(mEGA$_x$-*co*-HEA$_{100-x}$)	90–30[b]	0.5	5.2–40.8	3800–6800[g]	1.3–1.4	RAFT	DBTTC/AIBN, afterwards cleaved with AIBN	[64]
P(mEGA$_x$-*co*-HEA$_{100-x}$)	30[b]	0.5–3.0	41–30	3800[g]	1.4	RAFT	DBTTC/AIBN	[64]
P(mEGA$_x$-*co*-HEA$_{100-x}$)	30[b]	0.5–3.0	30–10	9900[g]	1.3	RAFT	DBTTC/AIBN	[64]
P(mEGA$_x$-*co*-HEA$_{100-x}$)	30[b]	0.5–3.0	5–2	3100[g]	1.3	RAFT	DBTTC/AIBN, afterwards cleaved with AIBN	[64]
P(mEGA$_x$-*co*-HEA$_{100-x}$)	30–90[c]	0.5	60–8	4950–9700[g]	1.15–1.25	NMP	BB/SG-1	[61]
P(mEGA-*co*-mDEGA)$_x$	60–191[d]	0.5	27–35[f]	8271–26,684[h]	1.08–1.13	ATRP	EBiB, CuBr/PMDETA	[65]
Cholesterol-P(eDEGA$_x$-*co*-mOEGA$_{100-x}$)[a]	80[c]	0.1	45	4000[h]	1.49	ATRP	CBI, CuBr/Bipy	[52,92]
P(eDEGA$_x$-*o*-mOEGA$_{100-x}$)[a]	70–90[b]	0.3	49.9–26.8	12,200–19,000[h]	1.19–1.57	ATRP	MBP, $CuBr_2$/Bipy	[90]
P(eDEGA$_x$-*co*-HEA$_{100-x}$)	75–25[b]	0.5	23.7–47.8	21,000–30,900[g]	2–3	FRP	AIBN	[75]
P(eDEGA$_x$-*co*-HEA$_{100-x}$)	75–25[b]	0.5	21.3–38.5	8400–12,800[g]	1.2–1.4	NMP	BB/SG-1	[75]
P(eDEGA$_x$-*co*-mOEGA$_{100-x}$) [a]	50–95[c]	0.2	72–22	18,500–22,300[i]	1.22–1.26	RAFT	BSPA/AIBN	[71,91]
P(HPA$_x$-*co*-HEA$_{100-x}$)	90–70[c]	0.25	36.2–50.2	7600–8800[g]	1.14–1.23	NMP	BB/SG-1	[80]
P(HPA$_x$-*co*-HEA$_{100-x}$)	90–50[c]	0.5	30.7–60.2	7600–8800[g]	1.14–1.23	NMP	BB/SG-1	[80]
P(HPA$_x$-*co*-HEA$_{100-x}$)	90–40[c]	1.0	26.5–59.7	7600–9400[g]	1.14–1.26	NMP	BB/SG-1	[80]
P(HPA$_x$-*co*-HEA$_{100-x}$)	90–40[c]	2.0	21.2–47.3	7600–9400[g]	1.14–1.26	NMP	BB/SG-1	[80]
P(HPA$_x$-*co*-HEA$_{100-x}$)	70–20[c]	10	23–60	n.d.	n.d.	n.s.		[78]

[a] M_n = 454 g/mol, 8–9 units; [b] Monomer ratio determined using ^{1}H NMR spectroscopy; [c] Molar feed ratio; [d] Monomer ratio determined using MALDI; [e] All values for concentration were calculated into wt%, e.g., 5 mg/ml = 0.5 wt%; [f] Estimated from graph, measured in PBS buffer, pH 8.0, 50 mM, 0.1 M NaCl. M_n and $Đ$ were calculated via SEC, given as a range between min. and max. values; [g] DMF (LiBr) vs. PMMA standards; [h] THF vs. PS standards; [i] DMA (LiBr) vs. PS standards.

Kinetic studies showed equal reactivity ratios of the two comonomers allowing the synthesis of well-defined, ideal random copolymers. By increasing the fraction of HEA in the monomer feed (f_{HEA}) from 12 to 80%, a T_{cp} range of 5.7–56.8 °C (0.5 wt%) could be achieved (Fig. 7). Investigation of the T_{cp} dependency on polymer concentration revealed a decrease in T_{cp} from 41 °C (0.5 wt%) to 30 °C (3.0 wt%) for P(mEGA$_{30}$-*co*-HEA$_{70}$) upon increasing concentration. The dependency on molecular weight and end-groups was evaluated by radical cleavage of the copolymer with AIBN, halving the polymer at the trithiocarbonate center while at the same time introducing a relatively hydrophilic isobutyronitrile end-group beside the already present benzyl group on the other chain end. The combination of the decreased length and enhanced hydrophilicity from the end-group exchange causes an expected increase in T_{cp}. The T_{cp} of P(mEGA-*co*-HEA) with F_{HEA} of 10% increases from <0 to 5.2 °C while the T_{cp} of the copolymer with F_{HEA} of 70% increased from 29.0 to 40.8 °C (0.5 wt%). Polymers with equal length, DP = 40, bearing two benzyl end-groups showed much lower T_{cp} demonstrating the importance of end-groups on the T_{cp}, especially for short polymers (Fig. 7) [64]. These results were expanded in 2012 by the same group using a different polymerization method. NMP-synthesized (BB/SG-1) P(mEGA-*co*-HEA) showed similar copolymerization kinetics compared to the RAFT polymerization (DBTTC), i.e. reactivity ratios equal to one. Increasing the F_{HEA} from 13 to 71% resulted in an exponential increase of T_{cp} from 8 to 60 °C (0.5 wt%) (Fig. 7) [61]. The overall comparison between the two methods of polymerization of P(mEGA-*co*-HEA) allows to conclude that while polymers prepared by RAFT bearing two benzyl end-groups have much lower T_{cp} compared the SG-1/acrylic acid end-groups, P(mEGA-*co*-HEA) bearing isobutryonirile/benzyl end-groups have comparable T_{cp}s with the latter [61]. Finally, mEGA was also combined with mDEGA using ATRP by Nolte and co-workers in 2010. They briefly report a similar reactivity of the two monomers allowing an incorporated monomer ratio close to 1:1. By increasing DP from 60 to 191, the T_{cp} could be increased from 27 to 35 °C. These copolymers were conjugated to green fluorescent protein (GFP) yielding thermoresponsive polymer–protein conjugates (see Section 5) [65].

The next combination of comonomers is based on eDEGA as hydrophobic monomer. Moeller and co-workers synthesized eDEGA using lipase-catalyzed transacylation [72]. Copolymerization with HEA was done using both FRP (AIBN) and NMP (BB/SG-1) with different F_{HEA}. Polymerization kinetics of NMP revealed similar reactivity ratios for eDEGA and HEA leading to the formation of ideal random copolymers. The reported T_{cp} values ranged from 23.7 to 47.8 °C for FRP and 21.3 to 38.5 °C (0.5 wt%) for NMP with increasing F_{HEA} from 22 to 71%. Results show that the large, hydrophobic SG-1 group increases the hydrophobicity of the copolymer, lowering the T_{cp}. When comparing the difference in T_{cp} for each F_{HEA}, the obtained results suggest that when the copolymer becomes increasingly hydrophilic, the effect of the end-group becomes bigger, hence increasing the difference between T_{cp} of the FRP and NMP synthesized polymers [75]. Other eDEGA containing copolymers have been reported with mOEGA (M_n = 454 g/mol, 8–9 units) as hydrophilic monomer. The first to report P(eDEGA-*co*-mOEGA) were

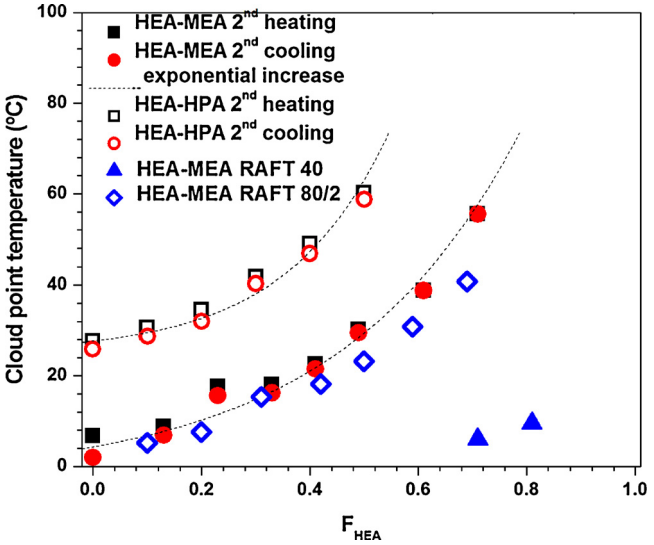

Fig. 7. Graph of T_{cp}s (0.5 wt%) as function of F_{HEA} containing multiple copolymers. P(mEGA-*co*-HEA) [61], P(HPA-*co*-HEA) [80], P(mEGA-*co*-HEA) RAFT DP = 40 (DBTTC) [64] and P(mEGA-*co*-HEA) RAFT DP = 80/2 (DBTTC – cleaved with AIBN) [61,64].

Lutz and co-workers who used ATRP, initiated by methyl 2-bromopropionate (MBP). They report T_{cp}s ranging from 26.8 to 49.9 °C (0.3 wt%) with increasing f_{mOEGA} from 10 to 30% [90]. In the same year they reported the synthesis of cholesterol end-capped P(eDEGA$_{20}$-*co*-mOEGA$_{80}$) via a cholesterol based ATRP initiator. The formed monodisperse aggregates showed a broad LCST transition with a T_{cp} of 45 °C (1.0 wt%). The slightly increased T_{cp} compared to the previously reported cholesterol free analogue was ascribed to the effect of the micelle formation below the T_{cp} [52,92]. Finally Davis and co-workers synthesized P(eDEGA-*co*-mOEGA) via RAFT (BSPA), reporting T_{cp}s ranging from 22 to 72 °C with increasing F_{mOEGA} from 6 to 45% [71].

The final combination of HPA and HEA into OEGA copolymers was already investigated in 1975 by Taylor and Cerankowski. They briefly reported a range of T_{cp}s between 23 °C and 60 °C (10 wt%) with increasing f_{HEA} from 30 to 80% [78]. This combination was further investigated by Moeller and co-workers using NMP (BB/SG-1). Kinetic investigations proved the synthesis of ideal random copolymers of HPA and HEA. The cloud points of P(HPA-*co*-HEA) revealed an exponential increase with increasing HEA content and an inverse dependency on the polymer concentration allowing T_{cp}s ranging from 19.2 °C (P(HPA$_{90}$-*co*-HEA$_{10}$), 2.0 wt%) up to 60 °C (P(HPA$_{50}$-*co*-HEA$_{50}$), 0.5 wt%) (Fig. 8). The dependency of the T_{cp} on the F_{HEA} could be fitted with an exponential growth function with an exponential factor of F_{HEA}/0.33. Surprisingly, this exponential factor is independent of the polymer concentration which is suggested to result from the very large, hydrophobic SG-1 end-group [80].

4. Thermoresponsive OEGA copolymers with other comonomers

Another way of increasing the T_{cp} range of POEGAs is by copolymerizing an OEGA monomer with another type of monomer. Incorporating a hydrophilic comonomer will increase the overall T_{cp} of the copolymer while a hydrophobic comonomer will decrease the T_{cp}. Depending on the type of comonomer, the incorporation might also introduce an entirely different type of responsivity beside modifying T_{cp}. All copolymers will be described according to increasing monomer hydrophilicity starting from eDEGA as no such thermoresponsive copolymers with mEGA were reported (Fig. 4). All data relevant for an easy comparison can be found in Table 3. All T_{cp}s were measured in aqueous solutions unless mentioned otherwise.

The only example of such a thermoresponsive copolymer based on eDEGA was recently published by Sumerlin and co-workers in which they copolymerized eDEGA with the hydrophilic *N*,*N*-dimethylacrylamide (DMAAm) by RAFT. The formed P(eDEGA-*co*-DMAAm) shows a near linear increase of the T_{cp} in function of f_{DMAAm}, ranging from 22 to 87 °C (0.1 wt%) with increasing f_{DMAAm} from 20 to 80%. Polymer concentration dependency was also investigated for P(eDEGA-*co*-DMAAm) showing T_{cp}s ranging from 45 to 36 °C (f_{DMAAm} = 40) and 55 to 44 °C (f_{DMAAm} = 50) upon increasing the concentration from 0.05 to 2.0 wt%. These results show a clear inverse dependency between T_{cp} and polymer concentration that is stronger for low concentration (<0.25 wt%), as commonly seen [76].

Schubert and co-workers reported the copolymerization of HPA with the hydrophilic comonomers DMAAm and *N*-acryloylmorpholine (Amor) via NMP (BB/SG-1) [79]. These copolymers were reported to show T_{cp}s (1.0 wt%) ranging from 25.3 to 88.0 °C with increasing F_{Amor} from 8 to 60% and 28.5 to 82.9 °C with increasing F_{DMAAm} from 10 to 43%. Lowering the polymer concentration from 1.0 wt% to 0.5 wt% increased the T_{cp}s with, on average, 12 °C for Amor and 8 °C for DMAAm. Further investigations were conducted on the reversibility of the thermal transition (Fig. 9) leading to the observation that P(HPA$_{50}$-*co*-DMAAm$_{50}$), while showing a T_{cp} of 82.9 °C (1.0 wt%) in the first heating

Table 3
Overview of all the reported cloud points (T_{cp}) in aqueous solution of copolymers containing an OEGA monomer and relevant data with regard to polymer structure and T_{cp} determination.

Copolymer	X (%)	Wt%[d]	T_{cp} (°C)	M_n (g/mol)	$Đ$	Polym. tech.	Remarks	Ref.
P(eDEGA$_x$-*co*-DMAAm$_{100-x}$)	80–20[b]	0.1	22–87	8580–10,260[g]	1.40–1.49	RAFT	DMP/AIBN	[76]
P(eDEGA$_x$-*co*-DMAAm$_{100-x}$)	60[b]	0.05–2.0	45–36	8950[g]	1.44	RAFT	DMP/AIBN	[76]
P(eDEGA$_x$-*co*-DMAAm$_{100-x}$)	50[b]	0.05–2.0	55–44	88,500[g]	1.42	RAFT	DMP/AIBN	[76]
P(HPA$_x$-*co*-Amor$_{100-x}$)	51–92[c]	0.5	79.5–33.9	8100–8800[g]	1.16–1.23	NMP	BB/SG-1	[79]
P(HPA$_x$-*co*-Amor$_{100-x}$)	40–92[c]	1.0	88.0–25.3	8100–8800[g]	1.16–1.23	NMP	BB/SG-1	[79]
P(HPA$_x$-*co*-Amor$_{100-x}$)	60[c]	0.5–2.5	73.5–41[e]	8300[g]	1.20	NMP	BB/SG-1	[79]
P(HPA$_x$-*co*-DMAAm$_{100-x}$)	66–90[c]	0.5	71.6–35.3	9600–10,900[g]	1.20–1.26	NMP	BB/SG-1	[79]
P(HPA$_x$-*co*-DMAAm$_{100-x}$)	57–90[c]	1.0	82.9–28.5	9600–10,900[g]	1.20–1.27	NMP	BB/SG-1	[79]
P(HPA$_x$-*co*-AMHS$_{100-x}$)	66–80[c]	3	36.5–17.8[f]	n.d.	n.d.	FRP	$K_2S_2O_8$-$NaHSO_3$	[77]
P(eTEGA$_x$-*co*-NBA$_{100-x}$)	88[b]	0.2	18.5	13,900[h]	1.13	ATRP	EBiB, CuBr/PMDETA	[83]
P(mDEGA$_x$-*co*-4-DMNMA$_{100-x}$)	99.6	0.01	52	21,000[i]	1.9	FRP	AIBN	[94]
P(mOEGA$_x$-*co*-DEA$_{100-x}$)[a]	14–27[c]	0.1	12.9–30.8	21,500–31,700[h]	1.10–1.23	ATRP	EBiB, CuBr/Me_6TREN	[18]
P(mOEGA$_x$-*co*-DEA$_{100-x}$)[a]	20[c]	0.1	24.4–25.0	16,000–31,700[h]	1.11–1.16	ATRP	EBiB, CuBr/Me_6TREN	[18]
P(mOEGA$_x$-*co*-DEA$_{100-x}$)[a]	24[c]	0.1	27.2–27.5	14,900–31,700[h]	1.11–1.16	ATRP	EBiB, CuBr/Me_6TREN	[18]
P(mOEGA$_x$-*co*-DMDEA$_{100-x}$)[a]	25–34[c]	0.1	22.1–35.8	25,800–28,400[h]	1.11–1.14	ATRP	EBiB, CuBr/Me_6TREN	[18]
P(mOEGA$_x$-*co*-DMDEA$_{100-x}$)[a]	25[c]	0.1	22.6–23.2	5900–28,400[h]	1.13–1.24	ATRP	EBiB, CuBr/Me_6TREN	[18]
P(HEA$_x$-*co*-VBE$_{100\ -x}$)	95–84.3[b]	0.02–1.0	57–4	165,900–320,500[j]	1.29–1.47	FRP	AIBN	[96]
P(HEA$_x$-*co*-BA$_{100-x}$)	85.2–91.2[b]	0.05–1.5	45–15	102,970–130,260[j]	1.58–1.96	FRP	AIBN	[95]

[a] M_n = 454 g/mol, 8–9 units; [b] Monomer ratio determined using ^{1}H NMR; [c] Molar feed ratio; [d] All values for concentration were calculated into wt%, e.g. 5 mg/ml = 0.5 wt%; [e] Estimated from graph and averaged over the heating and cooling of first cycle; [f] Visual observation. M_n and $Đ$ were calculated via SEC, given as a range between minimum and maximum values; [g] DMF (LiBr) vs. PMMA standards; [h] THF vs. PS standards; [i] DMF vs. PS; [j] DMF (Bu_4NBr) vs. PS.

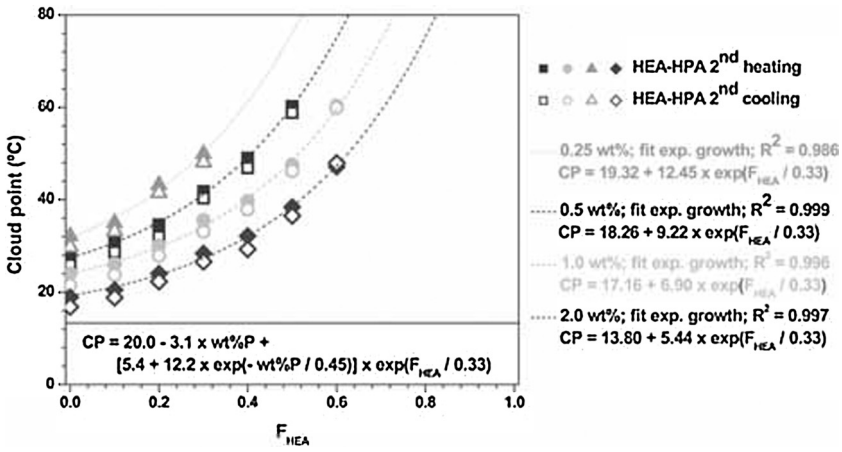

Fig. 8. Cloud points T_{cp} of P(HPA-*stat*-HEA) copolymers as function of HEA fraction (F_{HEA}) in aqueous solution with different polymer concentrations (wt%). The equation at the bottom of the graph is an empirical correlation of T_{cp} with both F_{HEA} and wt% [80].

run, became soluble after the third subsequent heating-cooling cycle. Also while P(HPA_{60}-*co*-$Amor_{40}$) showed a rather constant T_{cp} between 2.5 and 1.5 wt%, further lowering the concentration showed a mild increase in T_{cp} at 1.0 wt% and a bigger increase at 0.5 wt% after three subsequent heating-cooling cycles. The authors notice that only copolymers with a high T_{cp} show an increased solubility with the number of heating cycles. They suggest that this might be related to reduced hydrophobic interactions causing the high T_{cp} and/or the formation of smaller aggregates [79]. HPA was also reported to be copolymerized with aminoethyl methacrylate hydrochloride (AMHS) via FRP by Wang and co-workers. The hydrophilic comonomer increases the T_{cp} allowing a T_{cp} range from 17.8 to 66 °C (3.0 wt%) with increasing F_{AMHS} from 20 to 34% [77,93].

While the previous examples involve a hydrophilic non-OEGA comonomer to increase the T_{cp} of the POEGA, the following reports use a combination of a hydrophilic

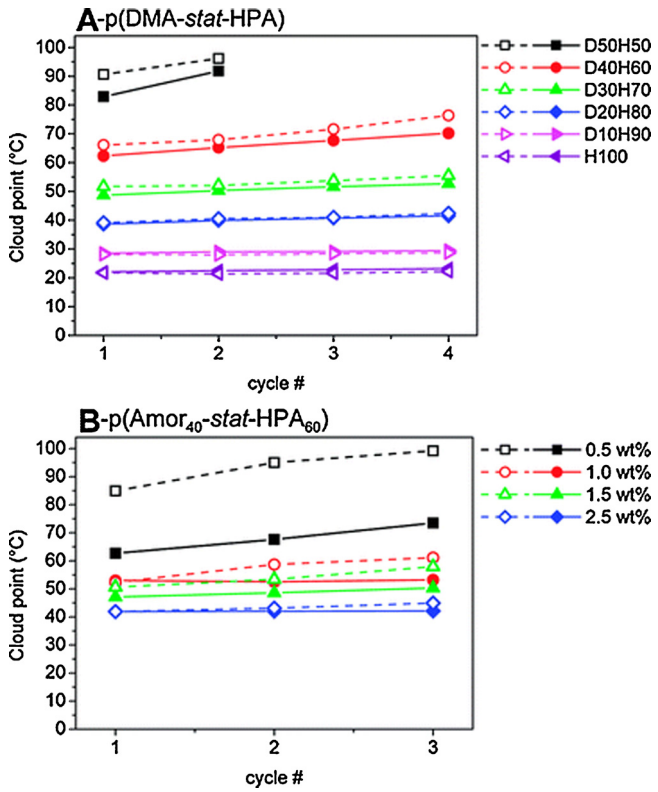

Fig. 9. Cycle effect on T_{cp} in heating curves (closed symbols) and cooling curves (open symbols). (A) Different compositions of P(HPA-*co*-DMAAm) at 1.0 wt%. (B) Different concentration of P(HPA_{60}-*co*-$Amor_{40}$) [79].

OEGA monomer like mOEGA and HEA with a hydrophobic non-OEGA comonomer to lower the T_{cp}. Zhao and co-workers reported the copolymerization of eTEGA with *o*-nitrobenzyl acrylate (NBA) via ATRP in order to decrease the T_{cp} to 18.5 °C (0.2 wt%) compared to 36 °C for an equal length P(eTEGA). This hydrophobic monomer also introduces a UV sensitive ortho-nitrobenzyl group in the copolymers that will be discussed in Section 5 [83]. Li and co-workers combined mOEGA (M_n = 45 g/mol, 8–9 units) with the hydrophobic HEA-precursors 2-(1,3-dioxan-2-yloxy)ethyl acrylate (DEA) or 2-(5,5-dimethyl-1,3-dioxan-2-yloxy)ethyl acrylate (DMDEA). These precursors not only decrease the T_{cp} but also add a pH-responsivity to the copolymer through pH-dependent hydrolysis. Both copolymers were synthesized using ATRP and showed a linear dependency of the T_{cp} on the F_{mOEGA}, ranging from 24.2 to 30.7 °C for 81–73% with DEA and from 22.1 to 35.8 °C for 78–66% with DMDEA. All copolymers revealed the same inverse dependency of the T_{cp} on M_n [18].

Neher and co-workers used an mDEGA copolymer to evaluate the possibility of translating an LCST-type transition into a fluorescent output signal by incorporating a fluorescent dye [94]. The dye 2-(6-(dimethylamino)-1,3-dioxo-1*H*-benzo[*de*]isoquinolin-2(3*H*)-yl)ethyl methacrylate (4-DMNMA) was copolymerized with mDEGA using FRP initiated by AIBN to synthesize P(mDEGA$_{99.6}$-*co*-4-DMNMA$_{0.6}$) with a DP of 120 showing a T_{cp} of 52 °C (BPS-solution, 0.01 wt%). Their investigations revealed a very weak effect of the phase transition on the spectral properties of 4-DMN in both emission intensity as in the λ_{max} shift in comparison to the effect of the phase transition of P(NIPAAm-co-4-DMNMA). This was explained by the significant residual hydration of the mDEGA copolymer above the LCST which only slightly changes the microenvironment of the dye and its mobility upon precipitation of the polymer globule.

Finally Park and co-workers used the hydrophilic HEA and adjusted the T_{cp} by copolymerization with different hydrophobic monomers. They firstly reported the FRP of HEA and vinyl butyl ether (VBE) showing T_{cp}s for copolymers with 5–15% VBE ranging from 57 to 4 °C at various concentrations. In order to synthesize more random copolymers, VBE was later replaced with butyl acrylate (BA) allowing a variation of the T_{cp} in between 45 and 15 °C with a BA content of 15–10% at various concentrations [95,96].

5. Block-copolymers and other applications of POEGA

This chapter highlights recent publications regarding more application-directed research including thermoresponsive hydrogels and block-copolymers containing at least one OEGA monomer. While statistical copolymers show an average T_{cp} that strongly depends on the ratio of comonomers, block copolymers often show two separate T_{cp}s that can be utilized for micelle or hydrogel formation. The discussed publications are prime examples of the wide variety of possible applications of thermoresponsive OEGA copolymers. Their main focus is often not to characterize the thermoresponsive properties of well-defined (co)polymers, but to study the temperature induced formation of larger and more intricate architectures and the evaluation of their applicability. These examples will be ordered according to increasing hydrophilicity of the most hydrophobic monomer and further details of the block-copolymers are summarized in Table 4.

Nolte and co-workers reported in 2010 the successful coupling of P(mEGA-*co*-mDEGA) to enhanced green fluorescent protein (EGFP) through copper-catalyzed azide-alkyne cycloaddition. These biohybrids were synthesized to create giant amphiphiles, which are fully water-soluble at low temperature but self-assemble into micellar structures due to the collapse of the POEGA-block upon heating [65]. The hydrophobic P(mEGA) was incorporated into a hydrophilic inorganic clay by Takeshi and co-workers to create a new class of soft polymer-clay hydrogels. The formed nanocomposite showed remarkable transparency and thermosensitive swelling behavior, as well as extremely large reversible elongation [62,63,97]. Very recently, Moeller and co-workers have copolymerized mEGA with HEA using RAFT (DBTTC) to form block- and gradient-copolymers. Turbidity measurements (0.5 wt%) show a fully reversible phase transition with different hysteresis, which can be ascribed to the different microstructures of the copolymers. The general observed trend is, however, the expected increase in T_{cp} with increasing F_{HEA}. The block copolymers show T_{cp} ranging from 5.5 to 54.2 °C for an F_{HEA} from 50 to 87%. Cleaving these polymers with AIBN not only leads to a halved length, but also the exchange of one benzyl end-group with a isobutrynitrile end-group, increasing the cloud point as previously also discussed for the corresponding random copolymers [98].

Davis and co-workers reported the synthesis of P(eDEGA-*co*-mOEGA) copolymers via RAFT displaying T_{cp}s from 9 to 72 °C (0.2 wt%) for 0–45% incorporated mOEGA. These copolymers were coupled to gold nanoparticles (GNP) using citrate reduction, forming polymer-grafted GNP with high stability and antifouling properties that have a red color in aqueous solution. The size of the formed hybrids was temperature dependent and could be increased by heating to above the cloud point of the attached copolymer leading to aggregation of the GNP, visually noticeable as a color change to purple. By using a mixture of P(eDEGA) and P(eDEGA-*co*-mOEGA) during the citrate acid reduction, they were able to synthesize GNPs that showed two distinct thermal transitions (Fig. 10) [71]. The optimized method of simultaneous attachment of multiple polymers to a gold surface was further employed to functionalize GNPs with a neutral P(eDEGA-*co*-mOEGA) with an LCST around 22 °C and a positive or negatively charged polymer. This introduces a temperature dependent zeta-potential of the formed GNPs. It was shown that below the LCST the GNPs exhibit antifouling properties while above the LCST the charged polymers would be revealed causing significant protein adsorption through electrostatic interactions [91]. The same copolymers were later modified with a pyrene end-group allowing the surface modification of graphene through π–π stacking. The LCST of the used P(eDEGA-*co*-mOEGA) ranged from 31 to 82 °C (f_{eDEGA}: 10–60%) and these values were significantly

Table 4
Overview of all the reported cloud points (T_{cp}) in aqueous solution of block-copolymers containing an OEGA monomer and relevant data with regard to polymer structure and T_{cp} determination or gelation behavior.

Block-copolymer	X (%)/M block units	Wt%[d]	T_{cp} (°C)	M_n (g/mol)	$Đ$	Polym. tech.	Remarks	Ref.
P(HEA$_x$-*b*-mEGA$_{100-2x}$-*b*-HEA$_x$)	26–44[a]	0.5	5.5–54.2	10,450–820[g]	1.2–1.2	RAFT	DBTTC/AIBN	[98]
P(mEGA$_{100-x}$-*b*-HEA$_x$)	29–88[a]	0.5	7.9–>97.0	7500–640[g]	1.1–1.2	RAFT	DBTTC/AIBN, afterwards cleaved with AIBN	[98]
P(BiBEM)$_{400}$-*g*-P(eDEGA)$_x$	48[b]	0.1	10	3,830,000[h]	1.28	ATRP	Grafting from P(BiBEM), FeBr/TBABr	[104]
P(eDEGA$_{100-x}$-*co*-AA$_x$)-*b*-P(mTEGA$_{170}$)	4.9/81[a]	0.02	13–23[e]	62,200[i]	1.24	RAFT	BDTB/AIBN, pH = 3.24–6.52	[101]
P(eDEGA$_{100-x}$-*co*-AA$_x$)$_2$-*b*-PEO$_{450}$	4.8/147[a]	0.02	15	47,900[j]	1.09	ATRP	Br-PEO-BR, CuBr/PMDETA, pH = 3.00	[102]
P(mTEGA$_{100-x}$-*co*-AA$_x$)-*b*-P(eDEGA$_{95}$)	5.7/194[a]	0.02	57–69	42,300[k]	1.2	RAFT	BDTB/AIBN, pH = 3.11––5.25	[67]
P(eDEGA$_{100-x}$-*co*-AA$_x$)-*b*-P(mTEGA$_{100-x}$-*co*-AA$_x$)	5/158; 74[a]	0.02	13–24[e]57–>75	22,600[i]	1.17	RAFT	BDTB/AIBN, pH = 3.29–6.50	[69]
P(eDEGA$_x$-*b*-DMAAm$_{100-x}$)	40[a]	0.1	18	11,900[g]	1.24	RAFT	DMP/AIBN	[76]
P(HPA$_x$-*co*-PEtOx$_{100-x}$)	30–70[c]	3–8	55–46	n.d.	n.d.	FRP	Segmented network, macroPEtOx	[105]
P(mDEGA$_x$-*b*-Sty$_{11}$)	101–513[a]	0.3	34.6–40.1	12,100–42,800[i]	1.27–1.48	RAFT	CTA2/AIBN, benzoic acid and butyl end-group	[86]
P(Sty$_8$-*b*-mDEGA$_x$-*b*-Sty$_8$)	41–659[a]	0.3	20.5–38.1	7900–48,800[i]	1.15–1.42	RAFT	CTA1/AIBN, symmetrical CTA with *tert*-butyl benzoate end-groups	[86,111]
P(mDEGA$_x$-*b*-Sty$_8$) X3	79–231[a]	0.3	27.2–34.1	23,600–51,400[i]	1.31–1.32	RAFT	CTA3/AIBN, three arm symmetrical CTA with *tert*-butyl benzoate end-groups	[86]
P(TEGEA$_x$-*co*-NBA$_{100-x}$)-*b*-PEO$_{113}$	100–88[a]	0.2	39–21	18,300–24,700[k]	1.07–1.11	ATRP	EBiB, CuBr/PMDETA	[83] [106]
PmTEGA$_{66}$-*b*-PEGSt$_x$	45–98[a]	1.0	32, 55–15, 44[f]	16,300–34,400[k]	1.16–1.22	NMP	TPPA/TPANO	[68]

Block-copolymers (gels)	X (%)/M block units[k]	Wt%[l]	$T_{sol-gel}$ (°C)	$T_{gel-sol}$ (°C)	$T_{clouding}$ (°C)	M_n (g/mol)	$Đ$	Polym. tech.	Remarks	Ref.
P(eDEGA$_{100-x}$-*co*-AA$_x$)$_2$-*b*-PEO$_{450}$	4.8/147	10	23.1–50.5[m]	n.r.	n.r.	47,900[o]	1.09	ATRP	Br-PEO-BR, CuBr/PMDETA, pH = 3.00–6.43	[102]
P(eDEGA$_{100-x}$-*co*-AA$_x$)-*b*-P(mTEGA$_{170}$)	4.9/81	25	15–39[m]	45	57	62,200[p]	1.24	RAFT	BDTB/AIBN, pH = 3.24–5.90	[101]
P(eDEGA$_{100-x}$-*co*-AA$_x$)-*b*-P(mTEGA$_{170}$)	9.1/88	25	15–32.5[m]	45	66	53,400[p]	1.26	RAFT	BDTB/AIBN, pH = 3.24–5.37	[101]
P(mTEGA$_{100-x}$-*co*-AA$_x$)-*b*-P(eDEGA$_{95}$)	5.7/194	20	19	40–77	61–>97	42,300[q]	1.2	RAFT	BDTB/AIBN, pH = 3.11–6.04	[67]
P(eDEGA$_{100-x}$-*co*-AA$_x$)-*b*-P(mTEGA$_{100-x}$-*co*-AA$_x$)	5/158; 74	20	18–36	38–51	55–85	22,600[p]	1.17	RAFT	BDTB/AIBN, pH = 3.29–6.00	[69]
P(eTEGA$_{100-x}$-*co*-NBA$_x$)-*b*-PEO$_{113}$	11/99	18–23	36–31	40–61[n]	n.m.	21,600[q]	1.12	ATRP	EBiB, CuBr/PMDETA	[106]
P(eTEGA$_{100-x}$-*co*-AA$_x$)-*b*-PEO$_{113}$	11/99	18–23	42–37	45–52	n.m.	n.m.	n.m.	ATRP	EBiB, CuBr/PMDETA, photocleavage with UV 365 nm	[106]

Table 4 (*Continued*)

Block-copolymers (gels)	X (%)/M block units[l]	Wt%[m]	$T_{sol-gel}$ (°C)	$T_{gel-sol}$ (°C)	$T_{clouding}$ (°C)	M_n (g/mol)	$Đ$	Polym. tech.	Remarks	Ref.
P(eTEGA$_{100-x}$-co-NBA$_x$)$_2$-b-PEO$_{450}$	0–17.8	10	51.5–27.5	n.m.	n.m.	40,300–44,800[q]	1.10–1.18	ATRP	Br-PEO-BR, CuBr/PMDETA	[107]
P(eTEGA$_{100-x}$-co-AA$_x$)$_2$-b-PEO$_{450}$	0–17.8	10	51.5–41.5	n.m.	n.m.	n.m.	n.m.	ATRP	Br-PEO-BR, CuBr/PMDETA, photocleavage with UV 365 nm	[107]
P(eTEGA$_{100-x}$-co-NBA$_x$)$_2$-b-PEO$_{450}$	9.3	3–14	46–37	n.m.	n.m.	40,300–44,800[q]	1.10–1.18	ATRP	Br-PEO-BR, CuBr/PMDETA	[107]
P(eTEGA$_{100-x}$-co-AA$_x$)$_2$-b-PEO$_{450}$	9.3	3–14	60–55[n]	n.m.	n.m.	n.m.	n.m.	ATRP	Br-PEO-BR, CuBr/PMDETA, photocleavage with UV 365 nm	[107]

[a]Monomer ratio determined using ^{1}H NMR; [b]Monomer ratio determined using GC; [c]Molar feed ratio; [d]All values for concentration were calculated into wt%, e.g. 5 mg/ml = 0.5 wt%; [e]Critical micelle temperature (CMT); [f]Solution showed two T_{cp}. M_n and $Đ$ were calculated via SEC, given as a range between min and max values; [g]DMF (LiBr) vs. PMMA standards; [h]THF vs. PMMA standards and MALLS detection; [i]DMF vs. PS standards; [j]THF vs. PS of the tBA protected polymer; [k]THF vs. PS standards; [l]All values for concentration were calculated into wt%, e.g. 5 mg/ml = 0.5 wt%; [m]Determined via vial inversion tests; [n]Estimated from graph. M_n and $Đ$ were calculated via SEC, given as a range between min and max values; [o]THF vs. PS standards of the tBA protected polymer; [p]DMF vs. PS standards; [q]THF vs. PS.

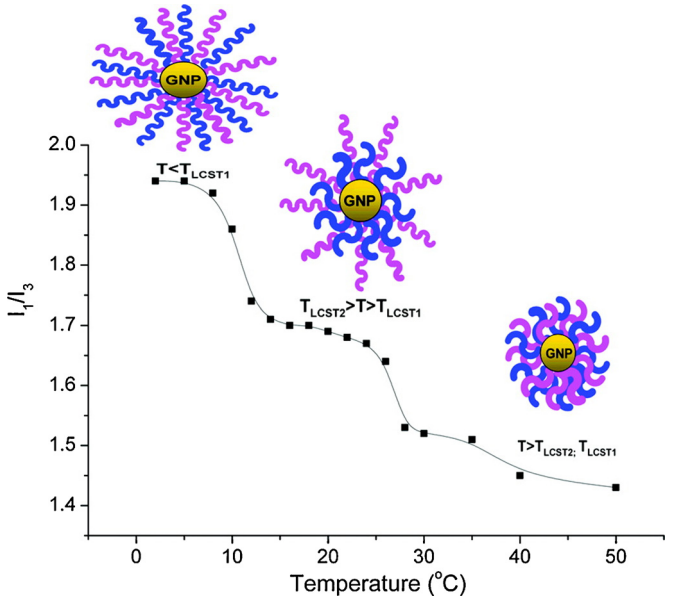

Fig. 10. Evolution of the hydrophobicity of the nanoparticle surface layer versus temperature, measured via pyrene fluorescence emission ratio I_1/I_3 for GNPs/mixed polymers [P(eDEGA)/P(eDEGA-*co*-mOEGA) = 50/50 wt%], hybrids [71].

lowered upon attachment to the graphene sheet to a range of 22–72 °C, creating a nanocomposite with thermoresponsive properties [99]. Recently, similar copolymers were used to thermally control the enzymatic activity of glucose oxidase (GOx). By RAFT copolymerizing eDEGA and mOEGA (M_w = 480 g/mol, 8–9 units) with a 2-mercaptothiazoline ester functional CTA. The formed well-defined thermoresponsive copolymers ($Đ$ < 1.2) could be attached to the enzyme surface through disulfide bridges. The resulting conjugate showed an increase in bioactivity when the temperature was heated above the LCST of the polymer. The authors ascribed this observation to the blocking of the active site by the elongated, hydrated copolymers at lower temperatures, while the collapsed state upon heating allows the substrate to pass [100].

Zhao and co-workers synthesized P(mTEGA$_{170}$)-b-P(eDEGA$_{100-x}$-co-AA$_x$) in order to evaluate the sol–gel–sol–cloud transition temperatures in function of the pH. These types of block-copolymers show three characteristic thermal transitions in high polymer concentrated, aqueous solutions: a sol-to-gel transition related to collapse of the eDEGA block, a gel-to-sol transition related to the shrinkage of the mTEGA block followed by a clear-to-cloud transition upon full collapse of the mTEGA block. The block-copolymers were synthesized using sequential RAFT polymerization initiated by benzyl dithiobenzoate (BDTB) of mTEGA followed by a mixture of eDEGA and tBA which was then deprotected with trifluoroacetic acid (TFA). The block-copolymer containing 4.9% AA showed three distinct transitions of which the first sol-to-gel was strongly dependent of the pH of the solution. The corresponding $T_{sol-gel}$ (25 wt%) increased almost exponentially from 15 °C at pH 3.24 to 39 °C at pH 5.90 due to increased ionization of the AA moieties. Further increasing the pH completely suppressed gelation. Since the mTEGA block did not contain any AA, the $T_{gel-sol}$ and T_{cp} were both insensitive to pH change and remained at 46 °C and 57 °C, respectively. DLS and turbidity measurements also showed this pH-sensitivity with a T_{cp} ranging from 13 to 23 °C (0.02 wt%) with a pH from 3.24 to 6.52. Similar results were obtained for a block-copolymer with increased AA content (x = 9.1%) with a faster increasing $T_{sol-gel}$ from 15 to 32.5 °C with pH from 3.24 to 5.37 after which no gelation could be observed. $T_{gel-sol}$ and $T_{clouding}$ were again not affected by the pH and remained at 45 and 66 °C, respectively [101]. Similar investigation were conducted by synthesizing P(eDEGA$_{95}$)-b-P(mTEGA$_{100-x}$-co-AA$_x$) with an AA content of 5.7% which introduces a pH-sensitivity in the $T_{gel-sol}$ and $T_{clouding}$ while keeping the $T_{sol-gel}$ constant at 19 °C. The high concentration (20 wt%) gel tests revealed a slow increase in $T_{gel-sol}$ from 40 to 77 °C with a pH ranging from 3.11 to 6.04 while the $T_{clouding}$ had a sharper increase from 61 °C at a pH from 3.11 to already above 97 °C at pH of 5.08. DLS and turbidity measurements (0.02 wt%) confirmed the pH sensitivity with a $T_{clouding}$ ranging from 57 °C (pH = 3.11) to 69 °C (pH = 5.25) [67]. The two previous investigations were then combined by creating a block-copolymer with the pH-sensitive blocks facilitating control over all three thermal transitions in highly polymer concentrated aqueous solution. P(eDEGA$_{70}$-*co*-AA$_4$)-*b*-P(mTEGA$_{150}$-*co*-AA$_8$) was investigated in a 20 wt% solution over a pH range of 3.29–6.00 showing a $T_{sol-gel}$ of 18–36 °C, a $T_{gel-sol}$ of 38–51 °C and $T_{clouding}$ of 55–85 °C. This dependence was again confirmed with DLS and turbidimetry [69].

Zhao and co-workers also used eDEGA as the outer block of an ABA type block-copolymer [102]. These types of block-copolymers are able to form 3D-network gels with micellar cores containing collapsed A blocks connected by soluble B block bridges. The synthesized P(eDEGA-*co*-AA)-*b*-PEO-*b*-P(eDEGA-*co*-AA) did not only show the expected

reversible sol-to-gel transition but also a pH responsivity causing an increased sol-to-gel transition temperature (12.0 wt%) from 23.1 °C (pH = 3.00) to 50.5 °C (6.43), broadening of the sol-to-gel transition and widening in the micelle core size. Further DLS and turbidity measurements showed a T_{cp} of 15 °C (0.02 wt%) in an aqueous buffer with pH = 3.00.

Sârbu et al. were inspired by the thermoresponsivity and biocompatibility of OEGAs to synthesize new block copolymer architectures. Using a tetrafunctional PEG macroinitiator, they synthesized star block copolymers consisting of a central PEG block and four P(eDEGA$_{95}$-*co*-mOEGA$_5$) arms using ATRP [103]. Thermal gelation analysis in 20 wt% aqueous solutions showed that with decreasing arm length, the gelation temperature increases from 27 to 37 °C. The frequency sweep tests carried out at 37 °C in a 20 wt% aqueous solution showed shear thinning at high frequencies, suggesting the possible application as injectable hydrogels. Matjaszewski and co-workers also investigated the thermoresponsive behavior of P(eDEGA) in more intricate polymer architectures [104]. Using iron-based ATRP in combination with a poly[2-(2-bromoisobutyryloxy)ethyl methacrylate] (PBiBEM) as macroinitiator (DP = 400), they were able to synthesize well-defined, densely grafted, molecular bottlebrush copolymers of eDEGA. A ratio of [eDEGA]/[BiBEM]/[$Fe^{II}Br_2$]/[$Fe^{III}Br_3$]/[tetrabutylammonium bromide (TBABr)] of 400/1/0.475/0.025/0.5 at 90 °C in 33% (v/v) anisole yielded a conversion of 12% after 48 h, corresponding to an average DP of 48 units of eDEGA as grafted side chain. These side chains were further analyzed by cleaving with alcoholysis and subsequent analysis with SEC, revealing an initiator efficiency of 83% and M_n of 8000 g/mol ($Đ$ = 1.29). Finally, the temperature-dependent size distribution was investigated using DLS revealing a drastic increase in the hydrodynamic volume in distilled water (0.1 wt%) from 28 nm at 8 to 280 nm at 15 °C, placing the LCST of the molecular brush around 10 °C. Recently Sumerlin and co-workers reported the synthesis of P(eDEGA$_{36}$-*b*-DMAAm$_{54}$) and the evaluation of its solution behavior. When an aqueous solution of this block-copolymer (0.1 wt%) was heated above 25 °C, micellar aggregates with an average hydrodynamic diameter of 24 nm could be observed with DLS [76].

Application examples of HPA include the synthesis of thermoresponsive segmented polymer networks by UV initiated copolymerization with a poly(2-ethyl-2-oxazoline) bis-macromonomer by Du Prez and co-workers. Decreasing T_{cp}s were visually observed ranging from 55 to 46 °C with increasing f_{HPA} from 30% to 70% [105]. Wang and co-workers reported the synthesis of P(HPA-*co*-AMHS) hydrogels via free radical polymerization, initiated by $K_2S_2O_8$-$NaHSO_3$. The resulting hydrogels showed a swelling ratio that depends on both temperature and pH. The formed hydrogels were loaded with caffeine as model drug and subjected to drug release studies. These studies revealed a strong dependency of the caffeine release to pH and temperature, making it a potential material for controlled drug release [77,93]. Finally, Wang and co-workers reported the thermoresponsive layer-by-layer assembly between P(HPA) and P(*N*-vinylcaprolactam) which could be stable at neutral pH due to strong hydrogen bonding. The relative stability of the assembly at physiological pH and the temperature dependent solubility properties were suggested as basis for possible application as dissolvable films or smart capsules [82].

Zhao and co-workers reported the copolymerization of eTEGA with *o*-nitrobenzyl acrylate (NBA) via RAFT. P(eTEGA) was reported to have a T_{cp} around 36 °C while the incorporation of 12% of NBA causes a decrease of T_{cp} to 18.5 °C in aqueous solution (0.02 wt%). When irradiated with UV light (365 nm), the NBA is released as *o*-nitrosobenzaldehyde, leaving hydrophilic AA on the backbone, which increases the cloud point temperature from 18.5 to ≈ 30 °C. This UV-sensitivity was used to create responsive PEO-*b*-P(eTEGA-*co*-NBA) based micelles that form stable aggregates at 30 °C and completely dissociate when irradiated with light, reforming as micelles when the temperature is further increased (Fig. 11).

Based on release studies with nile red, the potential application of these polymers is shown as a drug release

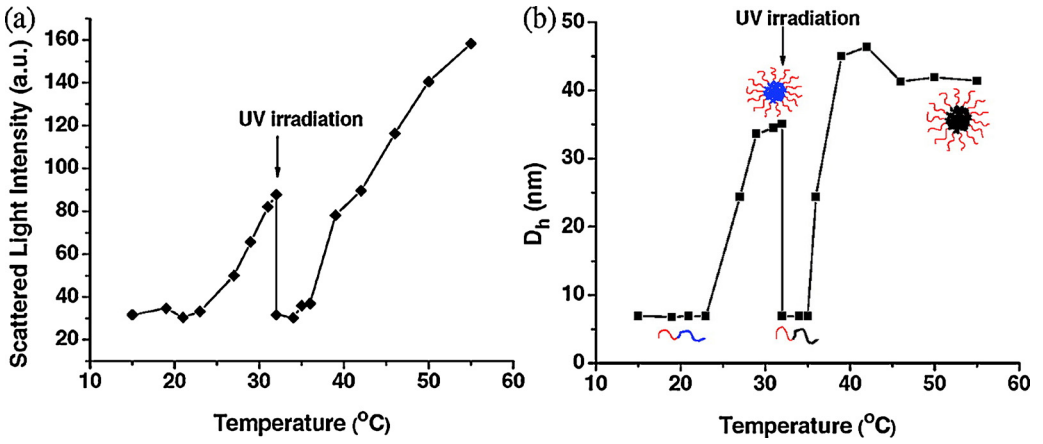

Fig. 11. Intensity of scattered light at scattering angle 90° (a) and hydrodynamic diameter (b) as a function of temperature in a dynamic light scattering study of multiple micellization and dissociation transitions of PEO-*b*-P(eTEGA$_{88}$-*co*-NBA$_{12}$) in response to temperature changes and UV irradiation in aqueous solution (0.02 wt%) [83].

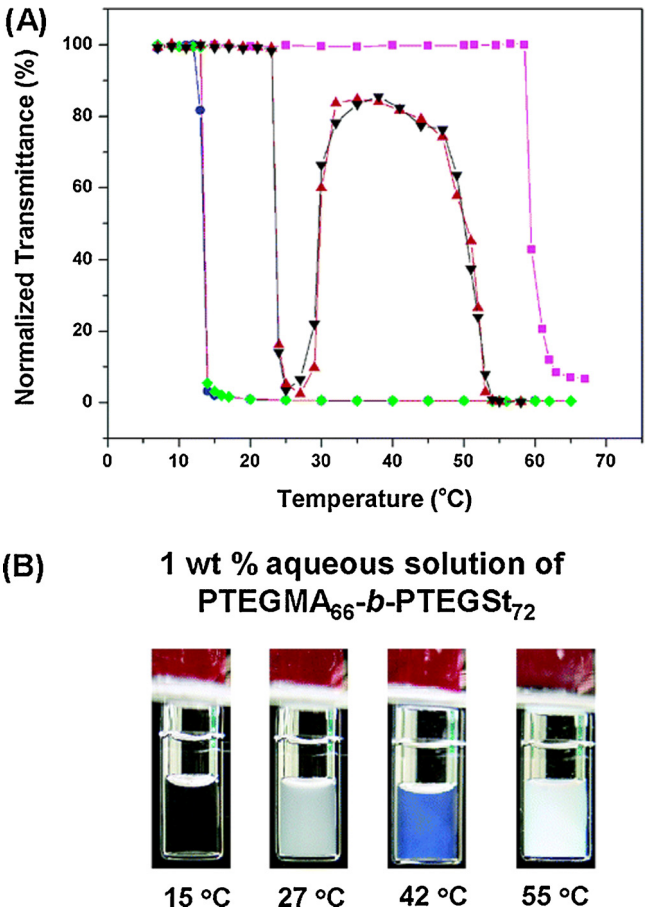

Fig. 12. Optical transmittances of aqueous solutions of PTEGMA$_{66}$-*b*-PTEGSt$_{72}$ ($M_{n,GPC}$ = 26,800 g/mol, $Đ$ = 1.21, 1 wt%) upon heating (▲) and cooling (▼), PTEGSt ($M_{n,GPC}$ = 10,400 g/mol, DP = 44, $Đ$ = 1.10, 0.5 wt%), PTEGMA (■, $M_{n,GPC}$ = 9500 g/mol, DP = 66, $Đ$ = 1.19, 0.5 wt%), and a mixture (♦) of PTEGSt ($M_{n,GPC}$ = 10,400 g/mol, DP = 44, $Đ$ = 1.10, 0.5 wt%) and PTEGMA ($M_{n,GPC}$ = 9500 g/mol, DP = 66, $Đ$ = 1.19, 0.5 wt%) at various temperatures. Right: photographs of a 1 wt% aqueous solution of PmTEGA$_{66}$-b-PTEGSt$_{72}$ at different temperature [68].

system that is able to re-encapsulate a previously released drug [83]. One year later, the same hydrophilic PEO$_{133}$-*b*-P(eTEGA$_{88}$-*co*-NBA$_{11}$) was used to investigate the thermo- and light-sensitivity of the sol–gel–sol transitions in highly polymer concentrated aqueous solutions. A 20 wt% aqueous polymer solution was gradually heated from 0 to 60 °C in steps of 1 °C with a visual examination of the gel properties of the solution. Up until 20 °C, the solution was a free flowing liquid. When the temperature was further increased to 33 °C, the solution turned into a free standing gel which reverted back to a free flowing liquid when heated further to 50 °C. Dynamic rheology measurements and polarized microscopy studies reveals that the gel at 33 °C was composed of cubic-packed micelles with a collapsed P(eTEGA$_{88}$-*co*-NBA$_{11}$) core and a PEO corona forming a micellar gel. UV irradiation of this gel increases the LCST of the P(eTEGA-*co*-NBA) block through dissociation of NBA into AA and *o*-nitrosobenzaldehyde, increasing the hydrophilicity of the center and converting the micellar gel into a solution at 33 °C. When this irradiated solution was heated up, similar sol-to-gel and gel-to-sol transitions could be observed [106]. The same light- and thermo-responsive P(eTEGA-*co*-NBA) block was synthesized using ATRP initiated by a bifunctional PEO macromonomer. These ABA triblock-copolymers were reported to show similar gel-to-sol transition in response to temperature changes and UV irradiation in aqueous solution (10 wt%) [107]. Lambov and co-workers synthesized thermoresponsive P(eTEGA) cryogels that underwent swelling/deswelling between 20–50 °C [108,109]. The cryogels show a thermoresponsivity in their pore size while retaining the porous open gel structure. Biocompatibility test of the gels on several human cell lines showed an almost complete lack of cytotoxicity, making these materials potentially applicable as, e.g., oral drug release system.

Beside the extensive study on the thermoresponsive behavior of P(mDEGA) reported in 2012, Laschewsky and co-workers also expanded this investigation to more complex copolymer architectures. In 2011 they already reported the temperature induced self-assembly of triple-responsive triblock copolymers. These polymers were synthesized via sequential RAFT polymerization of NIPAAm, mDEGA and *N*-(ethylacrylamide) (NEAm), which allows full control over the block sequence. All the

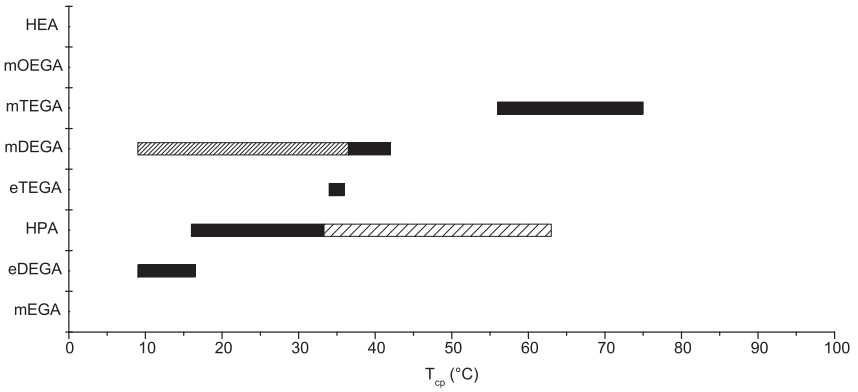

Fig. 13. Schematic overview of the range of reported T_{cp} (°C) of the corresponding POEGA homopolymers in aqueous solutions. The densely shaded areas for mDEGA are values reported for low DP polymers and are therefore greatly influenced by their hydrophobic end-groups [86]. The sparsely shaded areas for HPA are values reported for low DP polymers with hydrophilic end groups [81].

synthesized ternary block-copolymers showed high tendency for cluster formation with a strong temperature size-dependency [110]. During the previous study on mDEGA homopolymers, Laschewsky et al. synthesized P(Sty-mDEGA) diblock, symmetrical triblock and three-arm star PSty-PmDEGA block-copolymers, containing 8 PS units to ensure complete dissolution in water. These polymers were synthesized using two subsequent RAFT polymerizations with mono-, di- and trifunctional RAFT agents [86]. Cloud point investigations revealed an expected increase in T_{cp} (0.3 wt%) with increasing DP of each mDEGA block ranging from 34.6 to 40.1 °C for a DP of 101–513 for the diblock, 20.5 to 38.1 °C for a DP of 41–659 for the triblock and 27.2 to 34.1 °C for a DP of 78–231 for the three arm star. Interestingly, it appears that the additional PS block in the triblock and three arm star block copolymers, not only decreases the cloud point but also slows the rate of reswelling, causing a hysteresis effect. The authors presume that this effect is caused by steric constraint as a result of the interacting hydrophobic segments. This thermoresponsive behavior of P(Sty-*b*-mDEGA-*b*-Sty) was further investigated for polymer hydrogels [111], polymer thick films [112] and polymer thin films [113]. Another application of mDEGA copolymers was recently reported by Caykara et al. based on surface mediated RAFT copolymerization of mDEGA with mOEGA (M_w = 480 g/mol, 8–9 units) in order to synthesize thermoresponsive superparamagnetic Fe_3O_4 nanoparticles (SPNPs) [114]. After the initial ligand exchange of the oleic acid stabilized Fe_3O_4 with 2-[(dodecylsulfanylcarbonylthiolsulfanyl) propionic acid] (DCPA), P(mDEGA$_{45}$-*co*-mOEGA$_5$) with M_n of 12,000 g/mol ($Đ$ = 1.12) was polymerized onto the SPNPs surface with a grafting density of 0.69 chains/nm^2 as calculated from TGA. The authors showed a smooth and reversible transition in particle size measured by DLS from an average of 26 nm at 25–110 nm at 37 °C due to the collapse and aggregation of the polymer, leading to an LCST of the hybrid nanoparticles around 32 °C (0.1 wt%).

Zhao et al. synthesized a block copolymer based on 4-vinylbenzyl methoxytris(oxyethylene) ether (TEGSt) and mTEGA [68]. The formed diblock copolymer showed a first LCST transition at 24 °C as a result of the TEGSt block dehydration. The turbid mixture subsequently showed a clearance point at 32 °C caused by the formation of micelle, resulting in a clear and slightly blue solution (Fig. 12B). Upon further heating to 51 °C, the solution became turbid again due to collapse of the mTEGA block. The temperatures were influenced by the length of the polymer, but generally the first T_{cp} was higher than the LCST of PTEGSt homopolymer (≈13 °C) [34] and the second T_{cp} lower than LCST of the P(mTEGA) homopolymer (≈58 °C) [33] (Fig. 12). These observations can be rationalized by considering that P(mTEGA) acts as hydrophilic end-group of P(mTEGSt), thereby, increasing the T_{cp} of P(mTEGSt) while the collapsed P(mTEGSt) acts as hydrophobic end-group for P(mTEGA), thus lowering the T_{cp} of P(mTEGA). Further investigations using DLS showed the formation of monodisperse, spherical micelles in the intermediate temperature range with dehydrated P(TEGSt) core and hydrated P(mTEGA) corona.

6. General trends

As shown in Fig. 4, there are eight structurally different OEGA monomers reported, each with their own T_{cp} range. Beside the strong dependency of the T_{cp} on the polymer structure, determining the average cloud point, the range that is given in Fig. 13 for each monomer results from other parameters, such as polymer concentration, polymer end-groups and molecular weight. This figure emphasizes that by careful design of the polymer and the environmental conditions almost the entire range of available T_{cp}s in aqueous solution can be approached, even by simple POEGA homopolymers.

The general trend of T_{cp} versus POEGA copolymer composition is an obvious increase in T_{cp} when adding more hydrophilic comonomers. The more interesting evaluation however, is the actual trends in T_{cp} as function of incorporated hydrophilic comonomer fraction. It seems that when HEA is used as hydrophilic comonomer, the T_{cp} increases exponentially with F_{HEA}. This trend is noticeable up to very high amounts of HEA and is very strong for comonomers like HPA [78,80] and mEGA [61,64] while the exponential increase appears weaker with eDEGA as comonomer [75]. The other publications that investigated the effect of POEGA copolymer composition on the T_{cp} focus on mOEGA

(M_n = 454 g/mol, 8–9 units) as hydrophilic monomer in combination with eDEGA or the cyclic ortho ester DEA and DMDEA. In both cases, the observed trend is a clear linear increase of T_{cp} in function of F_{mOEGA} [18,71,79]. It should, however, be noted that the studied T_{cp} range in the latter cases was smaller.

One other important parameter is the length of the polymers that generally cause an increased T_{cp} with increased molecular weight, especially for lower molecular weight polymers. This effect has been reported for both P(mDEGA) [33,86] and P(mTEGA) [33], as well as for P(mEGA-*co*-HEA) [64] and P(mEGA-*co*-mDEGA) [65]. Other copolymers like P(mOEGA-*co*-DEA) and P(mOEGA-*co*-DMDEA) [18] also showed this effect. Surprisingly, the observed trend is opposite to general observations for P(mTEGMA) [24], PNIPAAm at low polymer concentration (1 g/l) [115] and P(HPA) [81] where an increase in molecular weight causes a decrease of the T_{cp} as expected according to the Flory–Huggins theory. The effect of adding an additional monomer unit is a balance between the addition of two opposites: the hydrophobic backbone and the hydrophilic side chain. The net gain of these two will determine the trend of the T_{cp} in function of molecular weight. This 'net gain' idea can explain the different trends of the final examples by the more hydrophobic backbone for poly(methacrylate)s and the less hydrophilic side chain for NIPAAm and HPA resulting in a net hydrophobic gain. The opposite trend for poly(acrylate)s can probably be explained by the less hydrophobic backbone compared to poly(methacrylate)s. It should be noted that more monomers, monomer combinations and the influence of the polymer end-group on the molecular weight trend need to be investigated before any general conclusion can be made.

The final parameter that causes a considerable effect on the T_{cp} is the polymer concentration. Generally, an inverse dependency between the T_{cp} and polymer concentration can be observed. This effect was thoroughly investigated by Zhang and co-workers for P(mDEGA) and P(mTEGA). They reported that this inverse dependency is very strong for small concentrations up to 1.0 wt% after which the T_{cp} reaches a plateau [33]. Schubert et al. observed for P(HPA) that beside the increased T_{cp}, the transition also became more diffuse and showed more hysteresis upon decreasing concentration [79,80]. Copolymers including P(eDEGA-*co*-DMAAm) [76], P(HEA-*co*-HPA) [80] and P(HEA-*co*-mEGA) [64] confirm this general trend. This dependency is no different from PNIPAAm, albeit that this effect is significantly smaller for PNIPAAm yet persisting for longer concentration range [116]. It is important to note that this effect at lower concentrations might simply, at least partially, be related to the formation of smaller hydrophobic phase separated globules that scatter less light and are thus not very well detected by turbidity, which is the general method to determine T_{cp}s.

7. Conclusion and outlook

This review highlights the versatility and especially the potential that oligo(ethylene glycol) acrylate based polymers posses as thermoresponsive polymers. Their well-defined side chain length allows the thorough investigation and evaluation of the phase transition characteristics while the lower hydrophobicity of the polyacrylate backbone, in comparison to poly(methacrylate)s, enables thermoresponsive behavior with smaller hydrophilic side chains. This also opens up the possibility of evaluating the effect of more intricate polymer architecture like gradient or brush copolymers using any of the common controlled radical polymerization techniques. Therefore, we are confident that such thermoresponsive poly(acrylate)s will significantly gain in interest in the coming years to strongly compete with PNIPAM and PmOEGMAs for a wide variety of applications.

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References

[1] Bawa P, Pillay V, Choonara YE, du Toit LC. Stimuli-responsive polymers and their applications in drug delivery. Biomed Mater 2009;4:1–15.
[2] Gil E, Hudson S. Stimuli-reponsive polymers and their bioconjugates. Prog Polym Sci 2004;29:1173–222.
[3] Schmaljohann D. Thermo- and pH-responsive polymers in drug delivery. Adv Drug Deliv Rev 2006;58:1655–70.
[4] Dong J, Wang Y, Zhang J, Zhan X, Zhu S, Yang H, Wang G. Multiple stimuli-responsive polymeric micelles for controlled release. Soft Matter 2013;9:370–3.
[5] Zhao C, Nie S, Tang M, Sun S. Polymeric pH-sensitive membranes—a review. Prog Polym Sci 2011;36:1499–520.
[6] Stuart MaC, Huck WTS, Genzer J, Müller M, Ober C, Stamm M, Sukhorukov GB, Szleifer I, Tsukruk VV, Urban M, Winnik F, Zauscher S, Luzinov I, Minko S. Emerging applications of stimuli-responsive polymer materials. Nat Mater 2010;9:101–13.
[7] Nath N, Chilkoti A. Creating "smart" surfaces using stimuli responsive polymers. Adv Mater 2002;14:1243–7.
[8] Sawa Y, Urayama K, Takigawa T, DeSimone A, Teresi L. Thermally driven giant bending of liquid crystal elastomer films with hybrid alignment. Macromolecules 2010;43:4362–9.
[9] Jiang Y, Xu D, Li X, Lin C, Li W, An Q, Tao C, Tang H, Li G. Electrothermally driven structural colour based on liquid crystal elastomers. J Mater Chem 2012;22:11943–9.
[10] Liu C, Qin H, Mather PT. Review of progress in shape-memory polymers. J Mater Chem 2007;17:1543–58.
[11] Lendlein A, Kelch S. Shape-memory polymers. Angew Chem Int Ed 2002;41:2034–57.
[12] Jeong B, Gutowska A. Lessons from nature: stimuli-responsive polymers and their biomedical applications. Trends Biotechnol 2002;20:305–11.
[13] Schild HG. Poly(N-isopropylacrylamide): experiment, theory and application. Prog Polym Sci 1992;17:163–249.
[14] Lutz JF, Akdemir O, Hoth A. Point by point comparison of two thermosensitive polymers exhibiting a similar LCST: is the age of poly(NIPAM) over? J Am Chem Soc 2006;128:13046–7.
[15] Neugebauer D. Graft copolymers with poly (ethylene oxide) segments. Polym Int 2007;56:1469–98.
[16] Lutz JF. Polymerization of oligo(ethylene glycol) (meth)acrylates: toward new generations of smart biocompatible materials. J Polym Sci Part A Polym Chem 2008;46:3459–70.
[17] Lutz J, Andrieu J, Üzgün S, Rudolph C, Agarwal S. Biocompatible, thermoresponsive, and biodegradable: simple preparation of all-in-one biorelevant polymers. Macromolecules 2007;40:8540–3.

[18] Qiao ZY, Du FS, Zhang R, Liang DH, Li ZC. Biocompatible thermoresponsive polymers with pendent oligo(ethylene glycol) chains and cyclic ortho ester groups. Macromolecules 2010;43:6485–94.
[19] Roth PJ, Jochum FD, Theato P. UCST-type behavior of poly[oligo(ethylene glycol) methyl ether methacrylate] (POEGMA) in aliphatic alcohols: solvent, co-solvent, molecular weight, and end group dependences. Soft Matter 2011;7:2484–92.
[20] Chua GBH, Roth PJ, Duong HTT, Davis TP, Lowe AB. Synthesis and thermoresponsive solution properties of poly[oligo(ethylene glycol) (meth)acrylamide]s: biocompatible PEG analogues. Macromolecules 2012;45:1362–74.
[21] Chang CW, Bays E, Tao L, Alconcel SNS, Maynard HD. Differences in cytotoxicity of poly(PEGA)s synthesized by reversible addition-fragmentation chain transfer polymerization. Chem Commun 2009;24:3580–2.
[22] Weber C, Hoogenboom R, Schubert US. Temperature responsive bio-compatible polymers based on poly(ethylene oxide) and poly(2-oxazoline)s. Prog Polym Sci 2012;37:686–714.
[23] Ishizone T, Han S, Hagiwara M, Yokoyama H. Synthesis and surface characterization of well-defined amphiphilic block copolymers containing poly[oligo(ethylene glycol) methacrylate] segments. Macromolecules 2006;39:962–70.
[24] Han S, Hagiwara M, Ishizone T. Synthesis of thermally sensitive water-soluble polymethacrylates by living anionic polymerizations of oligo(ethylene glycol) methyl ether methacrylates. Macromolecules 2003;36:8312–9.
[25] Hu Z, Cai T, Chi C. Thermoresponsive oligo(ethylene glycol)-methacrylate-based polymers and microgels. Soft Matter 2010;6:2115–23.
[26] Lutz JF, Hoth A, Schade K. Design of oligo(ethylene glycol)-based thermoresponsive polymers: an optimization study. Des Monomers Polym 2009;12:343–53.
[27] Lutz JF. Thermo-switchable materials prepared using the OEGMA-platform. Adv Mater 2011;23:2237–43.
[28] Becer C, Hahn S. Libraries of methacrylic acid and oligo (ethylene glycol) methacrylate copolymers with LCST behavior. J Polym Sci Part A Polym Chem 2008;46:7138–47.
[29] Zhao Y, Tremblay L. Doubly photoresponsive and water-soluble block copolymers: synthesis and thermosensitivity. J Polym Sci Part A Polym Chem 2010;48:4055–66.
[30] Luzon M, Boyer C, Peinado C, Corrales T, Whittaker MR, Tao L, Davis TP. Water-soluble, thermoresponsive, hyperbranched copolymers based on PEG-methacrylates: synthesis, characterization, and LCST behavior. J Polym Sci Part A Polym Chem 2010;48:2783–92.
[31] Ali M, Stöver H. Well-defined amphiphilic thermosensitive copolymers based on poly (ethylene glycol monomethacrylate) and methyl methacrylate prepared by atom transfer radical polymerization. Macromolecules 2004;37:5219–27.
[32] Jiang X, Zhao B. End group effect on the thermo-sensitive properties of well-defined water-soluble polystyrenics with short pendant oligo (ethylene glycol) groups synthesized by nitroxide-mediated radical polymerization. J Polym Sci Part A Polym Chem 2007;45:3707–21.
[33] Hua F, Jiang X, Li D, Zhao B. Well-defined thermosensitive, water-soluble polyacrylates and polystyrenics with short pendant oligo (ethylene glycol) groups synthesized by nitroxide-mediated radical polymerization. J Polym Sci Part A Polym Chem 2006;44:2454–67.
[34] Zhao B, Li D, Hua F, Green D. Synthesis of thermosensitive water-soluble polystyrenics with pendant methoxyoligo (ethylene glycol) groups by nitroxide-mediated radical polymerization. Macromolecules 2005;38:9509–17.
[35] Cheng G, Melnichenko YB, Wignall GD, Hua F, Hong K, Mays JW. Conformation of oligo(ethylene glycol) grafted polystyrene in dilute aqueous solutions. Polymer 2007;48:4108–13.
[36] Aoshima S, Sugihara S. Syntheses of stimuli-responsive block copolymers of vinyl ethers with side oxyethylene groups by living cationic polymerization and their thermosensitive physical gelation. J Polym Sci Part A Polym Chem 2000;38:3962–5.
[37] Aoshima S, Sugihara S, Shibayama M, Kanaoka S. Synthesis and self-association of stimuli-responsive diblock copolymers by living cationic polymerization. Macromol Symp 2004;215:151–63.
[38] Sugihara S, Kanaoka S, Aoshima S. Double thermosensitive diblock copolymers of vinyl ethers with pendant oxyethylene groups: unique physical gelation. Macromolecules 2005;38:1919–27.
[39] Sugihara S, Kanaoka S, Aoshima S. Stimuli-responsive ABC triblock copolymers by sequential living cationic copolymerization: multistage self-assemblies through micellization to open association. J Polym Sci Part A Polym Chem 2004;42:2601–11.
[40] Gu L, Qin Y, Gao Y. Hydrophilic CO_2-based biodegradable polycarbonates: synthesis and rapid thermo-responsive behavior. J Polym Sci Part A Polym Chem 2013;51:2834–40.
[41] Fu X, Shen Y, Fu W, Li Z. Thermoresponsive oligo(ethylene glycol) functionalized poly-L-cysteine. Macromolecules 2013;46:3753–60.
[42] Kouwer PHJ, Koepf M, Le Sage VAA, Jaspers M, van Buul AM, EksteenAkeroyd ZH, Woltinge T, Schwartz E, Kitto HJ, Hoogenboom R, Picken SJ, Nolte RJM, Mendes E, Rowan AE. Responsive biomimetic networks from polyisocyanopeptide hydrogels. Nature 2013;493:651–5.
[43] Hu G, Li W, Hu Y, Xu A, Yan J, Liu L, Zhang X, Liu K, Zhang A. Water-soluble chiral polyisocyanides showing thermoresponsive behavior. Macromolecules 2013;46:1124–32.
[44] Koepf M, Kitto HJ, Schwartz E, Kouwer PHJ, Nolte RJM, Rowan AE. Preparation and characterization of non-linear poly(ethylene glycol) analogs from oligo(ethylene glycol) functionalized polyisocyanopeptides. Eur Polym J 2013;49:1510–22.
[45] Soeriyadi AH, Li GZ, Slavin S, Jones MW, Amos CM, Becer CR, Whittaker MR, Haddleton DM, Boyer C, Davis TP. Synthesis and modification of thermoresponsive poly(oligo(ethylene glycol) methacrylate) via catalytic chain transfer polymerization and thiol-ene Michael addition. Polym Chem 2011;2:815–22.
[46] Magnusson JP, Khan A, Pasparakis G, Saeed AO, Wang W, Alexander C. Ion-sensitive "isothermal" responsive polymers prepared in water. J Am Chem Soc 2008;130:10852–3.
[47] Lutz J, Hoth A. Preperation of ideal PEG analogues with a tunable thermosensitivity by controlled radical copolymerization of 2-2(methoxyethoxy)ethylmethacrylate and oligo(ethylene glycol)methacrylate. Macromolecules 2006;39:893–6.
[48] Roth PJ, Collin M, Boyer C. Advancing the boundary of insolubility of non-linear PEG-analogues in alcohols: UCST transitions in ethanol–water mixtures. Soft Matter 2013;9:1825–34.
[49] Zarafshani Z, Akdemir Ö, Lutz J. A "Click" strategy for tuning in situ the hydrophilic–hydrophobic balance of AB macrosurfactants. Macromol Rapid Commun 2008;29:1161–6.
[50] Lutz JF, Weichenhan K, Akdemir Ö, Hoth A. About the phase transitions in aqueous solutions of thermoresponsive copolymers and hydrogels based on 2-(2-methoxyethoxy)ethyl methacrylate and oligo(ethylene glycol) methacrylate. Macromolecules 2007;40:2503–8.
[51] Yaşayan G, Saeed AO, FernándezTrillo F, Allen S, Davies MC, Jangher A, Paul A, Thurecht KJ, King SM, Schweins R, Griffiths PC, Magnusson JP, Alexander C. Responsive hybrid block co-polymer conjugates of proteins–controlled architecture to modulate substrate specificity and solution behaviour. Polym Chem 2011;2:1567–78.
[52] Akdemir O, Badi N, Pfeifer S, Zarafshani Z, Laschewsky AA, Wischerhoff E, Lutz JF. Design of thermoresponsive materials by ATRP of oligo(ethylene glycol)-based (macro)monomers. ACS Symp Ser 2009;1023:189–202.
[53] Jonas AM, Glinel K, Oren R, Nysten B, Huck WTS. Thermo-responsive polymer brushes with tunable collapse temperatures in the physiological range. Macromolecules 2007;40:4403–5.
[54] Yamamoto S, Pietrasik J, Matyjaszewski K. ATRP synthesis of thermally responsive molecular brushes from oligo(ethylene oxide) methacrylates. Macromolecules 2007;40:9348–53.
[55] Yamamoto S, Pietrasik J, Matyjaszewski K. The effect of structure on the thermoresponsive nature of well-defined poly (oligo (ethylene oxide) methacrylates) synthesized by ATRP. J Polym Sci Part A Polym Chem 2008;46:194–202.
[56] Lessard B, Ling E, Maricí M. Fluorescent, thermoresponsive oligo(ethylene glycol) methacrylate/9-(4-vinylbenzyl)-9 H-carbazole copolymers designed with multiple LCSTs via nitroxide mediated controlled radical polymerization. Macromolecules 2012;45:1879–91.
[57] Becer CR, Kokado K, Weber C, Can A, Chujo Y, Schubert US. Metal-free synthesis of responsive polymers: cloud point tuning by controlled "click" reaction. J Polym Sci Part A Polym Chem 2010;48:1278–86.
[58] Coessens V, Pintauer T, Matyjaszewski K. Functional polymers by atom transfer radical polymerization. Prog Polym Sci 2001;26:337–77.
[59] Guillaneuf Y, Gigmes D, Junkers T. Investigation of the end group fidelity at high conversion during nitroxide-mediated acrylate polymerizations. Macromolecules 2012;45:5371–8.
[60] Liu G, Qiu Q, Shen W, An Z. Aqueous dispersion polymerization of 2-methoxyethyl acrylate for the synthesis of biocompatible nanoparticles using a hydrophilic RAFT polymer and a redox initiator. Macromolecules 2011;44:5237–45.

[61] Hoogenboom R, Zorn AM, Keul H, Barner-Kowollik C, Moeller M. Copolymers of 2-hydroxyethyl acrylate and 2-methoxyethyl acrylate by nitroxide mediated polymerization: kinetics, SEC-ESI-MS analysis and thermoresponsive properties. Polym Chem 2012;3:335–42.
[62] Haraguchi K, Murata K, Takehisa T. Stimuli-responsive nanocomposite gels and soft nanocomposites consisting of inorganic clays and copolymers with different chemical affinities. Macromolecules 2012;45:385–91.
[63] Haraguchi K, Ebato M, Takehisa T. Polymer–clay nanocomposites exhibiting anormal necking phenomena accompanied by extremely large reversible elongations and excellent transparency. Adv Mater 2006;18:2250–4.
[64] Steinhauer W, Hoogenboom R, Keul H, Moeller M. Copolymerization of 2-hydroxyethyl acrylate and 2-methoxyethyl acrylate via RAFT: kinetics and thermoresponsive properties. Macromolecules 2010;43:7041–7.
[65] Lavigueur C, García JG, Hendriks L, Hoogenboom R, Cornelissen JJLM, Nolte RJM. Thermoresponsive giant biohybrid amphiphiles. Polym Chem 2011;2:333–40.
[66] Foulger SH, Jiang P, Lattam A, Smith Jr DW, Ballato J, Dausch DE, Grego S, Stoner BR. Photonic crystal composites with reversible high-frequency stop band shifts. Adv Mater 2003;15:685–9.
[67] Jin N, Woodcock JW, Xue C, O'Lenick TG, Jiang X, Jin S, Dadmun MD, Zhao B. Tuning of thermo-triggered gel-to-sol transition of aqueous solution of multi-responsive diblock copolymer poly(methoxytri(ethylene glycol) acrylate-co-acrylic acid)-b-poly(ethoxydi(ethylene glycol) acrylate). Macromolecules 2011;44:3556–66.
[68] Hua F, Jiang X, Zhao B. Temperature-induced self-association of doubly thermosensitive diblock copolymers with pendant methoxytris(oxyethylene) groups in dilute aqueous solutions. Macromolecules 2006;39:3476–9.
[69] Jin N, Zhang H, Jin S, Dadmun MD, Zhao B. Shifting sol–gel phase diagram of a doubly thermosensitive hydrophilic diblock copolymer poly(methoxytri(ethylene glycol) acrylate-co-acrylic acid)-b-poly(ethoxydi(ethylene glycol) acrylate-co-acrylic acid) in aqueous solution. Macromolecules 2012;45:4790–800.
[70] Kolodziej CM, Maynard HD. Shape-shifting micro- and nanopatterns controlled by temperature. J Am Chem Soc 2012;134:12386–9.
[71] Boyer C, Whittaker MR, Luzon M, Davis TP. Design and synthesis of dual thermoresponsive and antifouling hybrid polymer/gold nanoparticles. Macromolecules 2009;42:6917–26.
[72] Popescu D, Hoogenboom R, Keul H, Moeller M. Hydroxy functional acrylate and methacrylate monomers prepared via lipase-catalyzed transacylation reactions. J Mol Catal B Enzym 2010;62:81–90.
[73] Popescu D, Keul H, Moeller M. Highly functional poly(meth)acrylates via cascade reaction. Macromol Chem Phys 2008;210:123–39.
[74] Popescu D, Hoogenboom R, Keul H, Moeller M, Möller M. Free radical and nitroxide mediated polymerization of hydroxy functional acrylate and methacrylate monomers prepared via lipase-catalyzed transacylation reactions. J Polym Sci Part A Polym Chem 2010;48:2610–21.
[75] Popescu D, Hoogenboom R, Keul H, Moeller M. Thermoresponsive polyacrylates obtained via a cascade of enzymatic transacylation and FRP or NMP. Polym Chem 2010;1:878–90.
[76] De P, Sumerlin BS. Precision control of temperature response by copolymerization of di(ethylene glycol) acrylate and an acrylamide comonomer. Macromol Chem Phys 2013;214:272–9.
[77] Deng K, Tian H, Zhang P, Zhong H, Ren X, Wang H. pH-temperature responsive poly(HPA-co-AMHS) hydrogel as a potential drug-release carrier. J Appl Polym Sci 2009;114:176–84.
[78] Taylor LD, Cerankowski LD. Preparation of films exhibiting a balanced solutions—a study of lower consolute behavior. J Polym Sci Part A Polym Chem 1975;13:2551–70.
[79] Eggenhuisen TM, Becer CR, Fijten MWM, Eckardt R, Hoogenboom R, Schubert US. Libraries of statistical hydroxypropyl acrylate containing copolymers with LCST properties prepared by NMP. Macromolecules 2008;41:5132–40.
[80] Hoogenboom R, Popescu D, Steinhauer W, Keul H, Moeller M. Nitroxide-mediated copolymerization of 2-hydroxyethyl acrylate and 2-hydroxypropyl acrylate: copolymerization kinetics and thermoresponsive properties. Macromol Rapid Commun 2009;30:2042–8.
[81] Vo CD, Rosselgong J, Armes SP, Tirelli N. Stimulus-responsive polymers based on 2-hydroxypropyl acrylate prepared by RAFT polymerization. J Polym Sci Part A Polym Chem 2010;48:2032–43.
[82] Zhao Z, Yin L, Yuan G, Wang L. Layer-by-layer assembly of two temperature-responsive homopolymers at neutral pH and the temperature-dependent solubility of the multilayer film. Langmuir 2012;28:2704–9.
[83] Jiang X, Lavender CA, Woodcock JW, Zhao B. Multiple micellization and dissociation transitions of thermo- and light-sensitive poly(ethylene oxide)-b-poly(ethoxytri(ethylene glycol) acrylate-co-o-nitrobenzyl acrylate) in water. Macromolecules 2008;41:2632–43.
[84] Dimitrov P, Toncheva N, Weda P, Rangelov S, Trzebicka B, Dworak A, Tsvetanov CB. Nano-templates from thermoresponsive poly(ethoxytriethyleneglycol acrylate) for polymeric nanocapsules. Macromol Symp 2009;278:89–95.
[85] Toncheva-Moncheva N, Dimitrov P, Tsvetanov CB, Robak B, Trzebicka B, Dworak A, Rangelov S. Formation of mesoglobules in aqueous media from thermo-sensitive poly(ethoxytriethyleneglycol acrylate). Polym Bull 2011;67:1335–46.
[86] Miasnikova A, Laschewsky A. Influencing the phase transition temperature of poly(methoxy diethylene glycol acrylate) by molar mass, end groups, and polymer architecture. J Polym Sci Part A Polym Chem 2012;50:3313–23.
[87] Zhong Q, Wang W, Adelsberger J, Golosova A, Bivigou Koumba AM, Laschewsky A, Funari SS, Perlich J, Roth SV, Papadakis CM, Müller-Buschbaum P. Collapse transition in thin films of poly(methoxydiethylenglycol acrylate). Colloid Polym Sci 2011;289:569–81.
[88] Zhong Q, Metwalli E, Kaune G, Rawolle M, Bivigou-Koumba AM, Laschewsky A, Papadakis CM, Cubitt R, Müller-Buschbaum P. Switching kinetics of thin thermo-responsive hydrogel films of poly(monomethoxy-diethyleneglycol-acrylate) probed with in situ neutron reflectivity. Soft Matter 2012;8:5241–9.
[89] Maeda Y, Yamauchi H, Kubota T. Confocal micro-raman and infrared spectroscopic study on the phase separation of aqueous poly(2-(2-methoxyethoxy)ethyl (meth)acrylate) solutions. Langmuir 2009;25:479–82.
[90] Skrabania K, Kristen J, Laschewsky A, Akdemir O, Hoth A, Lutz J-F. Design, synthesis, and aqueous aggregation behavior of nonionic single and multiple thermoresponsive polymers. Langmuir 2007;23:84–93.
[91] Boyer C, Whittaker MR, Chuah K, Liu J, Davis TP. Modulation of the surface charge on polymer-stabilized gold nanoparticles by the application of an external stimulus. Langmuir 2010;22:2721–30.
[92] Lutz JJF, Pfeifer S, Zarafshani Z. In situ functionalization of thermoresponsive polymeric micelles using the "click" cycloaddition of azides and alkynes. QSAR Comb Sci 2007;26:1151–8.
[93] Deng KL, Tian H, Zhang P, Ren X, Zhong H. Synthesis and characterization of a novel temperature-pH responsive copolymer of 2-hydroxypropyl acrylate and aminoethyl methacrylate hydrochloric salt. Express Polym Lett 2009;3:97–104.
[94] Inal S, Kölsch JD, Chiappisi L, Janietz D, Gradzielski M, Laschewsky A, Neher D. Structure-related differences in the temperature-regulated fluorescence response of LCST type polymers. J Mater Chem C 2013;1:6603–12.
[95] Mun GA, Nurkeeva ZS, Beissegul AB, Dubolazov AV, Urkimbaeva PI, Park K, Khutoryanskiy VV. Temperature-responsive water-soluble copolymers based on 2-hydroxyethyl acrylate and butyl acrylate. Macromol Chem Phys 2007;208:979–87.
[96] Mun GA, Nurkeeva ZS, Akhmetkalieva GT, Shmakov SN, Khutoryanskiy VV, Cheon Lee S, Park K. Novel temperature-responsive water-soluble copolymers based on 2-hydroxyethylacrylate and vinyl butyl ether and their interactions with poly(carboxylic acids). J Polym Sci Part B Polym Phys 2006;44:195–204.
[97] Haraguchi K, Masatoshi S. Thermoresponsible cell adhesion/detachment on transparent nanocomposite films consisting of poly (2-methoxyethyl acrylate) and clay. J Biomater Sci 2011;22:2389–406.
[98] Steinhauer W, Hoogenboom R, Keul H, Moeller M. Block and gradient copolymers of 2-hydroxyethyl acrylate and 2-methoxyethyl acrylate via RAFT: polymerization kinetics, thermoresponsive properties and micellization. Macromolecules 2013;46:1447–60.
[99] Liu J. Imparting polymeric properties to graphene nanosheets by surface modification via π–π stacking. Aust J Chem 2011;64:1414.
[100] Liu H, Zhang J, Luo X, Kong N, Cui L, Liu J. Preparation of biodegradable and thermoresponsive enzyme–polymer conjugates with controllable bioactivity via RAFT polymerization. Eur Polym J 2013;49:2949–60.

[101] Jin N, Zhang H, Jin S. Tuning of thermally induced sol-to-gel transitions of moderately concentrated aqueous solutions of doubly thermosensitive hydrophilic diblock copolymers poly(methoxytri(ethylene glycol)acrylate)-b-poly(ethoxydi(ethylene glycol) acrylate-co-acrylic acid). J Phys Chem B 2012;116:3125–37.
[102] O'Lenick TG, Jin N, Woodcock JW, Zhao B. Rheological properties of aqueous micellar gels of a thermo- and pH-sensitive ABA triblock copolymer. J Phys Chem B 2011;115:2870–81.
[103] Negru I, Teodorescu M, Stănescu PO, Drăghici C, Lungu A, Sârbu A. Thermosensitive branched block copolymers of poly(ethylene glycol) and copolyacrylates of oligo(ethylene glycol)s: synthesis and thermal gelation properties of aqeous solutions. UPB Sci Bull Ser B 2011;73:49–64.
[104] Mukumoto K, Li Y, Nese A, Sheiko SS, Matyjaszewski K. Synthesis and characterization of molecular bottlebrushes prepared by iron-based ATRP. Macromolecules 2012;45:9243–9.
[105] Christova D, Velichkova R, Loos W, Goethals EJ, Du Prez F, Du Filip P. New thermo-responsive polymer materials based on poly(2-ethyl-2-oxazoline) segments. Polymer 2003;44:2255–61.
[106] Jiang X, Jin S, Zhong Q, Dadmun MD, Zhao B. Stimuli-induced multiple sol–gel–sol transitions of aqueous solution of a thermo- and light-sensitive hydrophilic block copolymer. Macromolecules 2009;42:8468–76.
[107] Woodcock JW, Wright RAE, Jiang X, O'Lenick TG, Zhao B. Dually responsive aqueous gels from thermo- and light-sensitive hydrophilic ABA triblock copolymers. Soft Matter 2010;6:3325–36.
[108] Kostova B, Momekova D, Petrov P, Momekov G, Toncheva-Moncheva N, Tsvetanov CB, Lambov N. Poly(ethoxytriethyleneglycol acrylate) cryogels as novel sustained drug release systems for oral application. Polymer 2011;52:1217–22.
[109] Petrov P, Momekova D, Kostova B, Momekov G, Toncheva-Moncheva N, Tsvetanov CB, Lambov N. Super-macroporous poly(ethoxytriethyleneglycol acrylate) hydrogels for sustained delivery of hydrophilic drugs. J Controlled Release 2010;148:e81–2.
[110] Weiss J, Laschewsky A. Temperature-induced self-assembly of triple-responsive triblock copolymers in aqueous solutions. Langmuir 2011;27:4465–73.
[111] Miasnikova A, Laschewsky A, De Paoli G, Papadakis CM, Müller-Buschbaum P, Funari SS. Thermoresponsive hydrogels from symmetrical triblock copolymers poly(styrene-block-(methoxy diethylene glycol acrylate)-block-styrene). Langmuir 2012;28:4479–90.
[112] Zhong Q, Adelsberger J, Niedermeier MA, Golosova A, Bivigou-Koumba AM, Laschewsky A, Funari SS, Papadakis CM, Müller-Buschbaum P. The influence of selective solvents on the transition behavior of poly(styrene-b-monomethoxydiethylenglycol-acrylate-b-styrene) thick films. Colloid Polym Sci 2013;291:1439–51.
[113] Zhong Q, Metwalli E, Rawolle M, Kaune G, Bivigou-koumba AM, Laschewsky A, Papadakis CM, Cubitt R, Müller-Buschbaum P. Structure and thermal response of thin thermoresponsive polystyrene-block-poly (methoxydiethylene glycol acrylate)-block-polystyrene films. Macromolecules 2013;46:4069–80.
[114] Zengin A, Tamer U, Caykara T. Synthesis of superparamagnetic and thermoresponsive hybrid nanoparticles via surface-mediated RAFT polymerization of di(ethylene glycol) ethyl ether acrylate and (oligoethylene glycol) methyl ether acrylate. J Polym Sci Part A Polym Chem 2013;51:3420–8.
[115] Xia Y, Yin X, Burke N, Stöver H. Thermal response of narrow-disperse poly (N-isopropylacrylamide) prepared by atom transfer radical polymerization. Macromolecules 2005;38:5937–43.
[116] Tong Z, Zeng F, Zheng X, Sato T. Inverse molecular weight dependence of cloud points for aqueous poly(N-isopropylacrylamide) solutions. Macromolecules 1999;32:4488–90.