HIGHLIGHT

Polymerization of Oligo(Ethylene Glycol) (Meth)Acrylates: Toward New Generations of Smart Biocompatible Materials

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ABSTRACT: Monomers composed of a (meth)acrylate moiety connected to a short poly(ethylene)glycol (PEG) chain are versatile building-blocks for the preparation of "smart" biorelevant materials. Many of these monomers are commercial and can be easily polymerized by either anionic, free-radical, or controlled radical polymerization. The latter approach allows synthesis of well-defined PEG-based macromolecular architectures such as amphiphilic block copolymers, dense polymer brushes, or biohybrids. Furthermore, the resulting polymers exhibit fascinating solution properties in aqueous medium. Depending on the molecular structure of their monomer units, non linear PEG analogues can be either insoluble in water, readily soluble up to 100 °C, or thermoresponsive. Thus, these polymers can be used for building a wide variety of modern materials such as biosensors, artificial tissues, smart gels for chromatography, and drug carriers.
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INTRODUCTION

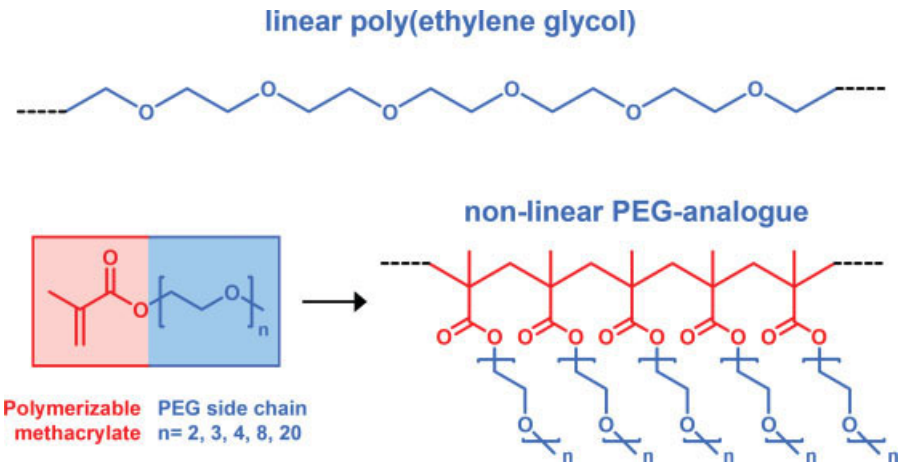
The range of applications of synthetic polymer materials has considerably broadened within the last few decades. Besides well-established commodity applications, synthetic and biological macromolecules have been recently extensively explored in numerous specialty areas as diverse as nanoelectronics, data storage devices, alternative energy resources, cosmetics, healthcare, and biotechnology. These emerging markets generated new directions in fundamental and applied polymer research. Indeed, the aforementioned technologies frequently require high-performance properties, which are often not attainable with standard polymer materials. The biomedical field is a good example to illustrate this point of view. Although some polymers such as poly(ethylene glycol) (PEG) (also known as poly(ethylene oxide) (PEO)) or poly(lactide-*co*-glycolide) (PLGA) have been successfully exploited in numerous commercial bioapplications for many years, several novel areas of biosciences and biotechnology (e.g., bioseparation, diagnostics, gene- or protein- therapy, controlled release, implants) certainly require "smarter" macromolecules with more sophisticated properties.[1,2] For instance, synthetic macromolecules undergoing rapid conformational change in response to an external stimulus such as pH, temperature, ionic strength, or irradiation (i.e., stimuli-responsive polymers) became lately very important in applied biological science.[3–5] Thus, polyelectrolytes, ionomers, or temperature-responsive polymers such as poly(*N*-isopropylacrylamide) (PNIPAM) are nowadays extensively investigated in biomedical research.[4]

The goal of the this highlight is to demonstrate that polymers prepared from oligo(ethylene glycol) (macro)-monomers are extremely versatile and relevant structures in this modern technological context, in particular for applications in the biomedical field. Such polymers are not standard linear poly(ethylene oxides) but graft structures composed of a carbon–carbon backbone and multiple oligo(ethylene glycol) side-chains (Scheme 1). Although heterogeneous structures, these nonlinear PEG analogues are principally composed of oligo(ethylene glycol) segments (up to 85% in weight) and are therefore, in most cases, water-soluble and biocompatible. Furthermore, these macromolecules may exhibit stimuli-responsive properties, which are typically not attainable with linear PEG. For instance, we[6,7] and others[8–10] recently evidenced that these graft polymers generally display a lower critical solution temperature (LCST) in pure water or in physiological medium. Hence, nonlinear PEG analogues appear as ideal structures, which combine both the properties of PEG and PNIPAM in a single macromolecule.

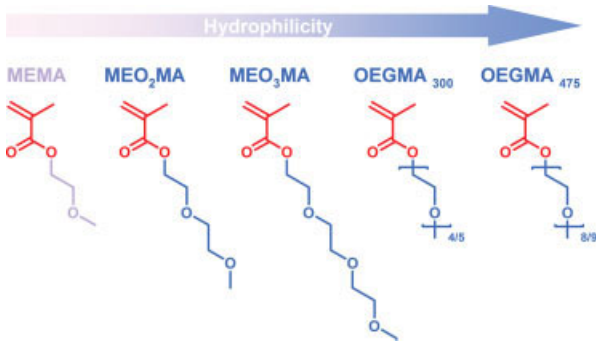
The first examples of PEG macromonomers and their grafting-through polymerization via free-radical, cationic, anionic, or ring-opening mechanisms have been reported more than 20 years ago. Thus, this manuscript is not meant to be an exhaustive review on PEG macromonomers but focuses instead on recent developments and applications. Comprehensive details about monomer synthesis and polymerization may be found in a recent review of Neugebauer.[11] In the following paragraphs, the synthesis, characterization, and properties of nonlinear PEG analogues will be principally illustrated by data from our research group but also by a few other examples selected from recent literature.

POLYMERIZATION AND MACROMOLECULAR ENGINEERING

PEG macromonomers (i.e., molecule composed of a polymerizable moiety connected to a short oligo(ethylene)



Scheme 1. Molecular structure of standard linear PEG and nonlinear PEG-analogues constructed with oligo(ethylene glycol) (macro)monomers.



Scheme 2. Molecular structures of various oligo(ethylene glycol) methacrylates. Hydrophobic and hydrophilic molecular regions are indicated in red and blue, respectively.

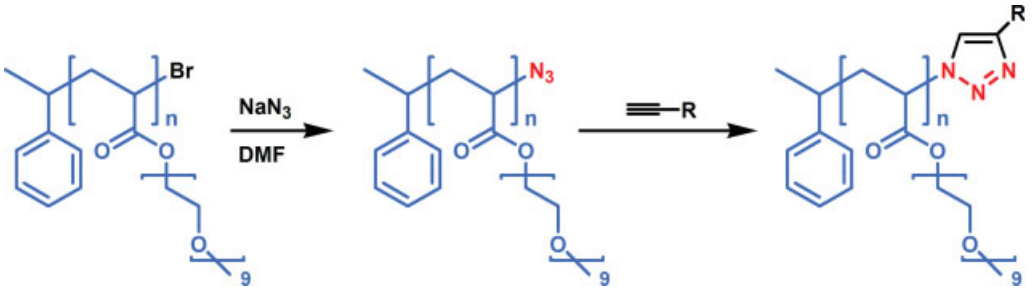
glycol chain, Scheme 1) first appeared in scientific literature during the 1980s.[12–14] The initial motivation behind the use of such compounds was clearly the design of novel macromolecular architectures (e.g., comb/graft polymers or networks). However, another significant advantage of PEG macromonomers is the possibility to access high-molecular-weight PEG-based polymers using relatively mild synthetic conditions. As mentioned in the introduction, PEG macromonomers may be polymerized via a variety of mechanisms such as anionic, cationic, ring opening metathesis, or free-radical polymerization.[11,15–17] Nevertheless, the latter approach is probably the most straightforward and versatile method for preparing nonlinear PEG analogues. Indeed, free-radical processes are relatively tolerant to a wide variety of functional groups and therefore may be applied in aqueous or biological environment. Furthermore, the recent discovery of controlled radical polymerization techniques such as atom transfer radical polymerization (ATRP), nitroxide mediated polymerization (NMP), and reversible addition-fragmentation transfer polymerization (RAFT) has considerably broadened the possibilities of macromolecular design with PEG macromonomers.[18–25] Thus, in the this highlight, the synthesis of nonlinear PEG analogues by radical polymerization is mainly emphasized.

Various types of radically polymerizable PEG macromonomers can be found in the literature.[11] Yet, the most frequently used structures are styrene, acrylate, or methacrylate derivatives.[7,8,10,26–28] Besides the α polymerizable moiety, the ω-end group of the PEG chain is, in most cases, a methoxy function but ethoxy- or hydroxy-terminal groups are also frequent. Among these possible structures, the oligo(ethylene glycol) methyl ether methacrylates series (Scheme 2) is particularly appealing as most of its members are commercially available (Table 1). The research group of Armes first described the ATRP of an oligo(ethylene glycol) methyl ether methacrylate (OEGMA) with 7/8 ethylene oxide (EO) units.[33,34] The controlled radical polymerization of this monomer was performed in aqueous environment at room temperature and lead to the formation of POEGMA with a narrow molecular weight distribution. However, although important for large-scale synthesis, ATRP in aqueous medium remains a complicated and rather challenging process.[35] On a lab scale, ATRP in organic solvents is probably preferable to access well-defined POEGMA. For instance, we reported that the ATRP of either 2-(2-methoxyethoxy)ethyl methacrylate (MEO_2MA) or oligo(ethylene glycol) methacrylate with 8/9 EO units ($OEGMA_{475}$, $M_n = 475$ g mol^{-1}) is rapid and well-controlled in pure ethanol.[7] Indeed, alcohols exhibit some advantages of organic solvents but are polar enough to generate fast polymerization kinetics. Alternatively, apolar media may also be used for polymerizing oligo(ethylene glycol) macromonomers.[36,37] For example, Matyjaszewski and coworkers evidenced that the ATRP of either MEO_2MA, tri(ethylene glycol) methyl ether methacrylate (MEO_3MA), or longer OEGMA proceeds very well in toluene or anisole solutions.[30,37,38] Besides ATRP, other controlled radical polymerization techniques can be used for polymerizing PEG macromonomers. Laschewsky and coworkers demonstrated for example that the RAFT technique allows a

Table 1. Properties of Polymers Prepared with Oligo(ethylene glycol) Methacrylates of Various Length[a]

Polymer		Properties in Aqueous Environment	Commercial Availability of the Monomer	References
1	PMMA	hydrophobic	yes	–
2	PMEMA	slightly hygroscopic	yes	70
3	$PMEO_2MA$	LCST $\sim$ 26 °C[a]	yes	7, 8
4	$PMEO_3MA$	LCST $\sim$ 52 °C[a]	no	8, 35
5	$POEGMA_{300}$	LCST $\sim$ 64 °C[a]	yes	71, 111
6	$POEGMA_{475}$	LCST $\sim$ 90 °C[a]	yes	37

[a]These LCST values depend on polymer concentration and molecular weight.



Scheme 3. General strategy for the "click" functionalization of well-defined POEGA synthesized by ATRP.[45]

successful control of the polymerization of $OEGMA_{475}$ or oligo(ethylene glycol) methyl ether acrylate (OEGA, $M_n = 454$ g mol^{-1}) in aqueous medium.[32,39] Nitroxide mediated polymerization cannot be used for polymerizing MEO_2MA, MEO_3MA, or OEGMA since this method is generally problematic for methacrylate monomers. On the other hand, as evidenced by Zhao and coworkers, NMP allows an efficient control of the polymerization of styrene- or acrylate-based PEG macromonomers.[10,26,40]

As mentioned above, CRP techniques such as ATRP, RAFT, or NMP allow multiple possibilities of macromolecular engineering (i.e., synthesis of tailor-made polymers with controlled chain-length, polydispersity, functionality, composition, and architecture).[25,41–44] Hence, a wide variety of PEG-like macromolecular structures may potentially be prepared by CRP. For instance, well-defined polymers such as telechelics,[45] amphiphilic block copolymers,[46,47] random copolymers,[7,48,49] or macromolecular brushes[38] have been constructed from PEG (macro)monomers using CRP approaches. Furthermore, and probably even more important, CRP techniques can be exploited for modifying organic or inorganic surfaces.[50,51] Thus, nonlinear PEG analogues can be easily connected to a wide variety of materials, including planar inorganic substrates (e.g., gold or glass surfaces),[52–54] solid or soft-matter nanoparticles (e.g., nanocarriers, contrast agents),[55,56] or biological structures (e.g., proteins).[57–59]

Additionally, nonlinear PEG analogues prepared by CRP possess defined reactive end-groups and therefore can be modified after polymerization.[60] For instance, we demonstrated that well-defined POEGA synthesized by ATRP can be efficiently postfunctionalized via copper catalyzed 1,3-dipolar cycloaddition of azides and alkynes (CuAAC).[45] This particular reaction is a known example of "click" chemistry (i.e., thermodynamically spring loaded, modular, and highly efficient reaction) and therefore extremely promising for macromolecular engineering.[61–64] In our approach, the bromine chain-ends of well-defined POEGA ($M_n = 6850$ g mol^{-1}, $M_w/M_n = 1.21$) prepared using ATRP were first transformed into azide functions by nucleophilic substitution with sodium azide and subsequently reacted with various low-molecular-weight model alkynes (Scheme 3).[45,65] In all cases, both substitution and cycloaddition steps were found to be quantitative, as evidenced by ^{1}H NMR, FTIR, and SEC-UV measurements.[45,66] Hence, this versatile synthetic approach may be considered as a universal method for functionalizing polymers. For instance, chemoselective CuAAC can be used for the "click" ligation of POEGA with highly functional biopolymers such as sequence-defined oligopeptides. Such CuAAC ligations can be performed in organic medium with protected peptides (i.e., the protecting side-groups of the amino-acids are not cleaved after solid-phase synthesis) or directly in aqueous medium with fully deprotected structures.[45,67]

Besides POEGA, poly(oligo ethylene glycol) methacrylates may also be functionalized by "click" chemistry.[54] However, the preparation of azido-functional poly (methacrylates) by nucleophilic substitution usually requires very large excess of sodium azide.[60]

PROPERTIES IN AQUEOUS SOLUTIONS

Polymers constructed from PEG (macro)monomers exhibit fascinating solution properties in aqueous medium. Depending on the molecular structure of their monomer units (i.e., nature of the polymerizable moiety, length of the PEG side chain, ω-end-group of the PEG chain), non linear PEG analogues can be insoluble in water, readily soluble up to 100 °C, or thermoresponsive. In fact, the balance between hydrophilic and hydrophobic moieties in the molecular structure of the polymers is the key-parameter that determines their solution properties. For instance, in the case of (oligo ethylene glycol) methyl ether methacrylates, the ether oxygens of PEG form stabilizing H-bonds with water,[68,69] whereas the apolar carbon–carbon backbone leads to a competitive hydrophobic effect (Scheme 2).[70,71] Thus, polymers with very

short PEG side-chains are not water soluble or only weakly hydrophilic. For example, polymers of 2-methoxyethyl methacrylate (MEMA, 1 EO unit, Scheme 2) are not water-soluble at room temperature (Table 1).[29] On the other hand, polymers with long PEG side chains (i.e., 10 EO units and more) are soluble in water, even at high temperatures. In between these two extremes, nonlinear PEG analogues with side-chains of intermediate length (i.e., $2 \leq$ EO units < 10) generally exhibit a lower critical solution temperature (LCST) in aqueous solution. In other words, these polymers are soluble in water below the LCST but precipitate at temperatures above it. For example, monomers such as MEO_2MA (2 EO units) or MEO_3MA (3 EO units) lead to water-soluble thermoresponsive polymers with a LCST of 26 or 52 °C, respectively, (Table 1).[8] Commercially available oligo(ethylene glycol) methyl ether methacrylates with slightly longer side-chains (i.e., 4/5 or 8/9 EO units in average, Scheme 2) lead to very hydrophilic polymers with rather high LCST values (i.e., in the range 60–90 °C, Table 1).[31,32] This interesting thermoresponsive behavior is almost certainly a consequence of the amphiphilicity of the polymer chains.[70,71] At room temperature, the balance between favorable polymer-water interactions and unfavorable hydrophobic interactions is sufficient to allow solubilization. Above LCST, this balance is disrupted and polymer–polymer interactions are thermodynamically favored as compared to polymer-water interactions. In that regard, the thermoresponsive mechanism of poly(oligo ethylene glycol) methyl ether methacrylates is very comparable to the one of poly(*N*-alkyl acrylamides) such as PNIPAM.[72] However, the phase transitions of nonlinear PEG analogues are generally reversible (i.e., heating and cooling behaviors are almost similar), whereas PNIPAM usually shows a significant hysteresis.[6] The latter phenomenon has been cautiously explained by Wu and coworkers.[73] Above LCST, PNIPAM chains become partially dehydrated globules. In this collapsed state, the amide groups of PNIPAM lead to the formation of intramolecular and intermolecular NH···O=C hydrogen bonding interactions. Hence, during the cooling process, the rehydration of PNIPAM is hindered by these additional interactions, leading to a marked hysteresis. In comparison, poly(oligo ethylene glycol) methyl ether methacrylates exhibit a reversible dehydration as there is no strong H-bond donor in the molecular structure of these polymers and therefore no possibility of forming stabilizing H-bonds in the collapsed state.[6] Moreover, the phase transitions observed for nonlinear PEG analogues are relatively insensitive to external physical conditions. In fact, for a given type of polymer, the cloud points depend to some degree on molecular weight, main-chain end-groups, tacticity, concentration, and ionic strength.[6,8] However, the observed variations in LCST are generally rather small.

Furthermore, we recently reported that the thermoresponsive behavior of nonlinear PEG analogues can be precisely adjusted using a simple random copolymerization strategy (Fig. 1).[7] In this approach, PEG macromonomers of different chain-lengths (i.e., of different hydrophilicity but similar chemical nature) were copolymerized by ATRP. For example, random copolymers of MEO_2MA and $OEGMA_{475}$ exhibit LCST values in between 26 and 90 °C, which can be precisely adjusted by varying the comonomer composition (Fig. 1). For example, cloud points of either 32 °C (comparable to the standard LCST of PNIPAM), 37 °C (body temperature, see inset in Fig. 1) or 39–40 °C (fever temperatures) were observed in pure water for copolymers possessing in average respectively, 5, 8, or 10% of $OEGMA_{475}$ units per chain.[7] Although copolymerization strategies for tuning LCST have been reported in the past,[4] the present approach is rather unique in the sense that both comonomers are of the same kind (i.e., both only contain a PEG segment and a methacrylate moiety). Thus, chemically speaking, random copolymers P(MEO_2MA-*co*-$OEGMA_{475}$) can be considered as homopolymers. Furthermore, the comonomer pair MEO_2MA/$OEGMA_{475}$ is not the only one, which can be exploited for preparing defined thermoresponsive polymers. In fact, virtually all the structures shown in Scheme 2 can be used in such copolymerization strategy, thus making oligo(ethylene glycol) methyl ether methacrylates a very appealing and versatile class of monomers for preparing stimuli-responsive materials. For example, Matyjaszewski and coworkers recently prepared polymers with adjustable solution properties by random copolymerization of MEO_2MA and MEO_3MA.[30] Additionally, besides PEG-methacrylates, we demonstrated that well-defined thermoresponsive polymers can also be obtained via the copolymerization of acrylate-based monomers.[28]

However, it is very important to specify that defined phase transitions can only be observed for random copolymers prepared by a living or pseudoliving polymerization technique. Indeed, the molar fraction of the comonomers in the copolymers is the main factor influencing the LCST.[7] Thus, it is essential to prepare copolymers with a uniform chain-to-chain composition. For instance, conventional radical polymerization (RP) should be avoided for preparing thermoresponsive random copolymers. In RP, polymer chains are initiated all along the reaction and therefore, if the comonomers have different reactivities, strong chain-to-chain deviations of composition can be expected. On the other hand, in a living polymerization (e.g., CRP techniques, anionic polymerization),[74] all the chains are initiated simultaneously and therefore exhibit rather homogeneous chain-

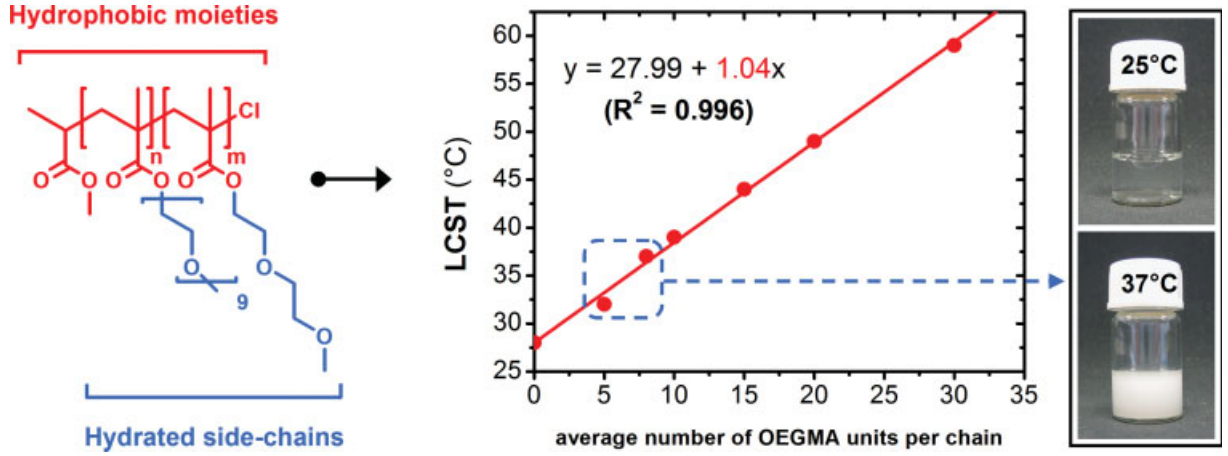


Figure 1. Plots of the measured lower critical solution temperature (LCST) as a function of the theoretical average number of $OEGMA_{475}$ units per chain for a series of P(MEO_2MA-*co*-$OEGMA_{475}$) copolymers of various composition. Hydrophobic and hydrophilic molecular regions in the copolymer are indicated in red and blue, respectively.[7]

to-chain compositions.[75,76] In this case, comonomers of different reactivity only generate single-chain composition gradients.[77] Yet, copolymers prepared by living polymerization methods are not perfectly monodisperse and consequently their deviations in composition, although slight, have an influence on the phase transitions. Hence, the phase transitions observed for random copolymers are usually a little broader than those observed for homopolymers. Furthermore, this composition effect is indeed more significant for short copolymers as compared to long ones. Figure 2 shows the phase transitions measured by turbidimetry for P(MEO2MA-*co*-$OEGMA_{475}$) samples with a similar composition but different degrees of polymerization (i.e., 25, 50, and 75). All samples display a reversible phase transition, but broader transitions can be observed for the short copolymers. Nevertheless, these deviations remain on the whole very reasonable. The overall range of temperature measured for the phase transition of the shortest copolymer (DP25) was $\Delta T = 5.5$ °C, whereas it was found to be $\Delta T = 4.3$ °C for the longest copolymer (DP75).

BIOCOMPATIBILITY AND BIORELEVANCE

As mentioned in the introduction, polymers constructed from PEG macromonomers could be particularly rele-

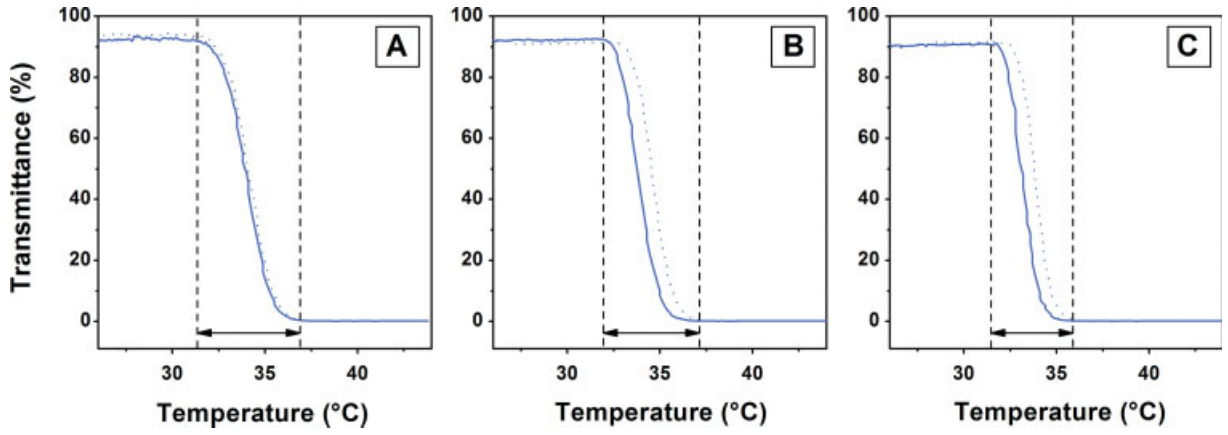


Figure 2. Plots of transmittance as a function of temperature measured for aqueous solutions (3 mg mL^{-1}) of P(MEO_2MA-*co*-$OEGMA_{475}$) samples containing 5 mol % of $OEGMA_{475}$ per chain: (A) DP25 (M_n = 5340 g mol^{-1}; M_w/M_n = 1.38), (B) DP50 (M_n = 9259 g mol^{-1}; M_w/M_n = 1.37), (C) DP75 (M_n = 12,350 g mol^{-1}; M_w/M_n = 1.40). Solid line: heating, dotted line: cooling.[6]

vant for applications in biomedical sciences. Nonlinear PEG analogues are expected to exhibit a fairly high degree of biocompatibility as they are principally composed of oligo(ethylene glycol) segments. Indeed, PEG is an uncharged, water soluble, nontoxic, nonimmunogenic, FDA-approved polymer, and thus is probably the most widely applied synthetic polymer in biotechnology and medicine in recent years. Actually, the first examples of biomedical applications of PEG were reported as early as the mid-1940s[78] (i.e., only a few years after the description of this fascinating macromolecule by Staudinger[79]) and since then several thousands of research articles have confirmed the importance of PEG in Life Science. However, standard linear PEG is commonly prepared by anionic polymerization of EO, a sensitive process, which is not always compatible with modern biotechnology applications. For instance, as the carbanionic polymerization mechanism requires the absence protic and electrophilic impurities, PEG cannot be directly grown on functional or biological surfaces. Thus, ligation approaches (i.e., so-called PEGylation methods) have to be employed for linking PEG to biological substrates.[51] These coupling strategies are usually efficient but expensive and limited to relatively low molecular weight polymers. In that regard, the use of nonlinear PEG analogues appears as an attractive alternative to conventional PEGylation.[36,80] Indeed, these polymers can be easily prepared or functionalized in aqueous medium (see first paragraph on synthesis) and moreover exhibit a much broader spectrum of solution properties (see previous paragraph) than linear PEG.

Yet, the biocompatibility of nonlinear PEG analogues had to be demonstrated. For instance, Figure 3 compares the cytotoxicity of various nonlinear PEG analogues and a standard commercial linear PEG.[81] In all cases, *in vitro* cell assays evidenced an excellent biocompatibility. For instance, $POEGMA_{475}$ and copolymers $P(MEO_2MA\text{-}co\text{-}OEGMA_{475})$ do not induce cell death, even when present at a concentration as high as 10 mg mL^{-1}. However, to observe such results, the polymers should be carefully purified. Indeed, some polymerization residues can be highly cytotoxic. For example, for polymers prepared using ATRP, traces of copper catalyst may induce significant cell death and should therefore be entirely removed. However, the polymers themselves are apparently not cytotoxic and are in that regard true analogues of linear PEG.

In fact, the analogy between linear and nonlinear PEG goes even further. For instance, similarly to self-assembled PEG monolayers,[82] model surfaces modified with POEGMA exhibit remarkable biorepellent properties. The research groups of Mayes and Chilkoti demonstrated for example that POEGMA-based coatings (either adsorbed amphiphilic polymers or surface initiated brushes) prevent efficiently protein-adsorption and cell adhesion.[52,83,84] These interesting properties have been recently exploited for practical bioapplications such as cell micropatterning or the fabrication of blood-compatible materials.[84–86] Moreover, POEGMA-based surfaces can be easily modified (see first paragraph on synthesis) and therefore their properties can also be switched, if desired, from biorepellent to bioadherent. For example, RGD-modified POEGMA surfaces were reported to be efficient cell-adhesion scaffolds.[83,87]

The biorepellent behavior of nonlinear PEG analogues can also be exploited for shielding particulates such as therapeutic proteins, drug-carriers, or gene-carriers.[58,59,80,88] Indeed, conventional PEGylation has been proven over many years to be a powerful method for stabilizing and protecting delivery carriers in an *in vivo* environment.[89,90] PEG coatings prevent the adsorption of plasma proteins that stimulate phagocytosis and therefore generally enhance the circulation time of injected particulates in the bloodstream (i.e., so-called "stealth" behavior).[91] Comparable shielding properties can also be obtained with POEGMA-based coatings. For instance, Figure 4 shows the *in vivo* behavior of ultrasmall iron oxide nanoparticles coated by $POEGMA_{475}$.[88] These superparamagnetic particles were injected in rats and studied *in vivo* using magnetic resonance imaging. The $POEGMA_{475}$-coating obviously led to an efficient "stealth" effect. Indeed, the nanoparticles were found to accumulate in the liver (i.e., phagocytosis by liver cells) after several hours of circulation *in vivo* [Fig. 4(C)]. Moreover, the particles exhibited an excellent *in vivo* biocompatibility and were not lethal to rats. Some recent results of Welch and coworkers also emphasized the *in vivo* advantages of POEGMA based nanocarriers.[92]

Yet, one potential limitation of nonlinear PEG-analogues is indeed the nondegradability of their carbon–carbon backbone. This aspect could hamper the widespread adoption of these macromolecules in the biomedical field, in particular for *in vivo* applications. Thus, we recently described the preparation of degradable nonlinear PEG analogues.[81] These polymers were synthesized in one pot by controlled radical copolymerization of oligo(ethylene glycol) methyl ether methacrylates with 5,6-benzo-2-methylene-1,3-dioxepane (BMDO). The latter is a cyclic ketene acetal, which polymerizes via a radical ring-opening mechanism and lead to the formation of main-chain polyesters.[93,94] For instance, we prepared a series of interesting biocompatible, biodegradable, and thermoresponsive copolymers via the bulk atom transfer radical terpolymerization of MEO_2MA, $OEGMA_{475}$, and BMDO. The resulting terpolymers exhibit a sharp LCST in aqueous solution, which have a very low cytotoxicity and moreover can be hydrolytically or enzymatically degraded into short oligomers (Fig. 5).[81]

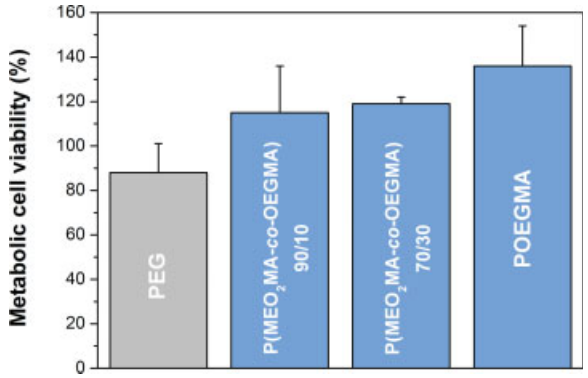


Figure 3. Metabolic cell viability measured for human hepatocellular carcinoma (HepG2) cell lines incubated at 37 °C in the presence of either a linear poly(ethylene glycol) (PEG, M_n = 20,000 g mol^{-1}, Aldrich), a copolymer P(MEO_2MA-*co*-$OEGMA_{475}$) containing 10 mol % of $OEGMA_{475}$ units (M_n = 21.400 g mol^{-1}, M_w/M_n = 1.35), a copolymer P(MEO_2MA-*co*-$OEGMA_{475}$) containing 30 mol % of $OEGMA_{475}$ units (M_n = 21,500 g mol^{-1}, M_w/M_n = 1.27) or a $POEGMA_{475}$ homopolymer (M_n = 26,200 g mol^{-1}, M_w/M_n = 1.22).[81]

Besides main-chain esters, other types of labile moieties may be exploited for preparing biodegradable materials. For instance, Matyjaszewski and coworkers reported the synthesis of biodegradable POEGMA nanogels based on labile disulfide crosslinks.[95]

STIMULI-RESPONSIVE MATERIALS

The thermoresponsive properties of nonlinear PEG analogues are potentially interesting for a wide range of applications. For instance, polymers exhibiting a LCST in aqueous medium are very promising materials for bioapplications such as enzyme recycling, protein chromatography, controlled bioadhesion, hyperthermia-induced drug delivery, or tissue engineering.[5,96–100] Classic examples of synthetic polymers exhibiting an aqueous LCST include poly(*N*,*N*′-diethyl acrylamide), poly(dimethylaminoethyl methacrylate), poly(*N*-acryloylpyrrolidine), poly(2-isopropyl-2-oxazoline), elastin-like artificial polypeptides, poly(vinyl methyl ether), and PNIPAM.[4,72,101] Yet, the latter has been by far the most

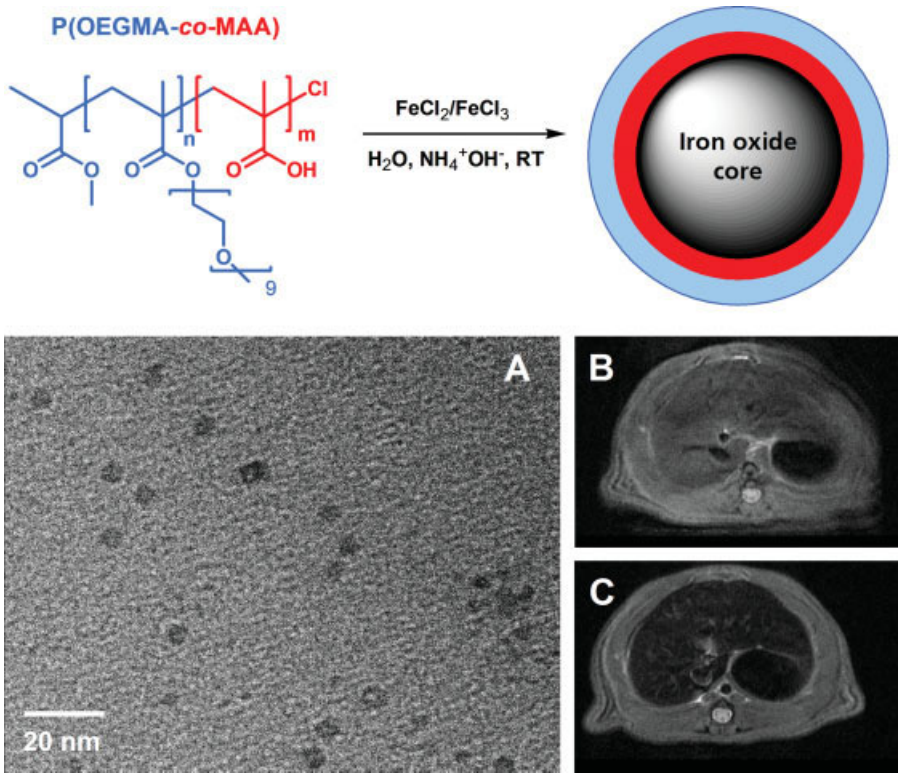


Figure 4. Utilization of a well-defined copolymer P($OEGMA_{475}$-*co*-MAA) for fabricating biocompatible contrast agents for magnetic resonance imaging. Bottom left (A): transmission electron micrograph of iron oxide superparamagnetic nanoparticles prepared in the presence of P($OEGMA_{475}$-*co*-MAA). Bottom right (B and C): images of liver sections of a live rat measured by magnetic resonance tomography after injection (B = t_0 and C = 6 h) of a physiological solution containing such PEGylated iron oxide nanoparticles.[88]

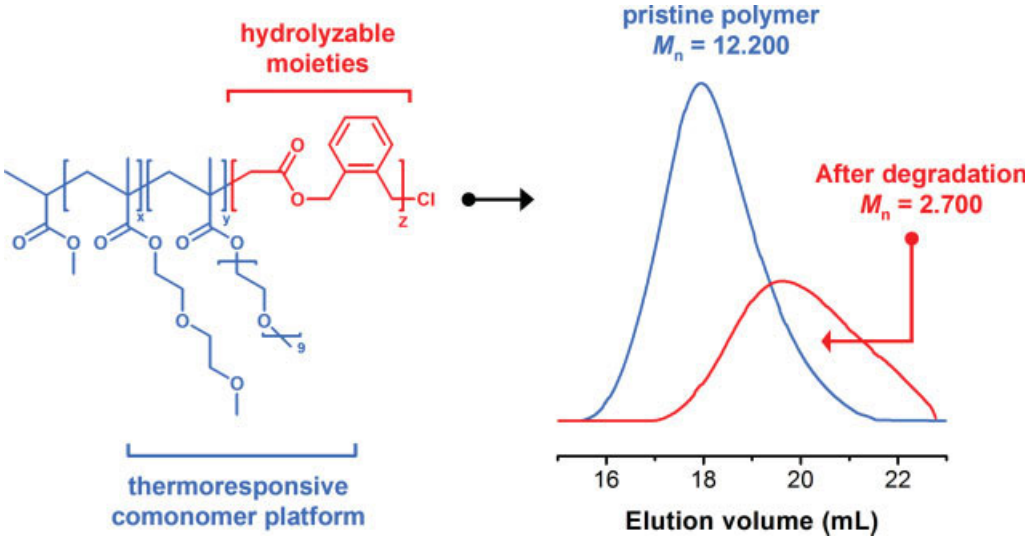


Figure 5. SEC chromatograms recorded in THF SEC chromatograms measured for a biodegradable terpolymer P(MEO_2MA-*co*-$OEGMA_{475}$-*co*-BMDO) before (blue line) and after (red line) chemical degradation.[81]

studied and applied thermoresponsive polymer and therefore can be considered as the gold standard in this research area. However, despite its widespread popularity in materials science, PNIPAM has inherent disadvantages such as an irreversible phase transition (see second paragraph) and, for short polymers, a significant influence of end-groups on the thermal behavior.[73,102] Moreover, the presence of multiple amide functions in the molecular structure of PNIPAM may lead to the formation of H-bonding interactions with other polyamides such as proteins.[103] Such behavior complicates the use of PNIPAM in some biotechnology applications.[104] Thus, thermoresponsive polymers containing short biocompatible oligo(ethylene glycol) side-chains appear as promising alternative to conventional PNIPAM for bioapplications and more generally for building any kind of thermoresponsive materials.

Huck and coworkers first reported the preparation of thermoresponsive P(MEO_2MA-*co*-$OEGMA_{475}$) polymer brushes on planar surfaces.[53] These polymers were grown on a model silicon wafer coated with a silane ATRP initiator (i.e., "grafting from" strategy). The resulting surface brushes exhibited a clear thermoresponsive behavior and displayed LCST values roughly similar to those observed for P(MEO_2MA-*co*-$OEGMA_{475}$) copolymers in solution. However, thin polymer brushes (i.e., thickness below 50 nm) were found to be much more hydrophilic than their solution analogues.

Our research group reported lately the synthesis of thermoresponsive P(MEO_2MA-*co*-$OEGMA_{475}$) hydrogels.[68] These macroscopic hydrogels were prepared using ethylene glycol dimethacrylate (EGDM) as a crosslinker. Although such hydrogels could be easily synthesized by conventional radical polymerization, the ATRP method was selected to ensure a homogeneous comonomer composition in each region of the macromolecular network. Such precaution would not be necessary if one is only interested in the swelling of the hydrogel at room temperature. However, if a thermoresponsive gel is targeted, a defined composition of the network is essential (see second paragraph). Figure 6 shows the

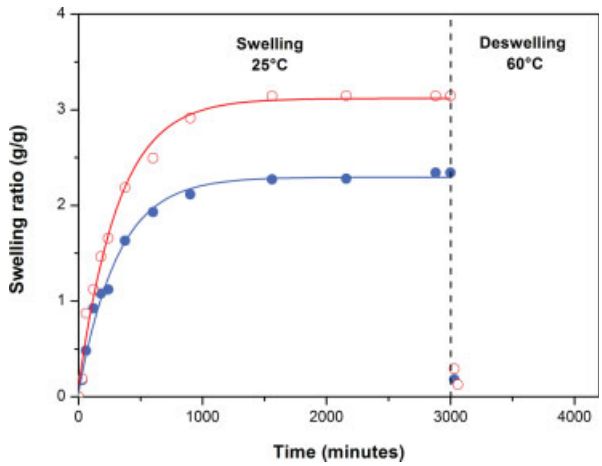


Figure 6. Evolution of the swelling ratio as a function of time for macroscopic hydrogels P(MEO_2MA-*co*-$OEGMA_{475}$) containing either 10% (blue symbols) or 20 mol % (red symbols) of $OEGMA_{475}$ per chain. At t = 3000 min, the temperature of the aqueous medium was quickly raised from 25 to 60 °C.[70]

swelling/deswelling behavior measured for two hydrogel samples of different composition. Both hydrogels exhibited a satisfying swelling capacity in pure water and appeared as homogeneous transparent materials in the swollen state. However, the swelling rates and the maximum swelling ratios were found to be proportional to the fraction of OEGMA grafts in the network, which is a logical behavior previously observed for PEG grafted hydrogels.[105] Moreover, both hydrogels were found to be thermoresponsive and exhibited LCST values comparable to those measured for their single-chains analogues. Preliminary evaluation of the deswelling kinetics of these thermoresponsive hydrogels indicated that their thermally induced shrinkage is extremely fast (Fig. 6). Such a behavior could be a consequence of the presence of the long $OEGMA_{475}$ grafted chains, which can potentially act as water release channels within the network and therefore boost the deswelling kinetics.[106]

Very recently, Hu and coworkers fabricated thermoresponsive microgels based on P(MEO_2MA-*co*-$OEGMA_{475}$) networks.[107] These monodisperse particles were prepared via conventional radical polymerization and therefore exhibited relatively broad phase transitions. Nevertheless, in semidilute aqueous solutions (4–10 wt %), these microgels self-assembled into interesting crystalline phases with iridescent properties. Other types of PEG-based stimuli-responsive colloidal dispersions were recently described in the literature, for example thermoresponsive silica particles, gold particles, carbon nanotubes, and block-copolymer micelles.[66,108–110,112]

CONCLUSIONS AND PERSPECTIVES

The purpose of this highlight was to demonstrate that nonlinear PEG analogues combine a unique set of advantages: (i) straightforward and versatile synthesis from commercially available monomers, (ii) possible attachment to a wide range of materials including biological compounds, and (iii) fascinating properties such as water-solubility, biocompatibility, thermosensitivity, and eventually biodegradability. Thus, this new family of macromolecules could become extremely important in a near future and replace established polymers such as PEG, PNIPAM, or PLGA in a wide range of applications. However, the development of smart PEG analogues is a very young field of research. Only a few studies have been reported so far and, therefore, a significant amount of work has to be done to fully explore the possibilities of these polymers. In fact, taking into account the number of publications and patents, which have been necessary to describe classic polymers such as PEG or PNIPAM, the study of nonlinear PEG analogues is certainly a wide open research field!

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