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Swelling behaviour of thermo-sensitive hydrogels based on oligo(ethylene glycol) methacrylates

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ABSTRACT

The thermo-sensitive swelling behaviour of hydrogels based on 2-(2-methoxyethoxy)ethyl methacrylate (MEO_2MA) and synthesized by free radical polymerization has been investigated. The homopolymer hydrogel presents a low critical solution temperature (LCST) close to room temperature, which can be modulated by copolymerization with longer oligo(ethylene glycol) side chain methacrylates (OEG_xMA). Then, three series of copolymeric hydrogels synthesized with MEO_2MA and several low ratios of OEG_xMA with M_n = 475 g mol^{-1} (OEG_8MA), M_n = 1100 g mol^{-1} ($OEG_{23}MA$) and M_n = 2080 g mol^{-1} ($OEG_{45}MA$) were studied. In addition to conventional tetra(ethylene glycol) dimethacrylate (TEGDMA) crosslinker, the use of biodegradable oligo(caprolactone) dimethacrylate (OCLDMA) was also tested. The hydrophilic/hydrophobic balance, function of the short and the long OEG side chains, establishes a swelling behaviour depending on monomer composition, side chain length and temperature. The swelling at equilibrium increases with increasing the amount of OEG_xMA in the copolymer and, at the same time, the collapsing moves progressively to higher temperature. The temperature dependent volumetric response of some of these hydrogels can be compare with the most extended thermo-sensitive hydrogel, which is based on poly(*N*-isopropylacrylamide) (P(*N*-iPAAm)). Therefore, they are potential candidates to replace it in applications where biocompatibility is required.

1. Introduction

In the last years polymers based on oligo(ethylene glycol) methyl ether methacrylate (OEG_xMA) have been revealed as a family of promising thermo-sensitive polymers [1–20]. In its pioneering work, Ishizone and coworkers [1] showed that these macromolecules with short OEG side chain exhibit a defined lower critical solution temperature (LCST) in aqueous or physiological medium. This behaviour was attributed to the amphiphilic character of the monomers [1–6]. The hydrophilic OEG side chains form H-bonds with water, whereas the backbones, which are usually less polar in nature, lead to a competitive hydrophobic effect [10]. According to nuclear magnetic resonance and dynamic light scattering studies, Lutz et al. [9] concluded that similarly to poly(*N*-isopropylacrylamide), P(*N*-iPAAm), the LCST is due to a coil-to-globule transition.

Among these systems, one of the most relevant is the poly(2-(2-methoxyethoxy)ethyl methacrylate, P(MEO_2MA), which exhibits a LCST at 26 °C [1]. Although this LCST is something lower than that exhibits by P(*N*-iPAAm), P(MEO_2MA) presents some advantages in comparison. Apart from the biocompatibility of oligo(ethylene glycol), the LCST can be modulated by copolymerization of MEO_2MA with longer OEG_xMA methacrylates [7–9,21]. That means that the LCST can be tuned without introducing comonomers of different chemical nature. Thus, Lutz et al. [7–9] recently reported that the atom transfer radical

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polymerization (ATRP) of MEO_2MA and OEG_xMA of $M_n = 475$ g mol^{-1} (OEG_8MA) leads to the formation of thermo-responsive copolymers with a precisely tuneable LCST in water. In addition, they showed that the phase transitions measured for the P(MEO_2MA-*co*-OEG_8MA) copolymers are reversible and relatively insensitive to important parameters such as concentration of the copolymer in water, ionic strength and chain length [11].

Polymers with stimuli responsive properties can be also synthesized in the presence of a crosslinker leading to stimuli responsive hydrogels, which exhibit volumetric changes in response to changes of their environment. This property can be useful for several applications, such as drug delivery [22–25], biotechnology [25–29], artificial muscles [30], optics [31,32] and sensors [33]. However, and in spite of their promising applications, we have found only a few studies of the swelling behaviour of thermo-responsive hydrogels based on oligo(ethylene glycol) methacrylate copolymers. On one hand, Lutz et al. [9] reported some interesting and preliminary results about the thermo-responsive swelling of two of these hydrogels synthesized by ATRP [9]. On the other hand, Cai et al. [21] synthesized monodisperse microgels of P(MEO_2MA-*co*-OEG_8MA), by free radical polymerization, with tuneable LCST depending on monomeric composition. Therefore and in order to complete the existing studies, a series of thermo-responsive macroscopic hydrogels based on commercially available MEO_2MA and OEG_8MA were easily synthesized by conventional free radical polymerization. Their swelling behaviour was studied in detail as a function of monomer composition, type of crosslinker and temperature. In addition, the effect of the OEG side chain length was also studied from the swelling analysis of two different series of hydrogels synthesized employing MEO_2-MA with OEG_xMA of $M_n = 1100$ g mol^{-1} (OEG_{23} MA) and $M_n = 2080$ g mol^{-1} ($OEG_{45}MA$) as comonomers.

2. Experimental

2.1. Materials

The monomers 2-(2-methoxyethoxy)ethyl methacrylate (MEO_2MA, Aldrich, 95%) and oligo(ethylene glycol) methyl ether methacrylate (OEG_xMA) with $M_n = 475$ g mol^{-1} (OEG_8MA, Aldrich) were passing by neutral alumina. The other macromonomers, OEG_xMA with $M_n = 1100$ g mol^{-1} ($OEG_{23}MA$, Aldrich) and $M_n = 2080$ g mol^{-1} ($OEG_{45}MA$, Aldrich 50 wt.% in water) were employed without previous purification. The monomer *N*-isopropylacrylamide (*N*-iPAAm, Acros Organics, 99%) was purified by recrystallization from a mixture *n*-hexane/toluene 90/10 (v/v). The activator *N,N,N′,N′*-tetramethylethylenediamine (TEMED, Fluka ⩾99%), the conventional crosslinker tetraethylene glycol dimethacrylate (TEGDMA, Fluka ⩾90%) and the initiator ammonium peroxodisulfate (APS, Fluka ⩾98%) were used as received. The solvents ethanol (Normapur, analytical reagent), *n*-hexane (Panreac 98%), dichloromethane (Fluka 99.9%), and *N,N′*-dimethylformamide (DMF, Scharlau 99%) were also employed as received. Polycaprolactone diol (Aldrich, $M_n = 530$ g mol^{-1}), methacrylic acid (MAA, Fluka 98%), 4-(dimethylamino)pyridine (DMAP, Aldrich 99%) and *N,N′*-dicyclohexylcarbodiimide (DCCI, Aldrich 99%) were employed for the synthesis of the non-commercial crosslinked agent. Water for all reactions, solutions for swelling experiments and hydrogels purification was MilliQ from water purification facility (millipore Milli-U10). Phosphate buffer solutions (PBS) was prepared employing sodium dihydrogen phosphate anhydrous (Fluka ⩾99%), disodium hydrogen phosphate (Panreac ⩾98%), ortho-phophoric acid (Panreac 85%) and sodium chloride (panreac ⩾99.5%) in order to keep constant the ionic strength (0.1 M).

2.2. Synthesis of the non-commercial crosslinking agent: oligo(caprolactone) dimethacrylate (OCLDMA)

An available oligo(caprolactone) diol of $M_n = 530$ g mol^{-1} was used to achieved a biodegradable crosslinker with a molecular weight similar to the conventional TEGDMA. The synthetic procedure was analogous to that described in a previous paper [34] with the exception that *n*-hexane was employed as precipitant solvent. The incorporation of the methacrylate functionality in both polymer chain ends was also confirmed by Fourier Transform Infrared (FTIR) and Nuclear Magnetic Resonance (NMR) [34].

2.3. Syntheses of the P(MEO_2MA-*co*-OEG_xMA) hydrogels

P(MEO_2MA-*co*-OEG_xMA) hydrogels were synthesized by free-radical cross-linking random polymerization in solution. Six different compositions of P(MEO_2MA-*co*-OEG_8MA) were obtained employing the monomer and crosslinker feed ratio described in Table 1. Polymerizations were carried out using a mixture water/ethanol 50/50 (v/v) as solvent with TEGDMA or DMF with OCLDMA. In all cases the monomer concentration was 1 g mL^{-1}. Crosslinker TEGDMA or OCLDMA, activator TEMED, and initiator APS were used with an initial ratio of 0.5 wt.% of the total monomer amount. Similar conditions were employed for the synthesis of the series of P(MEO_2MA-*co*-$OEG_{23}MA$) and P(MEO_2MA-*co*-$OEG_{45}MA$) copolymeric hydrogels (see Table 2) but employing a mixture water/ethanol 70/30 (v/v) as solvent. All monomer and crosslinker structures used in this investigation are shown in Scheme 1.

Table 1
First order rate constants obtained by fitting to Eq. (4) the swelling data of the P(MEO_2MA-*co*-OEG_8MA) copolymeric hydrogels. In all syntheses the monomer concentration was 1 g mL^{-1}. $[APS]_0 = [Crosslinker]_0 = [TEMED]_0 = 0.50\%$ (w/w). Solvent [water/ethanol = 1/1 (v/v)] = 5 mL.

Feed composition (mol%)		Crosslinker	Q_∞	$k \times 10^2$ (min^{-1})	R^2
MEO_2MA	OEG_8MA				
100	0	TEGDMA	0.6	1.0	0.9906
95	5		2.1	1.5	0.9988
90	10		3.3	1.9	0.9989
85	15		4.3	2.1	0.9992
80	20		5.2	2.1	0.9981
95	5	OCLDMA[a]	1.8	1.6	0.9995

[a] Employing DMF as solvent.