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Smart poly(oligo(propylene glycol) methacrylate) hydrogel prepared by gamma radiation

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ABSTRACT

The synthesis of poly(oligo(propylene glycol) methacrylate) (POPGMA) from functionalised oligo (propylene glycol) methacrylate (OPGMA) monomers by gamma radiation-induced radical polymerisation is reported for the first time; POPGMA homopolymeric hydrogel with oligo(propylene glycol) (OPG) pendant chains, as a non-linear PPGMA-analogue, was synthesised from an monomer–solvent ($OPGMA_{375}$–water/ethanol) mixture at different irradiation doses (5, 10, 25, and 40 kGy). Determination of the gel fraction was conducted after synthesis. The swelling properties of the POPGMA hydrogel were preliminarily investigated over wide pH (2.2–9.0) and temperature (4–70 °C) ranges. Additional characterisation of structure and properties was conducted by UV–vis and Fourier transform infrared (FTIR) spectroscopy as well as by differential scanning calorimetry (DSC). In order to evaluate the potential for biomedical applications, biocompatibility (cytocompatibility and haemolytic activity) studies were performed as well. Sol–gel conversion was relatively high for all irradiation doses, indicating radiation-induced synthesis as a good method for fabricating this hydrogel. Thermoresponsiveness and variations in swelling capacity as a result of thermosensitive OPG pendant chains with a lower critical solution temperature (LCST) were mainly observed below room temperature; thus, the volume phase transition temperature (VPTT) of POPGMA homopolymeric hydrogel is about 15 °C. Furthermore, POPGMA has satisfactory biocompatibility. The results indicate that the hydrogels with propylene glycol pendant chains can be easily prepared by gamma radiation and have potential for different applications as smart and biocompatible polymers.

1. Introduction

The increasing demand for "smartness" in biomedical and material science has generated a growing interest in synthetic materials that exhibit stimuli-responsive behaviour. Among various external stimuli such as pH, ionic strength, light, photochemical processes, pressure, antigens, etc., temperature is one of the most important. During the last two decades, significant scientific interest has been focused on the thermoresponsive properties of polymeric materials for use in such fields as drug delivery, sensors, separation systems, supported catalysts and microfluidics [1]. Drastic changes in solubility, turbidity, and other physicochemical properties of thermosensitive small organic compounds, polymers and hydrogels can be simply induced by small changes in heating/cooling; such feasibility is particularly important in designing "smart" polymeric materials that instantly respond to external stimuli. Careful engineering of the polymeric structure is needed in order to fine-tune the responding temperature as well as the sharpness of the transition [2]. Small organic compounds and polymeric structures can undergo a transition from a soluble to an insoluble phase upon heating. This phenomenon is called the lower critical solution temperature (LCST). Below the LCST, the aqueous polymer solution is transparent because most of its hydrophilic groups are exposed to water (the polymer is soluble due to extensive hydrogen bonding interactions with the surrounding water molecules and restricted intra- and inter-molecular hydrogen bonding between polymer molecules). Above the LCST, hydrogen bonds are broken and polymer chains are hydrophobic and folded as a result of dehydration, and so assemble to form a phase separation state [3].

The most studied thermoresponsive polymers are linear polyvinyl polymers exemplified by poly(N isopropylacrylamide) (PNIPAM), which has a lower critical solution temperature (LCST) of about 32 °C, close to physiological temperatures [4,5]. Other polymers with LCSTs include other poly(N-alkylacrylamides), poly(2-alkyl-2-oxazoline)s, poly(2-oxazine)s, polyethers, polyvinyl ether, poly(dimethylaminoethylmethacrylate), poly(alkylene

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glycol)s, etc. [1,4]. Poly(alkylene glycol)s, also known as poly(alkylene oxide)s, such as poly(ethylene glycol) (PEG) and poly(propylene glycol) (PPG), and their copolymers are well known due to their thermoresponsive behaviour; a variety of PEG and PPG copolymers with LCSTs varying from 20 to 85 °C are commercially available. Furthermore, there has been a great deal of interest in (co)polymers with short oligo(alkylene glycol) side chains, i.e. non-linear PEG/PPG-analogues [1]. Thus, thermoresponsive polymers based on acrylate or methacrylate with oligo(ethylene glycol) (OEG) side chains have been proposed as thermoresponsive poly(ethylene glycol) (PEG) analogues for biomedical applications [6]. Oligo(ethylene glycol) (meth)acrylates have been widely used in a number of thermoresponsive materials [3,6–22], while oligo(propylene glycol) methacrylates have been less exploited on account of their poor amphiphilic character [23–26]; nevertheless, OPGMA monomers have been used in biomaterials, coatings and nail polish, and photosensitive materials [27,28]. In general, the greater hydrophobicity of PPGs induces much lower LCST temperatures than in the case of PEGs. Increasing the molecular mass (M_w) of the PPG from 400 to 1000 decreases the LCST of the PPG water system from above 50 to near 0 °C [29]. However, the analogue of PPG, oligo(propylene glycol) methacrylate (OPGMA), has been successfully polymerised by atom transfer radical polymerisation (ATRP) to obtain linear and star-like POPGMA homo- and/or co-polymers [24,27]. Aqueous solutions of POPGMA (1 wt%) exhibit a LCST close to room temperature, and the transition temperature can be tuned by the pH of the solution (between 15 and 25 °C) [24]. When the temperature is raised above the LCST, the hydrophobicity of the POPGMA causes the polymer chains to collapse into each other, leading to the formation of particles. Thermoresponsive biocompatible copolymers based on OPGMA were recently prepared with OEGMA [30] and dimethylaminoethyl methacrylate (DMAEMA) [24,31] via ATRP. The LCST of the copolymers was varied by changing the ratios of the co-monomers. By increasing the ratio of the hydrophilic OEGMA and DMAEMA to hydrophobic OPGMA, the thermal transition temperature was increased significantly, leading to OPGMA copolymers with LCSTs close to body temperature and applicable for the delivery of drugs and cells [23,24,30]. Thermoresponsive water-soluble PEGMEMA–OPGMA–EGDMA co-polymers have also been prepared via a facile one-step deactivation enhanced ATRP copolymerisation of monofunctional and multifunctional vinyl monomers; these terpolymers have demonstrated LCST behaviour and photocrosslinkable properties [25]. Nevertheless, tuning of LCST in a given temperature range is not easily realised. Therefore, radical copolymerisation of hydrophilic or hydrophobic co-monomers is a strategy used more and more often to qualitatively adjust the LCST to higher or lower temperatures [32].

Polymers with stimuli responsive properties can also be synthesised in the presence of a crosslinker leading to stimuli responsive hydrogels that exhibit volumetric changes in response to changes in their environment. In contrast to polymers that can be dissolved, hydrogels are three-dimensional crosslinked polymers that are able to absorb large amounts of water without suffering dissolution [33]. They are of great interest in biomedical applications because of their tuneable three-dimensional network structures, high water content in an aqueous medium, good mechanical properties, and biocompatibility. These properties can be useful for several applications, such as drug delivery, biotechnology, artificial muscles, optics, sensors, etc. Thermoresponsive homopolymeric and co-polymeric hydrogels based on OEG(M)A have been investigated to a far greater extent than those based on OPGMA [14,22,26,34–42]. Essentially, there have only been a few studies that considered OPGMA-based co-polymeric hydrogels, without any consideration of POPGMA homopolymer [26,43,44].

In the last decade, we became interested in the synthesis of smart hydrogels with controlled compositions and architectures for biomedical applications using high energy radiation. This method offers unique advantages for the synthesis of new and modification of existing materials: it is a simple, additive-free process at all temperatures, reactions such as polymerisation, crosslinking and grafting can be easily controlled, and the treatment can be limited to a specific area, for example to the surface only. Some of the specific applications include: synthesis of hydrogels; chemical modification of biomaterial surfaces; synthesis of functional microspheres; crosslinking of hydrophobic and hydrogel biomaterials; and radiation processing of naturally derived biomaterials. Medical applications of these radiation processed biomaterials include implants, topical dressings, treatment devices, and drug delivery materials. Biotechnological applications include diagnostic assays, affinity separations, immobilised enzyme and cell bioprocesses, and cell culture surfaces [45–47].

In this work, new POPGMA homopolymeric hydrogel with OPG pendant chains, as nonlinear analogue of PPGMA, was investigated after successful synthesis by high energy radiation. In a first step, the POPGMA homopolymeric hydrogel was obtained by a gamma radiation-induced free radical polymerisation route from an monomer–solvent ($OPGMA_{375}$–water/ethanol) mixture at different irradiation doses. In the second step, the structure and swelling properties of the POPGMA homopolymeric hydrogel was investigated. In order to evaluate his potential for biomedical applications, biocompatibility (cytocompatibility and haemolytic activity) studies were also performed.

2. Experimental

2.1. Materials

Oligo(propylene glycol) methacrylate (OPGMA) (Cognis UK Ltd. as Bisomer PPM5 with M_w = 375 g mol^{-1}; ρ = 1.01 g cm^{-3} at 25 °C) was used as the main component for hydrogel preparation. Ethylene glycol dimethacrylate (EGDMA, Aldrich) was used as a crosslinking agent. Buffer solutions with different pH were prepared using hydrochloric acid (La Chema), potassium chloride (Fluka), potassium mono- and di-hydrogenphosphate (Fluka), sodium hydroxide (Fluka), ammonium hydroxide (Fluka) and ammonium chloride (Fluka). Deionised water was used for the synthesis of hydrogels and for the preparation of the buffer solutions.

2.2. Hydrogel preparation

Oligo(propylene glycol) methacrylate was dissolved in a water/ethanol (1/1, by volume) mixture by stirring at room temperature. A very small amount of EGDMA was added to the 10 wt% monomer–solvent mixture, 0.5% (weight EGDMA/weight OPGMA), as an efficient crosslinking agent. The reaction mixture was degassed and sealed under nitrogen between two glass plates, and irradiated in a ^{60}Co γ source under ambient conditions at a dose rate of 0.5 kGy/h to different absorbed doses (5, 10, 25 and 40 kGy). After irradiation, the specimens were dried in a vacuum oven at 40 °C to constant weight. To remove unreacted components, the obtained hydrogels were subjected to Soxhlet extraction with water/ethanol and dried again to constant weight. The POPGMA homopolymeric hydrogel obtained under an absorbed dose of 25 kGy was used in further characterisation as representative.

2.3. UV–vis spectroscopy

UV–vis measurements were performed at two OPGMA monomer concentrations (1 and 3 wt%) and in buffer solutions