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Thermoresponsive poly(di(ethylene glycol) methyl ether methacrylate)-*ran*-(polyethylene glycol methacrylate) graft copolymers exhibiting temperature-dependent rheology and self-assembly

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ABSTRACT

Graft copolymers with brush-type architectures are explored containing poly(ethylene glycol) methacrylates copolymerized with "thermoresponsive" monomers which impart lower critical solution temperatures to the polymer. Initially, the chemical structure of the thermoresponsive polymer is explored, synthesizing materials containing N-isopropyl acrylamide, N,N-diethyl acrylamide and diethylene glycol methyl ether methacrylate. Thermoresponsive graft-copolymers containing di(ethylene glycol) methyl ether methacrylate (DEGMA) exhibited phase transition temperature close to physiological conditions (ca 30 °C). The effect of polymer composition was explored, including molecular weight, PEG-methacrylate (PEGMA) terminal functionality and PEGMA/DEGMA ratios. Molecular weight exhibited complex relationships with phase behavior, where lower molecular weight systems appeared more stable above lower critical solution temperatures (LCST), but a lower limit was identified. PEGMA/DEGMA feed was able to control transition temperature, with higher PEGMA ratios elevating thermal transition. It was found that PEGMA terminated with methoxy functionality formed stable colloidal structures above LCST, whereas those the hydroxy termini generally formed two-phase sedimented systems when heated. Two thermoresponsive DEGMA-based graft polymers, poly($PEGMA_7$-*ran*-$DEGMA_{170}$) and poly($PEGMA_1$-*ran*-$DEGMA_{38}$), gave interesting temperature-dependent rheology, transitioning to a viscous state upon heating. These materials may find application in forming thermothickening systems which modify rheology upon exposure to the body's heat.

1. Introduction

Macromolecular systems exhibiting physical responses to an applied stimulus are at the forefront of polymer science. Stimuli-responsive polymers which undergo response to stimuli found in the human body, such as temperature, pH, and enzymatic activity are particularly attractive where this behavior may be exploited to generate novel healthcare technologies and consumer products [3]. Modern polymerization methodologies, together with a broad toolbox of monomeric building blocks, allow access to macromolecules bearing diverse functionality with plenty of topologies and architectures and thus the creation of complex stimuli-responsive materials [1,2]. In particular, thermoresponsive systems are attractive where the response may be triggered by specific temperatures in biological systems, for example contact with the human body [4], as well as commercial applications such as thermoresponsive windows which block the sun when the weather is hot [5]. One of the most studied applications of thermoresponsive polymers in biomedical field is the synthesis of "smart" micelles aiming to control drug encapsulation and release with temperature [6]. However, there are plenty of applications for these materials, such as temperature sensor [7], non-viral vectors for gene delivery [8] and 3D cell culture [9].

Thermoresponsive polymers may exhibit lower critical solution temperatures (LCSTs) or upper critical solution temperatures (UCST) in solution. In LCSTs, the soluble polymer phase separates when heated above the LCST, whereas in UCST the polymer only become soluble above this critical temperature. The origin of the LCST thermoresponse is given by an entropic gain on the release of water molecules bonded to side groups of polymer chains as the temperature increases [7]. Above LCST, the polymers typically undergo a coil-to-globule transition, thus, chains collapse and adopt a compact conformation, mainly driven by

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polymer–polymer associations. This leads to polymer aggregate formation, which can in turn dramatically scatter light, decreasing the transparency of the solutions, designated a "cloud point" [7]. Furthermore, polymer–polymer interaction above the LCST can be used to trigger the formation of structure across several length scales, such as flower-like core–shell micelles and larger percolating gel networks [4].

Poly(N-isopropyl acrylamide) is one of the most studied thermoresponsive polymers with a transition temperature of 32 °C, close to physiological temperature [10]. Nonetheless, its biocompatibility is contested since it is an acrylamide-based polymer, demonstrating platelet activation upon blood contact [11,12]. Researchers in this field have tried to address this issue by synthesizing new thermoresponsive materials with appropriate transition temperature and mitigated toxicity. As alternatives for N-isopropyl acrylamide there are many options available, including di(ethylene glycol) methyl ether methacrylate (DEGMA) and N,N-diethylacrylamide (DEA). Among the methacrylates group, there are poly(di(ethylene glycol)methylether methacrylate (PDEGMA) materials, which have demonstrated great potential in pharmaceutical and biomedical fields due to their resemblance to polyethylene glycol (PEG), which has been suggested to mitigate risk of toxicity [13,14]. Some studies have reported the interaction of poly(oligo(ethylene glycol)methacrylate)s with different cell lines such as HepG2, Caco-2 and HT29-MTX-E12, indicating the absence of toxicity and the biocompatibility of these materials over a range of concentration [13,15]. PDEGMAs have demonstrated tunable LCST in aqueous solution, which varies from 26 to 32 °C [10,16]. DEA is another attractive alternative to PNIPAM due to its LCST between 25 and 36 °C, allowing for transitions between room and body temperature [17].

Polymer architecture can play a key role in the behavior of thermoresponsive systems [18]. Block copolymers are commonly exploited to form structured materials with properties such as reversible gelation or self-assembly but their synthesis often requires multiple steps and purification of intermediates [19]. Graft copolymers are attractive in this regard where distinct blocks of each monomer are contained within a structure which can be formed in a one-pot synthesis. Graft copolymers of poly(NIPAM-co-PEG acrylate) have been reported which showed remarkable temperature-induced gelation [11]. Concentration solutions of the grant copolymer transitioned from a liquid-like state to a gel state at 27 °C, forming a notably tough material with G' > 100 kPa (at 1 Hz). Thus, these architectures have great potential in developing materials with temperature-dependent rheology.

In this research, we report the synthesis and thermal transition graft-copolymers with thermoresponsive backbones and PEG grafts. Initially, thermoresponsive component is varied in pilot studies. We then report the synthesis and properties of poly (PEGMA-*ran*-DEG(Me)MA) graft copolymers (comprising PEG-methacrylate (PEGMA) or PEG-methyl ether methacrylate (PEGMeMA) via RAFT polymerization (Fig. 1). These copolymers consist of a polyDEGMA backbone with PEG grafts arising from the PEGMA component. The effect of monomer ratios on thermoresponse in aqueous solution is reported. Since both DEGMA and PEG are biocompatible, non-toxic and non-immunogenic materials [15,20], the synthesized copolymers may also be suitable for application in biomedicine or drug delivery

2. Materials and methods

2.1. Materials

N-isopropylacrylamide (NIPAM), diethylene glycol methylether methacrylate (DEGMA), diethylacrylamide (DEA), poly(ethylene glycol) methacrylate (Mn = 500, terminus group –OH, PEGMA), poly(ethylene glycol) methyl ether methacrylate (Mn = 2000, terminus group -OMe, PEGMeMA2000), and poly(ethylene glycol) methyl ether methacrylate (MW = 500, terminus group -OMe, PEGMeMA) were purchased from Sigma-Aldrich (United Kingdom) and passed through a small column packed with basic alumina to remove monomethyl ether hydroquinone, which is contained in the monomers as inhibitor. 2,2′-Azobis(2-methylpropionitrile) (AIBN), 4-((((2-carboxyethyl)thio)carbonothioyl)thio)-4-cyanopentanoic acid (thioRAFT) and dialysis membrane (3500 Da) were also purchased from Sigma-Aldrich (United Kingdom). Tetrahydrofuran (THF) and dimethylformamide (DMF) HPLC grade were purchased from Fisher Scientific (United Kingdom).

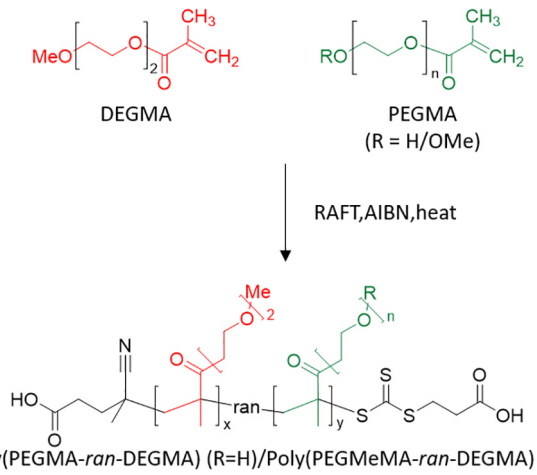

Fig. 1. (A) Synthesis of graft copolymers of DEGMA-*co*-PEGMA and DEGMA-*co*-PEGMe (Mn 500 or 2000 g/mol).

2.2. Preparation of graft copolymers

The synthesis of poly(PEGMA-*ran*-NIPAM), poly(PEGMA-*ran*-DEA), and poly(PEGMA-*ran*-DEGMA) was initially conducted to identify the effect of thermoresponsive component on transitions. The procedure followed the theoretical compositions of the graft copolymers reported by Cheng et al which would lead to 66.5 and 3.5 thermoresponsive and PEGMA units per chain, respectively [11]. An amount of 66.5 mmol (7.50, 8.46, and 12.52 g, for NIPAM, DEA and DEGMA respectively) of each thermoresponsive monomer was weighed and combined with 3.5 mmol of PEGMA (1.75 g), 0.49 mmol AIBN (0.08 g) and 100 mL THF. The mixtures were kept stirring at 65 °C, for 20 h, under nitrogen atmosphere to form the graft copolymers [9,11]. The graft copolymers were purified through dialysis, for at least 24 h, using dialysis membrane (3500 Da). They were then frozen and lyophilized before use [21].

An expanded library of poly(PEGMA-*ran*-DEGMA) (**1**–**7**) was synthesized by RAFT polymerization. Table 1 describes the combinations studied, varying the amount and type of PEG, amount of AIBN and thioRAFT agent. All the mixtures were submitted to the same conditions above mentioned, stirring for 20 h, at 65 °C, under nitrogen atmosphere. They were also dialysed in purified water for at least 24 h and, then, frozen and lyophilized before be analyzing.

2.3. Characterization

2.3.1. Nuclear magnetic resonance (NMR) spectroscopy

Samples were dissolved in $CDCl_3$ to record ^1H NMR spectra on a Bruker Advance AM 600 NMR instrument at room temperature. The residual solvent peak was used as an internal standard. The spectra were processed using Delta 5.3.1 NMR software [11]. To

Table 1
Composition of each statistical (graft) copolymer derived from poly(DEGMA-*co*-PEG).

Code	Theoretical composition	PEGMA (mmol)	DEGMA (mmol)	AIBN (mmol)	thioRAFT (mmol)	Target degree of polymerization
1	poly($PEGMA_7$-*ran*-$DEGMA_{170}$)	3.5	66.5	0.1	0.5	180
2	poly($PEGMA_2$-*ran*-$DEGMA_{38}$)	1.0	19	0.1	0.5	40
3	poly($PEGMA_1$-*ran*-$DEGMA_{38}$)	0.5	19	0.1	0.5	39
4	poly($PEGMA_4$-*ran*-$DEGMA_{38}$)	2.0	19	0.1	0.5	42
5	poly($PEGMeMA_4$-*ran*-$DEGMA_{38}$)	2.0	19	0.1	0.5	42
6	poly($PEG2000MeMA_4$-*ran*-$DEGMA_{38}$)	1.0	19	0.1	0.5	40

determine the monomer conversion of the statistical graft copolymers, ca 30 mg of each crude polymer was diluted with $CDCl_3$, and then it was checked by ^1H NMR. The monomer conversion was obtained by comparing integrated areas at δ = 6.2–5.5 ppm (H_2C = C) assigned to the monomer to a corresponding peak on the polymer [22].

2.3.2. Gel permeation chromatography (GPC)

GPC was conducted using DMF (0.8 mL.min^{-1}) as the mobile phase performed at 30 °C using a 1260 Infinity instrument (Agilent technologies, United Kingdom) equipped with a differential refractive index detector. The instrument was calibrated using polystyrene standards [9].

2.3.3. Phase diagrams of graft copolymers

Each graft copolymer was dissolved in deionised water at 5, 10, 15, 20, 25% (w/w) concentrations to determine the value and nature of their thermal transitions. Transitions were determined by gently heating the solution in thin glass vials immersed in a beaker containing water well stirred with a magnetic bar. The heating rate was controlled to 1 °C/min from 25 to 70 °C for the pilot study and from up to 60 °C for the second library. At each point macroscopic changes, such as cloud point, sedimentation of the aggregates or gel formation were evaluated by eye. The first appearance of turbidity was taken as the cloud point [23,24].

2.3.4. Dynamic light scattering (DLS)

Dynamic light scattering (DLS) experiments for measuring the particle size were made using a Malvern Zetasizer NanoZS. Polymer solutions at concentration of 10 mg/mL were prepared in deionised water and filtered before analysis. The measurements were conducted at 25 and 37 °C. The samples were allowed to equilibrate for one minute prior each measurement [7].

2.3.5. Oscillatory rheology

A TA Instruments AR 1500 ex-controlled stress/controlled rate rheometer, in oscillatory mode was used for the measurements. Parallel steel plate geometry (40 mm), separated by a fixed distance of 600 μm and equipped with a solvent trap to prevent evaporation were adopted through the performance. The storage modulus (G'), the loss modulus (G"), dynamic viscosity (η') and loss tangent (tan δ) were obtained by Advantage TA software. The analyses were performed using a shear stress of 1 Pa and shear rate of 1 s^{-1}, at the temperature range 20–70 °C, heating rate of 1 °C/min. The samples at concentration of 25% (w/w) were carefully spread on the lower plate of the rheometer and allowed to equilibrate for 2 min in order to stabilize the sample before starting the analysis [25-27]. The experiments were carried out at least in triplicate and the results expressed as mean ± S.D.

3. Results and discussion

3.1. Thermoresponse of graft copolymers obtained via free radical polymerization

Phase transition at the LCST is often associated with a cloud point, where the LCST drives demixing and the formation of aggregates which scatter light [28,29]. These aggregates may be well-defined nanostructures, such as micelles, or larger other aggregations which may then undergo sedimentation [30,31]. The absolute value of this transition dictates application, where often transitions are required at room or body temperatures.[32] For pharmaceutical and biomedical applications, polymeric systems with transition between 25 and 37 °C are highly desirable, since the formulation is warmed from storage/room temperature to body temperature [33,34].

Initially, the effect of three different thermoresponsive monomers (NIPAM, DEA, DEGMA) were evaluated in PEGMA-based graft-copolymers (Table S1) to isolate a candidate material with transition between 25 and 37 °C. Phase diagrams relating concentration in aqueous solution and temperature to macroscopic appearance were produced (Fig. 2). It can be seen that poly (NIPAM-*co*-PEGMA) demonstrated cloud point dependence on concentration in a manner commensurate with classical PNIPAM phase diagrams, albeit at a higher temperature [35]. The spinodal curve exhibits a broad, horizontal, minimum even at the highest concentration measured. Although the literature reports poly (NIPAM) presents an LCST at 32 °C [36], the minimum observed for poly(NIPAM-*co*-PEGMA) at > 5 wt% was 42–44 °C (Fig. 2A) which is attributed to the hydrophilic PEG chains disfavouring the demixing event due to their solvation over the temperatures measured. Moreover, increased PEG chains may sterically hinder chain-chain interactions, also increasing LCST [37]. Poly(DEGMA-*co*-PEGMA) exhibited a flat cloud point at 31 °C, in line with prior studies [38], again elevated above the native LCST of the poly-DEGMA thermoresponsive unit which is report to be 26 °C [20]. However, this stable cloudy phase only existed over a small temperature range, with sediment forming at 35 °C when the concentration was ≥ 10 wt%. This sedimentation process was not studied further but may be a result of destabilization of the aggregates in the cloudy phase induced by factors such as increasing hydrophobicity at larger elevation above LCST. Cloud points of poly(DEA-*co*-PEGMA) were not dependent on concentration, being found at 40 °C for all concentrations evaluated. This was again elevated above the LCST of native polyDEA, which is reported to be in the range 25–36 °C. This polymer exhibited sedimentation at 48–49 °C when the concentration was ≥ 10 wt%.

Rheology was conducted on 25% (w/w) concentrated solutions of poly(NIPAM-*co*-PEGMA), poly(DEGMA-*co*-PEGMA), and poly (DEA-*co*-PEGMA) (Fig. 3). It was observed that all three polymers exhibited narrow windows of increased viscosity around their respective cloud points, in a manner previously observed for diblock copolymers as they transition through different nanostructures [39]. Interestingly, increases in viscosity were seen in both G' and G", with a greater effect seen in G". This is interpreted as an

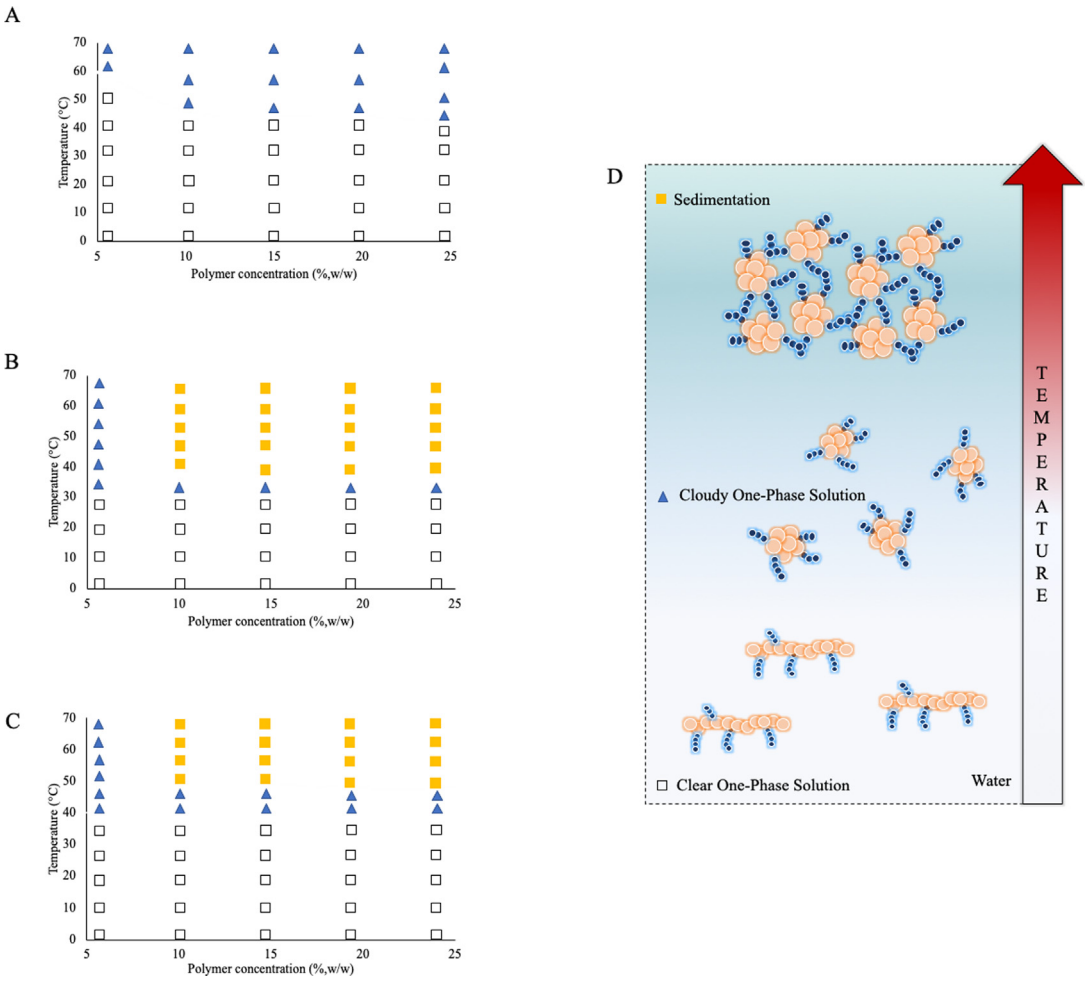

Fig. 2. Cloud point diagram of (A) poly(NIPAM-*ran*-PEGMA), (B) poly(DEGMA-*ran*-PEGMA), and (C) poly(DEA-*ran*-PEGMA) and (D) their schematic representation behavior.

indicator of the formation of particles which contribute to the viscosity of the system, without forming elastically active interactions, such as inter-particle bridging by polymer chains observed in triblock copolymer systems [40]. Thus, it is theorized that the polymer backbone composed mainly of the thermoresponsive block collapses above the LCST with PEG chains stabilizing it, but is unable to form a percolating network within the system on such a length scale as to impart bulk elasticity. The narrow window observed in these rheograms is in line with phase diagrams which demonstrated sedimentation in poly(DEGMA-co-PEGMA) and poly (DEA-co-PEGMA), but this phenomenon was not observed in poly (NIPAM-co-PEGMA).

Poly(DEGMA-co-PEGMA) exhibited advantage over others due to the transition temperature between room and body temperature, which is desirable for many applications. Since the phase transition temperature and nature depends on the polymer structure, architecture, end-groups, and polymerization procedures, it may vary in order to be adjusted for applications of interest [41]. The variety of available or easily accessible monomers make DEGMA a flexible material for designing macromolecules with biocompatibility and self-organization ability [13].

3.2. Effect of initial monomer and initiator feeds in DEGMA-co-PEG polymerization via RAFT

Conventional free-radical polymerization has many advantages, including ease of controlling reaction conditions and suitability for different monomers. However, it presents some issues controlling polymer molecular weight, the nanostructure of the polymer, and polydispersity [42]. RAFT polymerization is an advanced technique to synthesize polymers in a controlled and living manner [43], being able to synthesize well-defined, low-polydispersity block copolymers using a range of monomers [44,45]. Thermoresponsive graft-copolymers of DEGMA and PEG were synthesized via RAFT, using 4-((((2-carboxyethyl)thio)carbonothioyl)thio)-4-cyanopentanoic acid (Fig. 1). This RAFT process allows control over the number of added monomer units via the feed and achieves controlled polymerization to produce samples of narrow polydispersity [29]. Using RAFT in the synthesis of poly(DEGMA-co-PEGMA) decreased PDI from 10.5 to 1.0–2.1 compared to the prior conventional radical polymerization (Table 2). Copolymers **1**–**6** were prepared to explore the effect of feed ratios on thermoresponse. **1**–**2** were synthesized using the thermoresponsive monomer:PEGMA ratio reported by Cheng et al but with a variation of molecular weight where the original composition described prior failed to give comparable rheological profiles to the previously reported data (Fig. 3) [11]. Codes **3** and **4** then explore the effect of PEGMA feed relative to **2**. The ratio of PEGMA to DEGMA in these copolymers effectively controls grafting density, where number of PEG grafts increase with PEGMA feed. Meanwhile **5** explores the effect of PEGMA terminal functionality, where the PEG chains are terminated with methoxy groups rather than hydroxy groups as in **4**. Moreover, **6** explores the effect of PEGMA molecular weight, relative to **5**.

Molecular weight had a major influence on phase behavior (Fig. 4). The preliminary copolymer poly(DEGMA-*ran*-PEGMA), shown in Fig. 3B, formed a stable cloudy phase at 31 °C, but sedi-

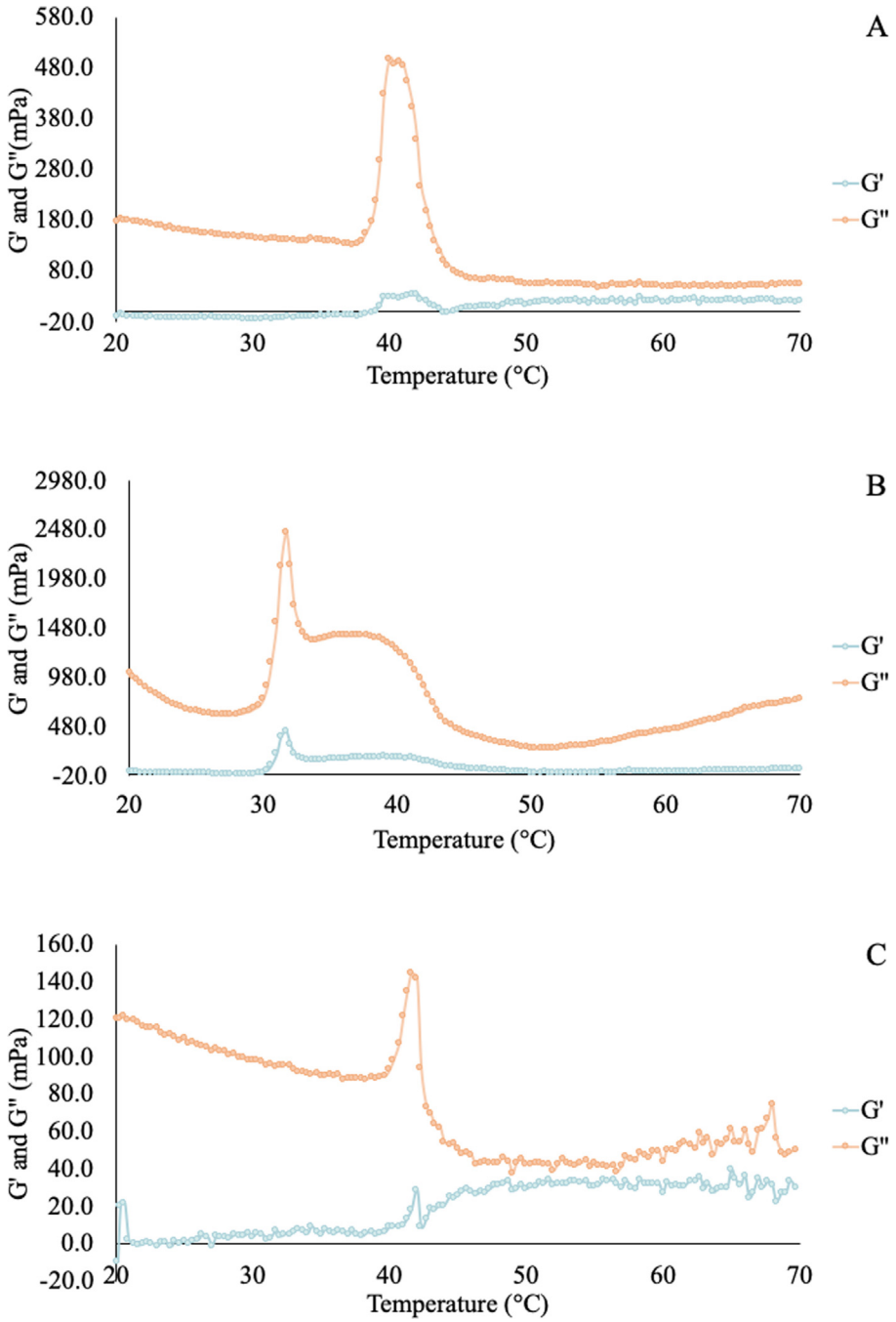

Fig. 3. Temperature-dependent storage modulus (G') and loss modulus (G") in mPa obtained from oscillatory rheology of (A) poly(Nipam-*co*-PEG), (B) poly(DEGMA-*co*-PEG), and (C) poly(DEA-*co*-PEG) at 25% (w/w).

Table 2
Molecular weight (kDa) calculated by theoretical values (Mn_{th}), gel permeation chromatography (Mn_{GPC}) and NMR (% conversion) of synthesized graft-copolymers.

Code	Theoretical composition	GPC		NMR
		Mn_{GPC} (kDa)*	PDI	%conversion
1	poly(PEGMA$_7$-*ran*-DEGMA$_{170}$)	11.3	2.1	98
2	poly(PEGMA$_2$-*ran*-DEGMA$_{38}$)	4.8	1.2	97
3	poly(PEGMA$_1$-*ran*-DEGMA$_{38}$)	4.1	1.3	97
4	poly(PEGMA$_4$-*ran*-DEGMA$_{38}$)	5.4	2.0	99
5	poly(PEGMeMA$_4$-*ran*-DEGMA$_{38}$)	5.1	1.2	90
6	poly(PEG2000MeMA$_4$-*ran*-DEGMA$_{38}$)	5.1	1.3	98

*relative to poly(methyl methacrylate) standards.

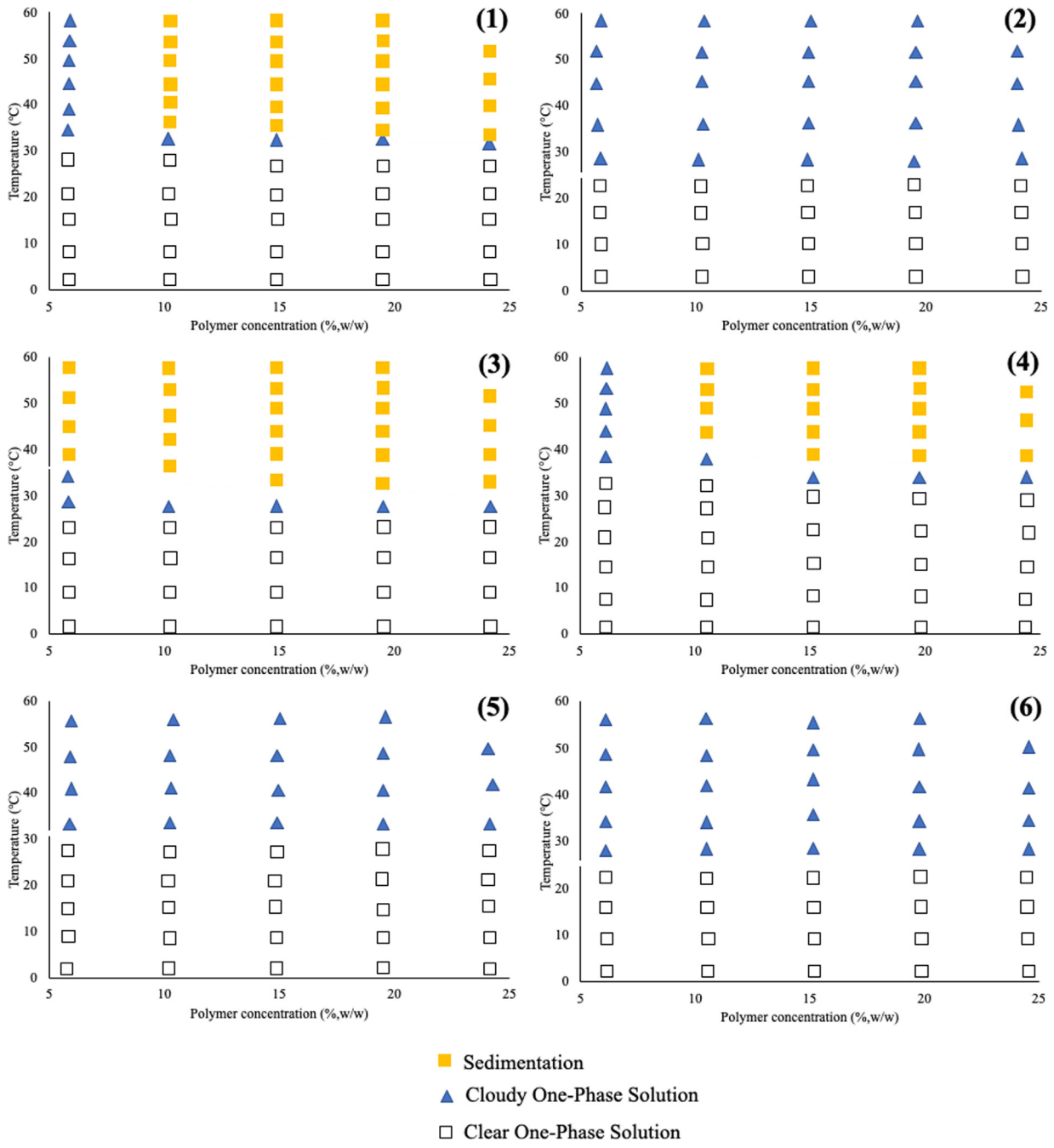

Fig. 4. Phase diagrams of aqueous solutions of poly(PEGMA$_7$-*ran*-DEGMA$_{170}$) (**1**), poly(PEGMA$_2$-*ran*-DEGMA$_{38}$) (**2**), poly(PEGMA$_1$-*ran*-DEGMA$_{38}$) (**3**), poly(PEGMA$_4$-*ran*-DEGMA$_{38}$) (**4**), poly(PEG500MeMA$_4$-*ran*-DEGMA$_{38}$) (**5**) and poly(PEG2000MeMA$_4$-*ran*-DEGMA$_{38}$) (**6**).

mented above 35 °C (at concentrations above 10 % (w/v)). The higher molecular weight copolymer **1** again formed a stable cloudy phase at 31 °C, but sedimented above 32–33 °C (at concentrations above 10 % (w/v)). The lower molecular weight copolymer **2** exhibited a lower transition temperature of 25 °C, forming a cloudy homogenous phase without any sedimentation, indicative of a colloidal phase across the temperatures measured. The molecular weight dependence may be rationalized by the larger molecular weight polymer chains forming micron-scale aggregates, which are affected by gravity, as a result of longer macromolecular chains and/or higher aggregation numbers. This is supported by dynamic light scattering measurements (Table 3) which indicate that particle size in **2** is reduced to the nanoscale where sedimentation processes are eliminated. It is not believed that bridging between multiple aggregates causing larger scale order is occurring due to the lack of elasticity in the system, as shown by rheology. Copolymer **3** and **4** examined the effect of PEGMA feed ratio, with clear shift to higher transition temperatures as the PEGMA feed is increased from one to four per chain in the two systems, respectively, in accordance with observations on this ratio observed by Lutz and co-workers [16]. Interestingly, copolymer **2** with an intermediate PEGMA feed of two units per chain exhibited distinct behaviours from copolymers **3** and **4**, being the only system which did not sediment and likewise the only system with nanoscale aggregates (Table 3).

PEG terminal functionality was assessed by switching hydroxy terminated PEG in copolymer feed **4** for a methoxy terminated PEG to generate copolymer **5**. This small change to macromolecular

Table 3
Dynamic light scattering size and polydispersity index (PDI) of **1**–**6** at 37 °C.

ID	Size (nm)	PDI
1	1490	0.3
2	890	0.6
3	1550*	1.0*
4	2400	0.2
5	850	0.5
6	210	0.2

* please note for these measurements the high degree of polydispersity in the sample is like to lead to considerable uncertainty in the average size and is interpreted as an indicator of a highly heterogeneous aggregate.

chemistry had a considerable effect on physical properties. Whilst the transition temperature was unchanged at ca 31 °C, the cloudy colloidal phase persisted at all temperatures above this measured, without sedimentation. Assuming that the poly(DEGMA) backbone is relatively hydrophobic above its LCST it is likely this block forms the core of a particle with the PEG chains acting as a corona. It is suggested that the ability of hydroxy PEG to donate interparticle H-bonds to PEG ether groups is a plausible clustering mechanism that would lead to larger particle size and sedimentation in the hydroxy-terminated systems, but not in the methoxy-terminated systems which can only act as H-bond acceptors. This is supported by DLS studies which indicate that whilst **4** forms microscale aggregates, **5** and **6** formed nanoparticles. Interestingly, increasing the length of the hydrophilic methoxy PEG chain from 500 to 2000 g/mol decreased transition temperature. It is hypothesized that the larger stabilizing PEG chain makes the formation of the particle more entropically favourable. Likewise, this copolymer formed small, well-defined, aggregates indicating that the individual polymer components are able to aggregate into stable nanoparticles.

The literature links the structure of graft copolymers with the influence of the grafting density. Although the most obvious trend is that thick, densely packed, brushes tend to show shrinkage rather than colloidal aggregation upon heating through their LCST, less densely packed brushes tend to colloidally aggregate following their transition [1]. These observations can be speculated to be due to the accessibility of chain backbones and the reduced grafting densities, which lead to an increased contribution from the underlying hydrophobic component above the LCST [1]. The relatively low grafting densities (i.e. the low quantity of PEGMA) of the copolymers investigated within this study may explain the tendency to form colloidal suspensions on the > 200 nm scale, rather than single polymer nanoparticles.

The rheology of the copolymer solutions was evaluated at 20 % (w/v) to evaluate thermoresponsive changes in viscosity (Fig. 5).

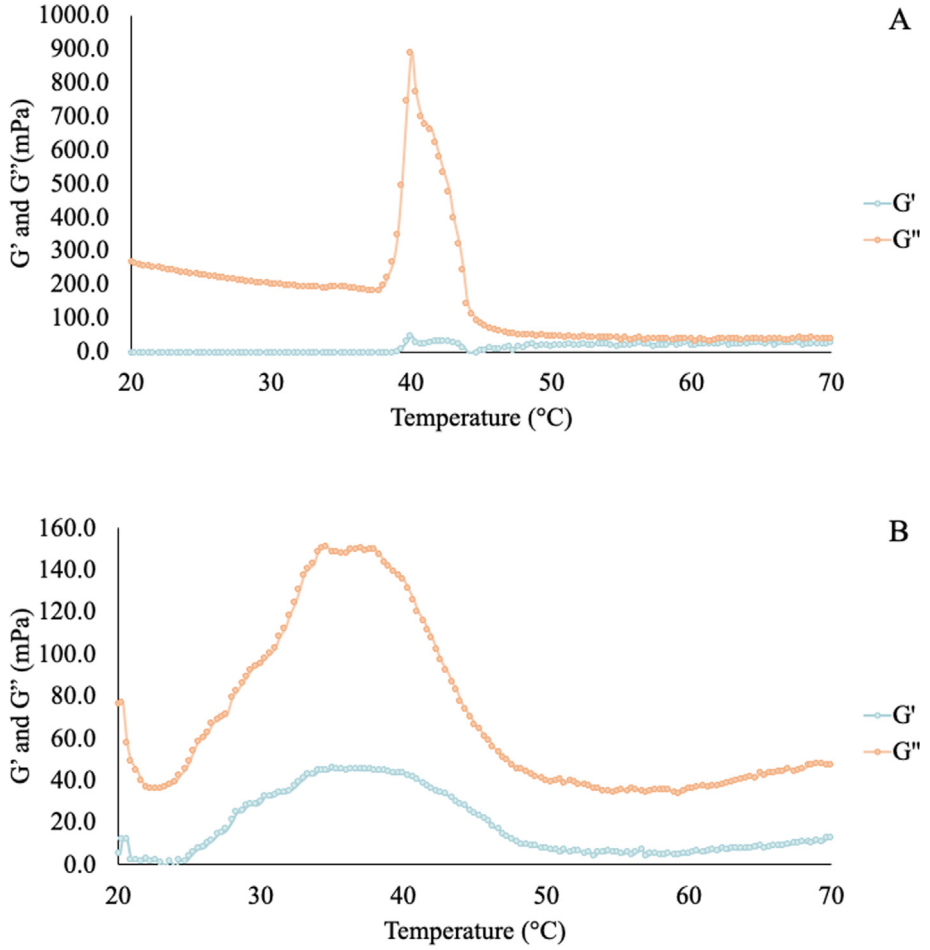

Fig. 5. Temperature-dependent storage modulus (G') and loss modulus (G") in mPa obtained from oscillatory rheology for poly($PEGMA_7$-*ran*-$DEGMA_{170}$) (**1**), and poly ($PEGMA_1$-*ran*-$DEGMA_{38}$) (**3**) synthesized via RAFT polymerization at 25% (w/w).

Oscillatory rheometry allows the evaluation of viscoelastic properties of the preparations. Besides the characterization, it simulates the behavior of the systems when they are at low shear, probing the native properties of the dispersions at shears relevant to physiological environments [46]. The elastic (G') and viscous (G") moduli obtained by oscillatory rheology relate to the stored and recovered energy in each deformation cycle at a given frequency [47,48]. The majority of the samples showed negligible temperature effects (data not shown), however, **1** and **3** exhibited regions of relatively high viscosity with the onset of transition at 38 and 33 °C, respectively, the latter being relevant for inducing changes in viscosity upon contact with the body. G" dominates the rheograms at all temperatures, indicating the absence of an elastic network at this frequency and suggesting the presence of weakly- or non– interacting aggregates in the systems. The precise mechanisms for this effect have not been studied, but poly(DEGMA-*ran*-PEGMe2000MA) solutions studied by Peng and collaborators [49] formed core–shell spherical micelles above LCST which shrank upon further heating due to further desolvation of the polymer. It is plausible that initially, at low temperatures, the polymer is in the unimer state and the solution has a low viscosity. Upon heating, this region of relatively high viscosity is associated with these larger nanoparticles which form shrunken micelles at higher temperatures which exhibit a lower phase volume, reducing viscosity, however confirmatory studies via scattering techniques are required to probe this behaviour further.

4. Conclusion

In this work thermoresponsive graft polymers were synthesized and their thermal transitions studied. Initially, poly(PEGMA-*ran*-DEGMA) was selected over poly(PEGMA-*ran*-NIPAM) and poly (PEGMA-*ran*-DEA) due to the physiologically-relevant transition temperature. The effect of polymer composition was then explored, with optimal copolymer ratios and molecular weights required to produce materials which formed stable colloids above the LCST. Furthermore, it was found that methoxy-terminated PEGMEMA formed colloids above LCST which were relatively small, in the nanoscale, and thus stable to sedimentation compared to hydroxy-terminated PEGMAs. Two materials, poly($PEGMA_7$-*ran*-$DEGMA_{170}$) and poly($PEGMA_1$-*ran*-$DEGMA_{38}$) were found to give thermothickening behaviour in solution, transitioning to a viscous state upon heating, the latter of which occurred above 25 °C making the material attractive for rheological modification upon contact with the human body, allowing systems to flow by extrusion, through syringes or spray devices for example, before transitioning to a viscous retentive state after administration.

CRediT authorship contribution statement

Jéssica Bassi Silva: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **Peter Haddow:** Methodology. **Marcos Luciano Bruschi:** Conceptualization, Writing – review & editing. **Michael Thomas Cook:** Conceptualization, Data curation, Methodology, Supervision, Funding acquisition, Project administration, Resources, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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