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RAFT polymerization and thiol-ene modification of 2-vinyloxyethyl methacrylate: Towards functional branched polymers

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ABSTRACT

A vinyl functional polymer, viz, poly(vinyloxyethyl methacrylate) (poly(VEMA) was synthesized by the RAFT polymerization of an asymmetric divinyl monomer, VEMA. This polymer, with pendant vinyloxyl groups, was subsequently reacted with three thiol compounds; 2-mercaptoethanol, cysteamine and 3-mercaptoproponic acid via the thiol-ene reactions. The resulting branched polymers contained hydroxyl, amino and carboxylic acid functionalities suitable for further reactions and conjugations.

1. Introduction

Polymers with pendant vinyl groups have a number of applications and this has led to a variety of recent publications [1–4]. The vinyl functionality can be exploited via a number of different functionalization approaches such as, cross-linking [5–7], thiol-ene click (TEC) chemistry [8–10], and other transformations [11]. Normally, branched polymers with abundant pendant vinyl groups are directly synthesized via the polymerization of divinyl monomers, under conditions whereby cross-linking can be suppressed. These reaction conditions can include using high dilution or restriction to low conversion. Other creative approaches can also be adopted as exemplified by Guan et al. who reported the radical polymerization of ethylene glycol dimethacrylate (EGDMA) in the presence of an efficient cobalt chain-transfer catalyst to give hyperbranched polymers [12,13]. ATRP has also been used by Wang and co-workers who synthesized hyperbranched polymer via a deactivation-enhanced ATRP of EGDMA or divinylbenzene (DVB) [14]. However, the most reliable synthetic strategy is to utilize functional monomers with two vinyl groups, with disparate reactivity, per molecule (otherwise known as asymmetric vinyl monomers). This approach, using asymmetric monomers has previously been exploited in ionic and coordination polymerizations, where selectivity of vinyl addition is relatively easy to achieve [4,15]. More recently, polymerization of asymmetric divinyl monomers (vinyl functionalized derivatives of acrylate, methacrylate and styrene) by reversible addition-fragmentation chain transfer (RAFT) [16–18] polymerization technique has been employed to synthesize polymers with pendant vinyl functional groups [11],[19,20]. However, when radical polymerization is employed it is impossible to avoid some radical addition to the lower reactivity vinyl functionality and complete selectivity is always compromised to some degree. Despite the drawbacks it is possible to minimize branching and cross-linking with the judicious selection of reaction conditions. Nonetheless, some branching leading to increased polydispersity is inevitable. Copolymerization of asymmetric divinyl monomers with common monomers has also been shown to significantly decrease the PDI [8,20] by minimizing branching.

Thiol-ene reactions for polymer modification, have received a lot of recent interest, and some researchers have likened the positive attributes of thiol-ene reactions to the widely known ‘click’ chemistry of Cu(I)-mediate Huisgen 1,3-dipolar cycloaddition. Thus thiol-ene click chemistry (TEC) has a number of very attractive characteristics, viz, fast reaction rates, high efficiencies, and no requirement for heavy metal catalysis [9].

Many of the published studies on TEC have focused on reaction studies involving small multi-vinyl compounds and thiols [21,22].

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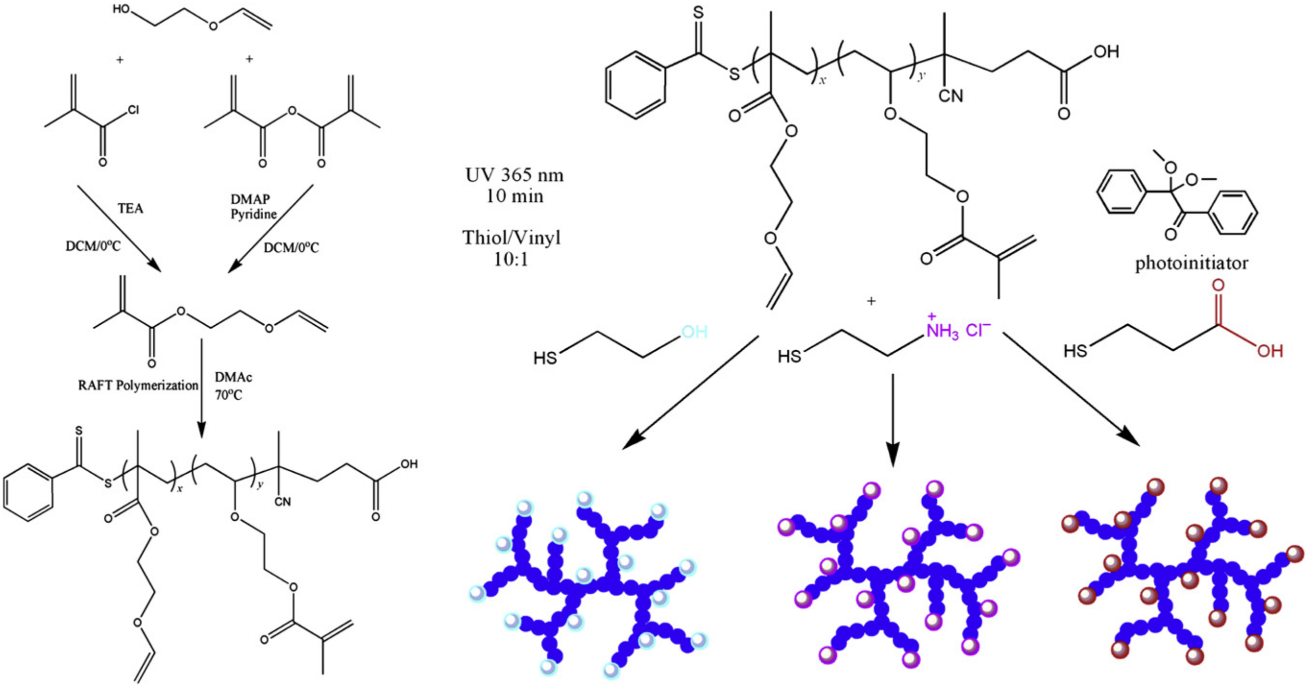

Scheme 1. Synthesis of VEMA and poly(VEMA) (left) and TEC reaction of poly(VEMA) (right).

Complex architectures can also be assembled using TEC as exemplified by the work of Lowe et al. [23], who synthesized a three-armed star polymer exploiting the reaction between a multivinyl core molecule and linear polymers with thiol end-groups, in the work of Chan et al. [23] and Boyer et al.[24,25] polymers made by RAFT were shown to undergo simultaneous aminolysis and thiol-ene addition, demonstrating that synthetic strategies involving both RAFT and thiol-ene can be regarded as a highly efficient and versatile synthesis combination. Recently, Campos et al. [8] and Chen et al. [26] synthesized copolymers with pendant alkene functionalities for modification via TEC reactions (using different synthetic strategies to the one described in this current paper). Finally, Valade et al. [27] have demonstrated the potential utility of RAFT/TEC to make DNA polyplexes with potential for gene silencing therapies.

In this communication, the synthesis and RAFT polymerization of 2-vinyloxyethyl methacrylate monomer (VEMA) is described. Each monomer molecule contains two vinyl groups; the vinyloxyethyl group and the methacrylate group, with the latter possessing a much higher reactivity in free radical polymerization. The vinyl-functional polymeric precursors thus formed were subsequently reacted with three thiol compounds (as examples) 2-mercaptoethanol (ME), cysteamine (Cy) and 3-mercaptoproponic acid (MPA) to yield branched polymers with hydroxyl, amino and carboxylic acid functionalities, as shown in Scheme 1.

2. Experimental part

2.1. Materials

Chemicals were purchased from Sigma-Aldrich unless otherwise indicated. The initiator, 2,2′-azobisisobutyronitrile (AIBN) was recrystallized twice from methanol prior to use. High purity nitrogen (Linde gases) was used for purging the reaction solutions before polymerization. Ethylene glycol vinyl ether (EGVE), methacrylic anhydride, 3-mercaptoproponic acid, 2-mercaptoethanol,

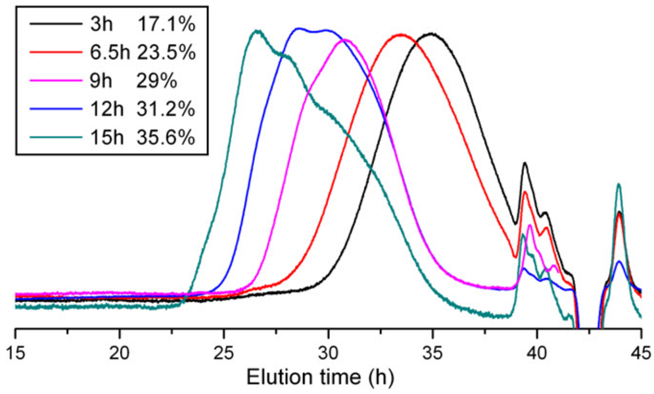

Fig. 1. GPC traces of poly(VEMA) at increasing monomer conversions.

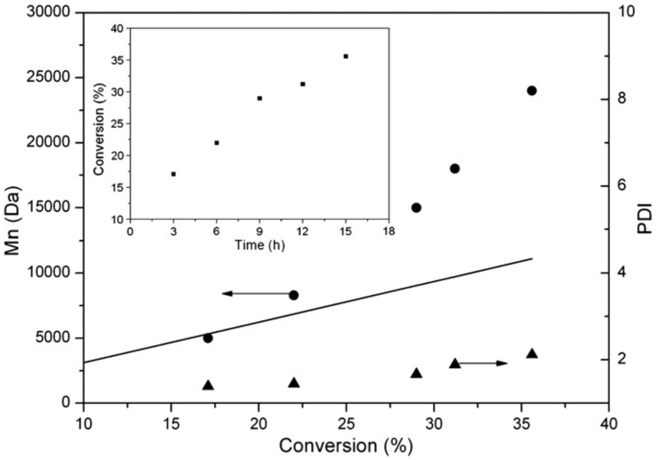

Fig. 2. Polymerization kinetics of VEMA: MW by GPC (●), PDI (▲) and theoretical MW (—) versus monomer conversion; inset monomer conversion versus polymerization time (■).

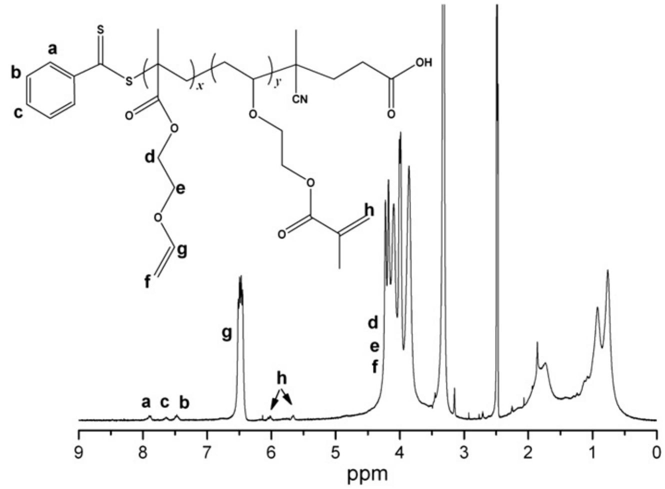

Fig. 3. ^{1}H NMR spectrum of poly(VEMA) in DMSO-d_6.

cysteamine hydrochloride and methacryloyl chloride (TCI) were used as received. Dichloromethane (Univar, reagent) was distilled in presence of CaH_2 prior to use. *N, N*-dimethylacetamide, (HPLC,≥99.9%) (DMAc) was used for polymerizations. 2,2-Dimethoxy-2-phenylacetophenone was used as a photoinitiator. 4-(Cyanopentanoic acid)-4-dithiobenzoate (CPADB), RAFT agent, was synthesized according to a previously reported procedure [28].

2.2. *Synthesis of monomer 2-Vinyloxyethyl methacrylate (VEMA)*

Methacrylic anhydride (10 g, 0.066 mol), EGVE (5.3 g, 0.06 mol), DMAP (160 mg, 1.3 mmol) and pyridine (5 g, 0.066 mol) were dissolved in dry dichloromethane (40 ml). The stirred mixture was cooled in an ice bath for two hours and then at room temperature overnight. The mixture was then concentrated using rotary evaporation, removing all the dichloromethane. The colorless residue was then purified by column chromatography using silica as a stationary phase and ethyl acetate/n-hexane (1:1 v/v) as the eluent. The product, a colorless liquid, VEMA was obtained (yield 6.3 g, 68.3%).

^{1}H NMR ($CDCl_3$, 298 K, 300 MHz), δ (ppm from TMS): 6.46 (1H, q, $-\mathrm{O}-\mathrm{C}H{=}\mathrm{CH}_2$), 6.11 and 5.55 (2H, s, $-(\mathrm{CH}_3)\mathrm{C}{=}\mathrm{C}H_2$), 4.33 (2H, t, $-\mathrm{COO}-\mathrm{C}H_2-\mathrm{CH}_2-$), 4.15 and 4.03 (2H, q, $-\mathrm{O}-\mathrm{CH}{=}\mathrm{C}H_2$), 3.92 (2H, t, $-\mathrm{COO}-\mathrm{CH}_2-\mathrm{C}H_2-$), 1.92 (3H, s, $-(\mathrm{C}H_3)\mathrm{C}{=}\mathrm{CH}_2$).

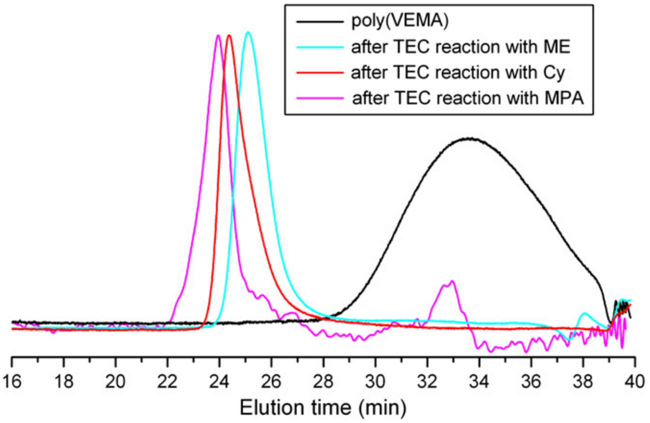

Fig. 5. GPC traces of poly(VEMA) precursor and its products after TEC reaction.

2.3. *Synthesis of Poly(VEMA) by RAFT polymerization*

VEMA (1.56 g, 0.01 mol), CPADB (14 mg, 0.05 mmol), AIBN (1.64 mg, 0.01 mmol) were dissolved in DMAc (9 ml). The resulting solution was split and charged to 5 vials. The vials were sealed using rubber septa and purged using N_2 for 30 min before incubation in a preheated 65 °C oil bath. The samples were taken out at different times and quenched by immersing in liquid nitrogen. The polymerization mixture was precipitated in *n*-hexane. After repeated purifications and drying, a pink powdery polymer was obtained.

2.4. *Thiol-ene click reaction of poly(VEMA) with thiol compounds*

Three thiol compounds, 3-mercaptoproponic acid, 2-mercaptoethanol and cysteamine hydrochloride were used for thiol-ene click reactions. Typically, poly(VEMA) (15 mg) (~0.1 mmol vinyl groups), 2-mercaptoethanol (78 mg) and 2,2-dimethoxy-2-phenylacetophenone (2.56 mg) were dissolved in THF (2 ml). The shaken mixture was then irradiated by UV light at 365 nm for 10 min. The mixture was then dialyzed against acetone for 24 h (the

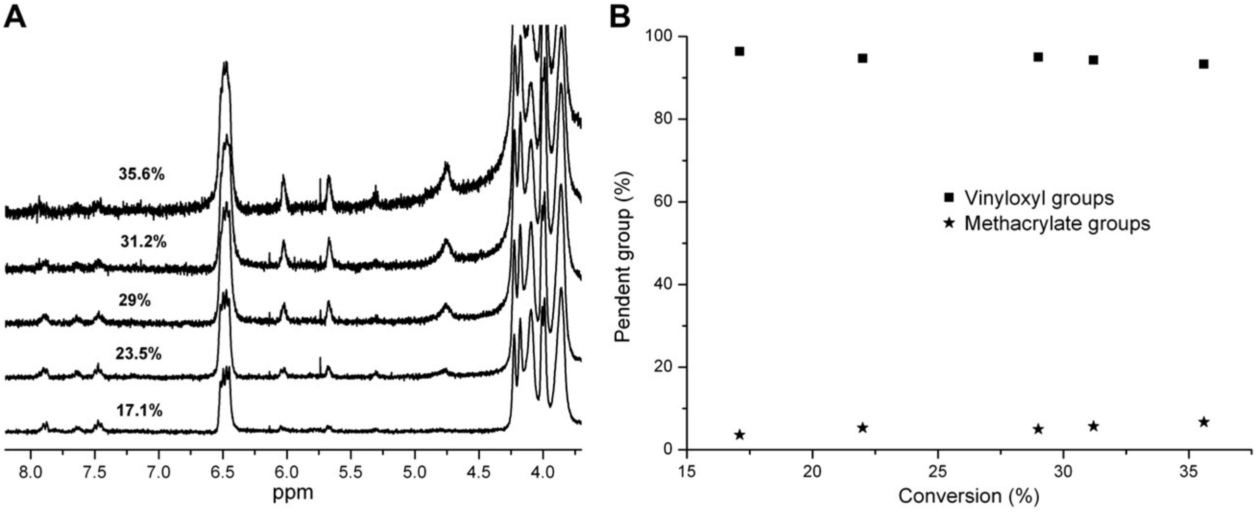

Fig. 4. ^{1}H NMR spectra of poly(VEMA) at different monomer conversions (A) and the relative pendant group functionality plotted against monomer conversion (B).

acetone was changed after 12 h). The dialyzed solution was dried directly in air and then in vacuo. Finally, product (16 mg) was obtained for subsequent analyses. In the case of the reaction of poly(VEMA) with cysteamine, a mixed solvent MeOH/THF (7/3 v/v) was used.

2.5. Characterization

^{1}H NMR experiments were conducted on a Bruker Avance DMX300 spectrometer. Molecular weights (MW) and molecular weight distributions (PDI) were measured by gel permeation chromatography (GPC) on a Shimadzu modular LC system comprising a DGU-12A solvent degasser, a LC-10AT pump, a SIL-10AD autoinjector, a CTO-10A column oven, and a RID-10A refractive index detector. The system was equipped with a 50 × 7.8 mm guard column and four 300 × 7.8 mm linear columns (Phenomenex 500, 103, 104, and 105 Å pore size; 5 μm particle size). *N,N′*-Dimethylacetamide (DMAc) (HPLC, 0.03% w/v LiBr, 0.05% BHT) was used as eluant at a flow rate of 1 mL min^{-1} while the columns temperature was maintained at 40 °C. Polymer solutions (3–5 mg mL^{-1}) were injected in 50 uL volumes. Calibration was performed with narrow polydispersity polystyrene standards (Polymer Laboratories) in the range 0.5–1000 kDa.

Absolute molecular weights of polymers were determined using a Polymer Labs GPC50 Plus equipped with dual angle laser light scattering detector, viscometer and differential refractive index detector. HPLC grade THF was used as eluent at flow rate 1 mL/min. Separations were achieved using two PLGel Mixed C (7.8 × 300 mm) GPC columns connected in series held at a constant temperature of 40 °C. The triple detection system was calibrated using a 2 mg/mL PS Standard (Mwt = 110 K, dn/dc = 0.185 and IV = 0.4872 mL/g).

Fourier Transform Near Infrared (FT-NIR) The FT-NIR measurements were performed with a Bruker IFS66\S Fourier transform spectrometer equipped with a tungsten halogen lamp, a CaF$_2$ beam splitter, and a liquid nitrogen-cooled InSb detector. Each spectrum, in the spectral region of 8000–4000 cm,$^{-1}$ was calculated from the coadded interferograms of 12 scans with a resolution of 4 cm^{-1}.

3. Results and discussion

VEMA has previously been synthesized via the reaction between 2-chloroethyl vinyl ether and sodium methacrylate [29]. In this current work, VEMA was synthesized by the reaction of EGVE with either methacryloyl chloride or methacrylic anhydride. Both reactions gave good yields (~70%).

Earlier polymerization studies on VEMA focused on anionic polymerization and subsequent acidic hydrolysis to yield poly(HEMA) [29]. Herein, the VEMA was polymerized using RAFT polymerization, and the resulting molecular weight distributions are shown in Fig. 1. The mono-modal distributions at low monomer conversions broaden at increasing polymerization times. Inevitably the pendant vinyloxyl groups participate in the polymerization to some extent, and this becomes increasingly evident at high conversions, generating branched structures. The polymerization kinetics were monitored and reported in Fig. 2. It is evident that the monomer conversions increased with polymerization time as expected. The MW values (measured by GPC with linear calibration) were higher than the predicted theoretically. The MW of the sample taken at 12h (nominal MW=18,000) was also determined using triple detector GPC yielding an absolute MW of 28,700. However, the vinyl functionality (to a limited extent) did participate in the polymerization, causing branching and thus influenced the MW [11]. All the PDIs were in the range 1.3–2.1, typical of the polymerization of asymmetric divinyl monomers [11,19]. A typical ^{1}H NMR spectrum of poly(VEMA) is shown in Fig. 3. NMR peaks at 7.82, 7.60 and 7.43 ppm were ascribed to the aromatic protons of RAFT end groups. A peak at 6.51 ppm was ascribed to the characteristic methine protons of pendant vinyloxyl groups. The peaks at 5.62 and 6.05 ppm were ascribed to the pendant group of the methacrylic double bond.

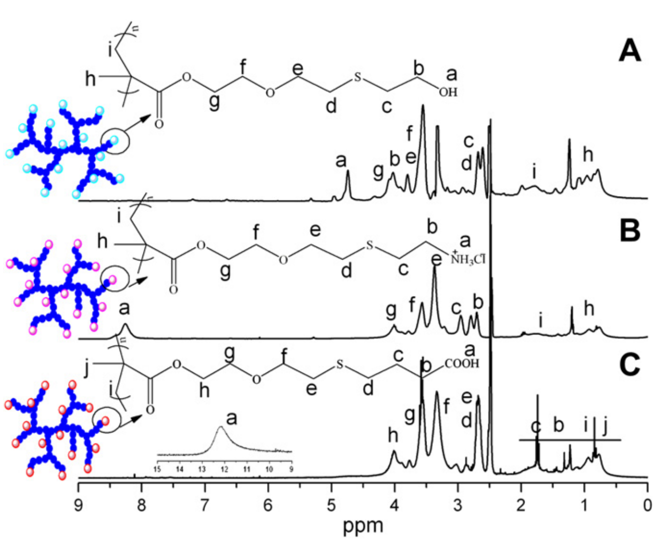

Fig. 6. ^{1}H NMR spectra of branched polymers generated from poly(VEMA) post-reacted with 2-mercaptoethanol (A), cysteamine (B) and 3-mercaptoproponic acid (C), all recorded in DMSO-d_6.

Subsequently ^{1}H NMR was used to follow a typical RAFT polymerization of VEMA, as shown in Fig. 4A. The peak integral ascribed to pendant methacrylalic functionality increased with increasing conversion, consistent with the vinyloxyl groups participating in the polymerization. The ratio of pendant methacrylate groups increased from 3.7% to 5.6% with increasing monomer conversion as shown in Fig. 4B. In summary, the NMR results are consistent with a polymer structure, dominated by pendant vinyl groups, together with a small fraction of pendant methacrylic groups.

TEC has already been widely employed for complex-structure polymer synthesis [23], post-polymerization functionalization to

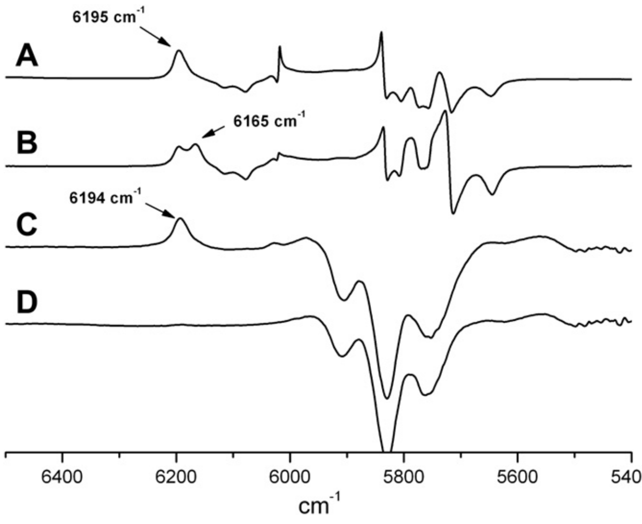

Fig. 7. FT-NIR spectra of the final functional branched polymer and its precursors, (A) vinyloxyl ethyl ether (B) VEMA monomer (C) poly(VEMA) and (D) final branched structure following the reaction of poly(VEMA) with MPA.

produce functional polymers and nanoscale materials [30,31] and biomaterials for dentistry [32,33]. Consistent with our results, recent published research has shown that polymers synthesized from asymmetric divinyl monomers display abundant pendant alkene functionality [20] useful as potential scaffolds for further modification [11]. In this communication, branched poly(VEMA) with pendant vinyloxyl groups was used as precursors for TEC reactions with different hetrofunctional thiols. Thus, compounds ME (thiol with hydroxyl group), Cy (thiol with amine group) and MPA (thiol with carboxyl acid group) were reacted with poly(VEMA) to produce polymers with hydroxyl, amino and carboxylic groups respectively. The TEC reaction was performed under UV light irradiation using 2,2-dimethoxy-2-phenylacetophenone as a photoinitiator, with excess thiol (10 eq thiols was used). We found that photocross-linking of pendant vinyloxyl groups could not be totally avoided even with such an excess of thiol. The GPC traces of poly(VEMA) both pre- and post- TEC reaction are shown in Fig. 5. After functionalization, the apparent MWs increased significantly from around 12,000 to 1,45,000 after reaction with ME, 2,36,000 with MPA and 3,89,000 with Cy, respectively. The sample after TEC reaction with ME was also determined by triple detector GPC to give the absolute MW with 1,87,000. It is noteworthy that the PDI of poly(VEMA) precursor significantly decreased from 1.5 to 1.1–1.2. This is probably, a reflection of the shift to a highly branched structure with the accompanying alteration in hydrodynamic volume.

The TEC reaction products were characterized by ^{1}H NMR in DMSO-d_6 as shown in Fig. 6. In Fig. 6, the peak at 6.51 corresponding to the methine protons of pendant vinyloxyl groups is absent in all the spectra. Fig. 6A, B and C show the spectra of poly(VEMA) post-reacted with ME, Cy and MPA, respectively. New peaks at 4.67 ppm, 8.3 ppm and 12.5 ppm are characteristic of hydroxyl groups, ammonium groups and carboxylic acid groups, respectively.

FT-NIR was also used to monitor the reactions as shown in Fig. 7. A comparison of spectra 7A and 7B, reveals an absorbance at 6165 cm^{-1} (spectrum 7B) originating from the stretching overtone of the methacrylate C=C double bond in the VEMA monomer. After polymerization, the peak at 6165 cm^{-1} virtually disappeared (spectrum 7C) indicating that poly(VEMA) mainly contains pendant vinyoxyl groups consistent with the ^{1}H NMR results. Finally, the highly efficient post-polymerization modification via TEC is confirmed by the disappearance of the absorbance at 6195 cm^{-1} as shown in spectrum 7D.

4. Conclusion

In this communication, we describe the synthesis of a branched poly(VEMA) structure with pendant vinyloxyl functionality. The polymerization of VEMA was controlled by a RAFT agent to obviate high degrees of cross-linking. A minor branching contribution to the polymerization, caused by some radical addition to vinyloxy, was observed. These functional polymer scaffolds were then subjected to TEC reactions with a representative thiol compound library to yield highly branched polymers with hydroxyl, amino and carboxylic functionalities.

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