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A versatile method for functionalization and grafting of 2-hydroxyethyl cellulose (HEC) *via* Click chemistry

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ABSTRACT

This article describes a versatile method for the modification of 2-hydroxyethyl cellulose (HEC) involving azide-alkyne cycloaddition reaction to impart neutral (ester) and ionic (carboxylic acid and 1[ry] amine) functionalities. The synthetic approach involved, first the introduction of the azide functionality to HEC and then followed by its cycloaddition reaction with several alkyne terminated compounds: namely ethyl propiolate, 5-hexynoic acid and propargyl amine. Sequential Click reactions were also demonstrated to be feasible by the successful synthesis of polydimethylsiloxane (PDMS) grafted HEC containing neutral (ester) and ionic (carboxylic acid and 1[ry] amine) functionalities. The Click chemistry was then further utilized similarly to graft poly(lactic acid) (PLA) and poly(ethylene glycol) (PEG) segments to HEC to access its hydrophobic and hydrophilic analogs, respectively. AFM analysis revealed that while HEC itself formed uniform oval features, the PLA grafted HEC exhibited a brushlike architecture. The formation of these brushlike structures suggested that the HEC backbone exhibits an extended conformation with the side chains stretched out. The resulting polymeric materials were characterized by solution and solid state ^{13}C NMR and FTIR spectroscopy.

1. Introduction

Polysaccharides are the most versatile class of biomaterials due to their biological and pharmaceutical functions (Goa & Benfield, 1994; McAlindon, LaValley, & Felson, 2000; Rinaudo, 2004; Shao et al., 2004; Witczak & Nieforth, 1997; Zhang, Yang, Chen, Hou, & Han, 2005). Based on their unique multifunctionality, polysaccharides play a very important role in personal care and cosmetic formulations; as thickeners, suspending agents, hair conditioners, moisturisers, emulsifiers, emollients, and wound-healing agents (Brode, Kreeger, Partain, & Pavlichko, 1988; Buschmann & Schollmeyer, 2002; Goddard & Gruber, 1999; Muzzarelli & Muzzarelli, 2005). Special interest has been paid to polysaccharides with polysiloxane grafts, known as glyco-silicones. Such amphiphilic structures have been used as transdermal penetration enhancers (Akimoto, Kawahara, Nagase, & Aoyagi, 2000), surfactants (Henkensmeier, Abele, Candussio, & Thiem, 2004; Racles & Hamaide, 2005; Racles, Hamaide, & Ioanid, 2006; Wagner et al., 1996, 1998), and surface modifiers in cosmetics and detergent formulations (Carrillo et al., 2006; Joffre, Johnson, Swanton, & Starch, 2006). Polydimethylsiloxane (PDMS) is of particular interest for this purpose due to its unique properties. It has low glass transition temperature (T_g), high flexibility, low toxicity, good biocompatibility, high oxygen permeability and good thermal stability (Quinn & Courtney, 1988; Rutnakornpituk, Ngamdee, & Phinyocheep, 2005; Schulze Nahrup, Gao, Mark, & Sakr, 2004). Polysaccharides with poly(aliphatic ester) grafts (PLA and PCL) are another interesting examples of the hydrophobic polysaccharides. However, the limited mixing affinity between these hydrophobic polymers (PDMS, PLA and PCL) and hydrophilic polysaccharides has been a practical barrier in the synthesis of the hydrophobic polysaccharides. In contrast, the incorporation of PEG to produce hydrophilic polysaccharides is expected to suffer less from the poor compatibility issue. However, the regio-selective and quantitative chemical modifications of polysaccharide backbones have been hardly accomplished because it usually involved tedious synthetic routes due to the similar reactivity of the hydroxy-groups toward electrophiles (Jahn et al., 2003; Kobayashi, Uyama, & Kimura, 2001). Therefore, efficient and facile strategies to prepare modified-polysaccharide materials are highly desired.

The high efficiency of copper catalyzed azide-alkyne cycloaddition (CuAAC), Click chemistry (Kolb, Finn, & Sharpless, 2001; Rostovtsev, Green, Fokin, & Sharpless, 2002), has offered a versatile and an appropriate methodology to be used with compounds with different solubility characteristics (Diaz et al., 2004; Helms, Mynar, Hawker, & Frechet, 2004; Lutz, Borner, & Weichenhan,

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2005; Tsarevsky, Sumerlin, & Matyjaszewski, 2005; Wu et al., 2004). Liebert (Liebert, Hansch, & Heinze, 2006) and Hafrén (Hafren, Zou, & Cordova, 2006) demonstrated that cellulose can be modified *via* Click chemistry. Both azide and terminal alkyne functional groups were introduced onto cellulose backbone and successful CuAAC reactions were reported despite steric hindrance. Recently, the synthesis of glyco-polyorganosiloxanes by Click chemistry has been reported. Since, this method involved the attachment of the alkyne functionality at the glycoside end of xyloglucan, a limited amount of the azide functionalized PDMS can be introduced. Nevertheless, it was claimed that the produced material exhibits a good surfactant properties (Halila et al., 2008). Moreover, Click chemistry has been used for surface grafting of PCL onto cellulose fibers in heterogeneous condition. However, a spacer molecule was needed to move away the reactive functions from the fiber's surface and, consequently, making them more accessible for PCL grafts (Krouit, Bras, & Belgacem, 2008).

Cationically modified 2-hydroxyethyl cellulose (HEC) with quaternary ammonium functional groups has been used in cosmetics and personal care formulations, since it has the unique advantage to bind tightly to proteins (negatively charged) of the human skin and hair and hence acting as a damage-repairing agent (Bombeli). Therefore, the development of novel HEC-based materials with different charges as well as hydrophobic/hydrophilic grafts has been an attractive research target.

This paper describes the exploitation of Click chemistry to introduce neutral (ester groups) and ionic (carboxylic acid and/or primary amine) compositions on HEC. To the best of our knowledge, there are no reports, up to date, on modification of HEC *via* Click chemistry. Moreover, sequential Click reactions are used to functionalize and graft HEC with different molecules (ester, carboxylic acid and 1^{ry} amine) and/or macromolecules (PDMS, PLA and PEG) to generate materials with interesting features for possible industrial/medical applications.

The chemical modification strategy carried out in the present work should significantly broaden the structural diversity of polysaccharide-based materials. The utilization of Click chemistry would yield materials, which are not accessible *via* the commonly applied modification reactions such as etherification and esterification.

2. Experimental

2.1. Materials

2-Hydroxyethyl cellulose (HEC) (M_w of ~250,000 g mol^{-1}, DS = 1, MS = 2) and Poly(ethylene glycol) (PEG) methyl ether (M_n of ~550) were purchased from Sigma–Aldrich and fully characterized by NMR spectroscopy before usage. Mono-epoxy terminated polydimethylsiloxanes (epoxy terminated PDMS) (M_w of ~1000 g mol^{-1}) was purchased from Gelest and fully characterized by ^{1}H NMR spectroscopy before usage.

All other chemicals and reagents used in the synthesis were purchased from Sigma–Aldrich and used without further purification. All dry solvents were obtained from the Solvent Purification System (SPS), Chemistry Department, Durham University.

2.2. Instrumentation and measurements

^{1}H NMR spectra were recorded using deuteriated solvent lock on a Varian Mercury 400 or a Varian Inova 500 spectrometer at 400 MHz and 500 MHz, respectively. Chemical shifts are quoted in ppm, relative to tetramethylsilane (TMS), as the internal reference. ^{13}C NMR spectra were recorded at 101 MHz or 126 MHz (2000 scans) using continuous broad band proton decoupling and a 3 s recycle delay, and therefore not quantitative; chemical shifts are quoted in ppm, relative to $CDCl_3$ (77.55 ppm).

Solid-state NMR spectra were obtained using either a Varian VNMRS spectrometer operating at 100.56 MHz for ^{13}C (399.88 MHz for ^{1}H) or a Varian Unity Inova instrument operating at 75.40 MHz for ^{13}C (299.82 MHz for ^{1}H). They were obtained under magic-angle spinning conditions with spin-rates in the range 10,000–14,000 Hz. Carbon NMR spectra were recorded with cross-polarization (typically with a recycle delay of 1.0 s and a contact time of 1.00 ms) or direct excitation (typically with a recycle delay of 1.0 s) and with ^{1}H decoupling. ^{1}H spectra were obtained with direct excitation. Samples were run as-prepared and spectral referencing is with respect to external, neat tetramethylsilane.

FTIR spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer fitted with Diamound ATR crystal unit.

Silicon analysis was carried out by Atomic Absorbance Spectrometry using Varian Spectra AA 220 FS with N_2O/acetylene flame. Digestion of samples was carried out by adding 3 ± 0.1 mL of concentrated HNO_3 to each sample in a 20 mL volumetric flask. Samples were then heated to 90 ± 5 °C for 15 min, allowed to cool and made up to the 20 mL mark with deionized water.

A Digital Instruments Nanoscope IV AFM was used to record tapping mode micrographs of the irradiated polymers. 256×256 line images were recorded at a scanning speed of 1 Hz, and an integrated hot stage was used to carry out annealing steps between scans. Annealing was carried out for 1800 s at 110, 121.5, and 132.2 °C. Surface height *versus* cross-section was measured for each AFM image with the Nanoscope V6 online software. Tapping-mode micrographs were used in an attempted to visualize individual polymer chains. Spin-casting of a dilute polymer solution (~1 mg/100 mL) was necessary to disperse individual polymer chains for imaging. HEC was spin-cast from water on the surface of a clean silicon wafer to produce a thin film with an average thickness of ~1 nm.

2.3. Synthesis of azido-deoxy HEC 1

The azidation of HEC was performed following a modified procedure to those reported by Cimecioglu et al. (Cimecioglu, Ball, Kaplan, & Huang, 1994; Cimecioglu, Ball, Huang, & Kaplan, 1997) and Shey et al. (2006), for amylose and starch.

HEC (10 g, 0.04 mmol; approximately 60 mmol of 1^{ry} OH), sodium azide (15.6 g, 240 mmol) and dry DMF (400 mL) were added to an oven-dried N_2-flushed three-neck round bottomed flask equipped with a stir bar, dropping funnel and thermometer. The reaction mixture was heated to 100 °C under N_2 atmosphere for 1 h. Sodium azide facilitated the dissolution of HEC in DMF. Homogeneous solution was obtained within 1 h at 100 °C, and remained clear upon cooling to ambient temperature. The reaction mixture was then cooled in an ice water bath and triphenyl phosphine (47.2 g, 180 mmol) was added. Carbon tetrabromide (59.7 g, 180 mmol) dissolved in dry DMF (50 mL) was added slowly. The reaction was allowed to warm up to ambient temperature and left for 18 h under positive N_2 pressure. Treatment with Ph_3P/CBr_4, caused a slight exotherm and a color change from off-white to brownish yellow. The reaction mixture otherwise remained homogeneous throughout. Methanol (50 mL) was added to quench the reaction, and the polymer was precipitated by addition of ethanol. The precipitated polymer was recovered by filtration and washed with a mixture of ethanol/water solution (7:3) followed by ethanol. The polymer was then dried under reduced pressure in an oven at 50 °C for 24 h to give **1** (Fig. 1; supporting information), yield 70% (8.1 g, 0.028 mmol).

HEC was purchased from Sigma–Aldrich. According to the provided information, the D.S. = 1 and since we observe complete

conversion of primary alcohol to azide functionality hence we estimate that the D.S. remains the same.

The yield was calculated based on the ^{13}C NMR evidence showing all primary alcohols were converted to azide functionality.

^{13}C NMR (126 MHz, DMSO-d_6, at 80 °C): δ 103.5 (C_1), 82.05 ($C_{4,4'}$, $C_{3,3'}$ (R ≠ H)), 80.1 ($C_{3,3'}$ (R = H), $C_{2,2'}$ (R ≠ H)), 74.8 ($C_{2,2'}$ (R = H)), 74.24 ($C_{5,5'}$), 72.70 (C_8), 70.12 (C_7, $C_{6,6'}$ (R ≠ H)), 51.04 (C_9).

FTIR: ~2090 cm^{-1} (C—N_3 stretching vibration).

The elemental analysis obtained for HEC and **1** were found to be inaccurate, due to the presence of significant amount of moisture in the samples, which was difficult to remove even after extensive drying in oven at reduced pressure.

2.4. Synthesis of 4-ethylcarboxy triazolo HEC 2

In a reaction flask, azido-deoxy HEC **1** (0.5 g, 0.0017 mmol; approximately 2.6 mmol of N_3 groups) was dissolved in DMSO (20 mL) at 70 °C. Ethylpropiolate (3 mL, 3.0 mmol), copper (II) sulphate pentahydrate (65 mg, 0.26 mmol, in 1 mL of water) and sodium ascorbate (103 mg, 0.52 mmol, in 1 mL of water) were added and the mixture was stirred at 70 °C for 24 h. The polymer was precipitated in methanol (200 mL), filtered and washed three times with a mixture of ethanol/water solution (7:3) followed by methanol. The polymer was then dried under reduced pressure in an oven at 50 °C for 24 h to give **2** (Fig. 4; supporting information), yield 87% (0.61 g, 0.0014 mmol).

^{13}C NMR (126 MHz, DMSO-d_6, at 80 °C): δ 161.01 (C_{12}), 139.97 (C_{11}), 129.73 (C_{10}), 103.5 (C_1), 82.05 ($C_{4,4'}$, $C_{3,3'}$ (R ≠ H)), 80.1 ($C_{3,3'}$ (R = H), $C_{2,2'}$ (R ≠ H)), 74.8 ($C_{2,2'}$ (R = H)), 74.24 ($C_{5,5'}$), 72.70 (C_8), 70.12 (C_7, $C_{6,6'}$ (R ≠ H)), 61.03 (C_{13}), 50.53 (C_9), 14.75 (C_{14}).

FTIR spectrum showed disappearance of azide peak at ~2090 cm^{-1}.

2.5. Synthesis of 4-(n-butanoic acid) triazolo HEC 3

In a manner similar to the procedure stated in Section 2.4, **3** (Fig. 6; supporting information) was obtained, yield 79% (1.23 g, 0.0027 mmol).

Solid-state ^{13}C NMR (101 MHz, cross polarization technique): δ 176.03 (C_{15}), 147.39 (C_{11}), 125.31 (C_{10}), 103.53 (C_1), 82.63 ($C_{4,4'}$, $C_{3,3'}$, $C_{2,2'}$ (R ≠ H)), 74.5 ($C_{2,2'}$, $C_{5,5'}$, C_8), 70.09 (C_7, $C_{6,6'}$ (R ≠ H)), 51.54 (C_9), 40.58 (C_{12}), 33.82 (C_{14}), 25.55 (C_{13}).

FTIR spectrum showed disappearance of azide peak at ~2090 cm^{-1}.

2.6. Synthesis of 4-aminomethyl triazolo HEC 4

In a manner similar to the procedure stated in Section 2.4, **4** (Fig. 9; supporting information) was obtained, yield 81% (1 g, 0.0028 mmol).

Solid-state ^{13}C NMR (101 MHz, cross polarization technique): δ 144.26 (C_{11}), 125.46 (C_{10}), 103.92 (C_1), 82.47 ($C_{4,4'}$, $C_{3,3'}$, $C_{2,2'}$ (R ≠ H)), 70.63 ($C_{2,2'}$, $C_{5,5'}$, C_8, C_7, $C_{6,6'}$ (R ≠ H)), 51.59 (C_9), 41.21, 35.68 (C_{12}), 21.88.

FTIR spectrum showed disappearance of azide peak at ~2090 cm^{-1}.

2.7. Synthesis of mono-alkyne terminated PDMS 5

In an ampoule equipped with a young's tap, mono-epoxy terminated PDMS (2 g, 2 mmol) and propargyl amine (PAm) (2 mL, 31 mmol) were mixed and the ampoule was sealed. The mixture was stirred in an oil bath at 83 °C for 18 h. The excess PAm was removed under reduced pressure to give **5** (Fig. 12; supporting information), yield 100% (2.1 g, 2 mmol).

^1H NMR (400 MHz, $CDCl_3$) δ 3.89 (m, 1H, H_{12}), 3.46 (m, 6H, $H_{10,11,16}$), 2.85 (dd, J = 3.8 Hz, 12.0 Hz, 1H, H_{13}), 2.75 (dd, J = 7.7 Hz, 12.1 Hz, 1H, H_{13}), 2.24 (t, J = 2.43 Hz, 1H, H_{17}), 1.71 (bs, 1H, H_{15}), 1.63 (m, 2H, H_9), 1.33 (m, 4H, $H_{2,3}$), 0.91 (m, 3H, H_1), 0.55 (m, 4H, $H_{4,8}$), 0.08 (m, 72H, $H_{5,6,7}$).

Detailed analysis can be found in the supporting information.

2.8. Synthesis of 4-polydimethylsiloxane, 4-ethylcarboxy triazolo HEC 6

In a reaction flask, azido-deoxy HEC **1** (1 g, 0.0034 mmol; approximately 5.2 mmol of N_3 groups) was dissolved in DMSO (30 mL) at 70 °C. Mono-alkyne terminated PDMS **5** (275 mg, 0.26 mmol), copper (II) sulphate pentahydrate (130 mg, 0.52 mmol, in 1 mL of water) and sodium ascorbate (206 mg, 1.04 mmol, in 1 mL of water) were added and the mixture was stirred at 70 °C for 24 h. Ethyl propiolate (0.53 mL, 5.2 mmol) was added and the mixture was stirred at 70 °C for further 24 h. The polymer was precipitated in ethanol (300 mL), filtered and washed three times with a mixture of ethanol/water solution (7:3) followed by ethanol. The polymer product was extracted with diethyl ether to remove any unreacted PDMS. The polymer was finally dried under reduced pressure in an oven at 50 °C for 24 h to give **6** (Fig. 16; supporting information) (1.5 g).

Solid-state ^{13}C NMR (101 MHz, cross polarization technique): δ 161.17 (C_{12}), 139.78 (C_{11}), 130.53 (C_{10}), 103.41 (C_1), 82.65 ($C_{4,4'}$, $C_{3,3'}$, $C_{2,2'}$ (R ≠ H)), 73.00–65.00 ($C_{2,2'}$, $C_{5,5'}$, C_8, C_7, $C_{6,6'}$ (R ≠ H)), 61.70 (C_{13}), 51.32 (C_9), 14.75 (C_{14}), 1.39 (CH_3—Si).

Si elemental analysis (concentration of Si): theoretical (estimated) = 6.4%; found 8.15%.

FTIR spectrum showed disappearance of azide peak at ~2090 cm^{-1}.

2.9. Synthesis of 4-polydimethylsiloxane, 4-aminomethyl triazolo HEC 7

In a manner similar to the procedure stated in Section 2.8, **7** (Fig. 18; supporting information) was obtained (1.4 g).

Solid-state ^{13}C NMR (101 MHz, cross polarization technique): δ 142.57 (C_{11}), 124.46 (C_{10}), 103.60 (C_1), 82.00 ($C_{4,4'}$, $C_{3,3'}$, $C_{2,2'}$ (R ≠ H)), 74.82 ($C_{2,2'}$, $C_{5,5'}$, C_8), 70.71 (C_7, $C_{6,6'}$ (R ≠ H)), 51.91 (C_9).

Solid-state ^{13}C NMR (101 MHz, direct polarization technique): δ 142.57 (C_{11}), 124.46 (C_{10}), 103.60 (C_1), 82.00 ($C_{4,4'}$, $C_{3,3'}$, $C_{2,2'}$ (R ≠ H)), 74.82 ($C_{2,2'}$, $C_{5,5'}$, C_8), 70.71 (C_7, $C_{6,6'}$ (R ≠ H)), 49.95 (C_9), 40.26 (C_{12}), 1.49 (CH_3—Si).

Si elemental analysis (concentration of Si): theoretical (estimated) = 6.4%; found 4.02%.

FTIR spectrum showed disappearance of azide peak at ~2090 cm^{-1}.

2.10. Synthesis of 4-polydimethylsiloxane, 4-(n-butanoic acid) triazolo HEC 8

In a manner similar to the procedure stated in Section 2.8, **8** (Fig. 21; supporting information) was obtained (1.3 g).

Solid-state ^{13}C NMR (101 MHz, cross polarization technique): δ 148.03 (C_{11}), 124.26 (C_{10}), 103.50 (C_1), 82.55 ($C_{4,4'}$, $C_{3,3'}$, $C_{2,2'}$ (R ≠ H)), 74.72 ($C_{2,2'}$, $C_{5,5'}$, C_8), 71.1 (C_7, $C_{6,6'}$ (R ≠ H)), 51.52 (C_9), 41.24 (C_{12}), 34.48 (C_{14}), 25.96 (C_{13}), 1.58 (CH_3-Si).

Solid-state ^{13}C NMR (101 MHz, direct polarization technique): δ 108.82 (C_1), 82.45 ($C_{4,4'}$, $C_{3,3'}$, $C_{2,2'}$ (R ≠ H)), 70.90 ($C_{2,2'}$, $C_{5,5'}$, C_8, C_7, $C_{6,6'}$ (R ≠ H)), 51.42 (C_9), 40.75 (C_{12}), 33.89 (C_{14}), 26.06 (C_{13}), 18.42, 14.31, 1.49 (CH_3—Si).

Si elemental analysis (concentration of Si): theoretical (estimated) 6.4%; found 5.22%.

Table 1
Effect of the molar quantities of reagents on the degree of azidation.

Molar equivalents				Degree of azidation %
HEC	NaN_3	Ph_3P	CBr_4	
1	4	2	2	100
1	2	1	1	25
1	1	0.5	0.5	11
1	1	0.25	0.25	0

FTIR spectrum showed disappearance of azide peak at ~2090 cm^{-1}.

2.11. Synthesis of alkyne end capped PLA 9

Alkyne end capped PLA **9** was prepared by ring opening polymerization (ROP) of lactide using propargyl alcohol as an initiator and stannous octoate $Sn(Oct)_2$ as a catalyst (Albertsson & Gruvegard, 1995; Gilding & Reed, 1979; Nijenhuis, Grijpma, & Pennings, 1992).

LA (10 g, 69.4 mmol) was dissolved in degassed THF (25 mL) in a three-necked round-bottom flask, equipped with magnetic stirrer, reflux condenser and rubber seal septum. Propargyl alcohol (0.078 g, 1.39 mmol) and $Sn(Oct)_2$ (0.140 g, 0.347 mmol) dissolved in a minimum amount of toluene were added under N_2 atmosphere. The mixture was heated to reflux for 30 h. The polymer was precipitated into methanol, filtered and reprecipitated from CH_2Cl_2 into methanol. The polymeric material was filtered and dried in an oven at 40 °C under reduced pressure for a minimum of 24 h. The polymer product was brittle off-white powder (PLA_{100}) **9** (Fig. 24; supporting information), yield 73% (7.3 g).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.25–5.15 (m, 65H, H_5), 4.70 (m, 1H, H_8), 4.35 (m, 2H, H_3), 2.83 (bs, 1H, H_{10}), 2.50 (t, J = 2.5 Hz, 1H, H_1), 1.70–1.45 (m, 198H, $H_{6,9}$).

GPC: M_n = 5120 g mol^{-1}, M_w = 7900 g mol^{-1}, PDI = 1.5.

The M_n of **9** calculated from the integration of repeat unit (H_5) to that of alkyne unit (H_1) (Fig. 25; supporting information) and from GPC analysis was found to be 4800 g mol^{-1} (Table 1; supporting information). This indicates that all PLA chains are end-capped with alkyne units.

2.12. Synthesis of 4-polylactide triazolo HEC (HEC-g-PLA) 10

In a reaction flask, azido-deoxy HEC **1** (0.2 g, 0.00068 mmol; approximately 1.04 mmol of N_3 groups) was dissolved in DMSO (30 mL) at 70 °C. Mono-alkyne end capped PLA (PLA_{100}) (5.2 g, 1.04 mmol), copper (II) sulphate pentahydrate (26 mg, 0.104 mmol, in 0.5 mL of water) and sodium ascorbate (41 mg, 0.208 mmol, in 0.5 mL of water) were added and the mixture was stirred at 70 °C for 24 hr. The polymer was precipitated in ethanol (200 mL), filtered and washed three times with a mixture of ethanol/water solution (7:3) followed by ethanol. The polymer product was extracted with THF to remove any unreacted PLA. The polymer was finally dried under reduced pressure in an oven at 50 °C for 24 hr to give **10** (Fig. 27; supporting information) (1.1 g).

Solid-state ^{13}C NMR (101 MHz, cross polarization technique): δ 169.88 (C_{16}), 161.10 (C_{12}), 140.41 (C_{11}), 130.79 (C_{10}), 103.15 (C_1), 82.28 ($C_{4,4'}$, $C_{3,3'}$, $C_{2,2'}$ (R ≠ H)), 74.41 ($C_{2,2'}$, $C_{5,5'}$, C_8), 69.64 (C_7, $C_{6,6'}$ (R ≠ H)), 61.59 (C_{15}), 51.64 (C_9), 41.17 (C_{13}), 17.17 (C_{18}), 14.96 (C_{14}).

FTIR spectrum showed disappearance of azide peak at ~2090 cm^{-1}.

2.13. Synthesis of mono-alkyne terminated PEG methyl ether 11

A solution of mono-hydroxy terminated PEG methyl ether (M_n ~ 550) (10 g, 0.0182 mol) in dry THF (20 mL) was added dropwise to a slurry of NaH (458 mg, 19.1 mmol) in dry THF (20 mL) at 0 °C in a three-necked round-bottom flask, equipped with magnetic stirrer, thermometer, addition funnel and rubber seal septum, under N_2 atmosphere. The mixture was stirred for 30 min and propargyl bromide (80% in toluene, 2.1 mL, 0.0191 mol) was added *via* a syringe. The mixture was kept at 0 °C for further 30 min and then stirred at ambient temperature for 24 h. The reaction mixture was filtered and DCM was added to the filtrate which was then washed with HCl (1 N aqueous solution) followed by distilled water (3×). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to give **11** (Fig. 30; supporting information), yield 89% (9.315 g, 0.0162 mol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (d, J = 2.4 Hz, 2H, H_3), 3.59 (m, 48H, $H_{4,5}$), 3.32 (s, 3H, H_6), 2.41 (t, J = 2.4 Hz, 1H, H_1).

2.14. Synthesis of 4-methoxypolyethyleneglycol triazolo HEC (HEC-g-PEG) 12

In a reaction flask, azido-deoxy HEC **1** (0.2 g, 0.00068 mmol; approximately 1.04 mmol of N_3 groups) was dissolved in DMSO (30 mL) at 70 °C. Mono-alkyne terminated PEG methyl ether **11** (0.612 g, 1.04 mmol), copper (II) sulphate pentahydrate (26 mg, 0.104 mmol, in 0.5 mL of water) and sodium ascorbate (41 mg, 0.208 mmol, in 0.5 mL of water) were added and the mixture was stirred at 70 °C for 24 h. The polymer was precipitated in ethanol (150 mL), filtered and washed three times with a mixture of ethanol/water solution (9:1) followed by ethanol. The polymer was finally dried under reduced pressure in an oven at 50 °C for 24 h to give **12** (Fig. 32; supporting information), yield 78% (0.63 g).

^{1}H NMR (500 MHz, DMSO-d_6, at 80 °C) showed a peak at δ 7.95 (H_{10}).

^{13}C NMR (126 MHz DMSO-d_6, at 80 °C): δ 144.88 (C_{11}), 124.66 (C_{10}), 75.00–67.00 ($C_{2,2'}$, $C_{5,5'}$, C_8, C_7, $C_{6,6'}$ (R ≠ H), C_{13}, C_{14}), 64.48, 58.61 (C_{12}), 50.14 (C_9).

FTIR spectrum showed disappearance of azide peak at ~2090 cm^{-1}.

3. Results and discussion

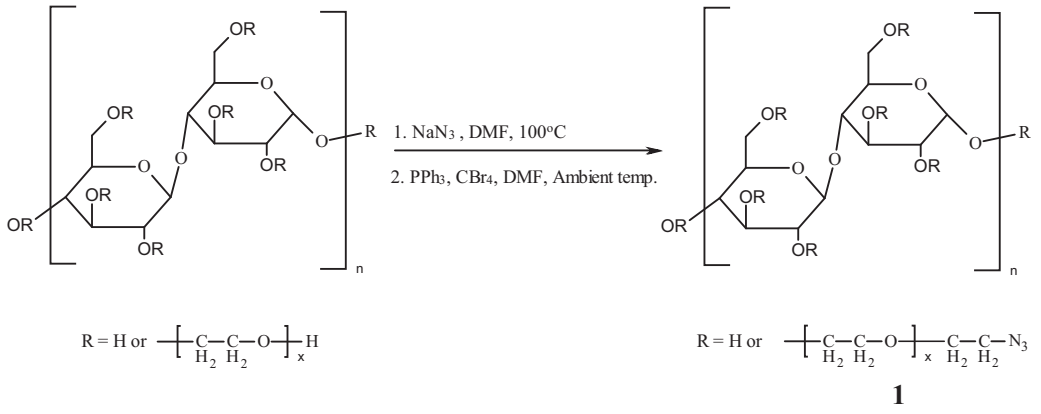
The synthetic approach adapted for the modification of HEC involved first a one pot azide functionalization at the primary carbon to give azido-HEC with complete substitution. The copper catalyzed azide–alkyne cycloaddition Click reactions of this fully azido-deoxy HEC with different functional molecules (ester, carboxylic acid and 1^{ry} amine) and/or macromolecules (PDMS, PLA and PEG) yielded a set of HEC modified derivatives with various compositions.

3.1. Azido-deoxy HEC 1

The selective azidation reaction of the primary hydroxyl groups using sodium azide was successfully carried out for the first time on HEC in a one pot reaction as shown in Scheme 1.

The FTIR spectra of the azido-deoxy HEC **1** (Fig. 1B) compared to that of HEC (Fig. 1A) showed a strong absorption at 2090 cm^{-1}, corresponding to C—N_3 stretching vibration. Moreover, there is a dramatic decrease in the intensity of the broad OH peak at ~3360 cm^{-1}, indicating the qualitative decrease of the hydroxyl functionalities of the HEC.

The ^{13}C NMR spectra of **1** (Fig. 2B; supporting information) compared to that of HEC (Fig. 2A; supporting information) showed a



Scheme 1. Synthesis of azido-deoxy HEC **1**.

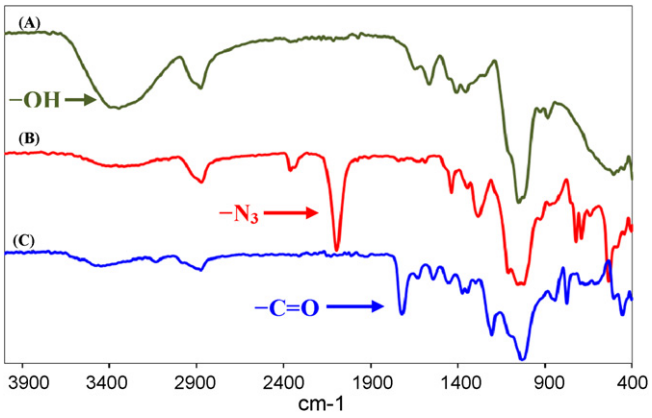


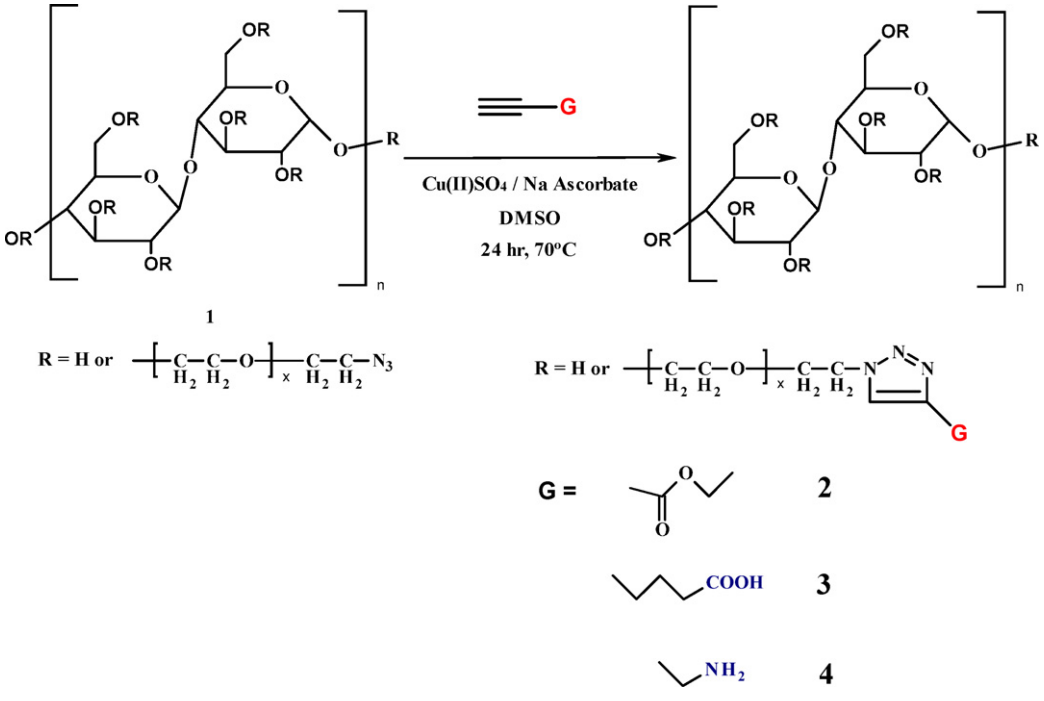
Fig. 1. FTIR spectra of (A) HEC, (B) azido-deoxy HEC **1** and (C) HEC with ethylcarboxy functionality **2**.

shift to lower δ-value for the CH_2 peak from 60.70 to 50.87 ppm, indicating the attachment of the azide group to the CH_2. The absence of any residual peak for the CH_2 attached to OH also indicated the full azide functionalization of HEC.

The control of the degree of azidation of HEC was investigated by varying the molar equivalents of NaN_3, Ph_3P and CBr_4. ^{13}C NMR spectroscopy was used to determine the approximate degree of conversion from primary alcohol to azide functionality. The approximate percentage of azidation was calculated from the ratios of the integration of the unreacted $-CH_2-OH$ peak to the newly formed $-CH_2-N_3$ peak (Fig. 3; supporting information). The results showed that the complete azide functionalization was achieved by treatment with 4-fold molar excess of NaN_3 and 2-fold molar excess of Ph_3P and CBr_4. The excess of NaN_3 was needed most likely to assist the solubility and to compensate its loss due to presence of moisture, Table 1.

3.2. 4-Ethylcarboxy triazolo HEC 2

HEC with ester functionality **2** was successfully prepared *via* Click reaction between fully azido-deoxy HEC **1** and ethyl



Scheme 2. Synthesis of HEC with neutral and ionic compositions; **2–4**.

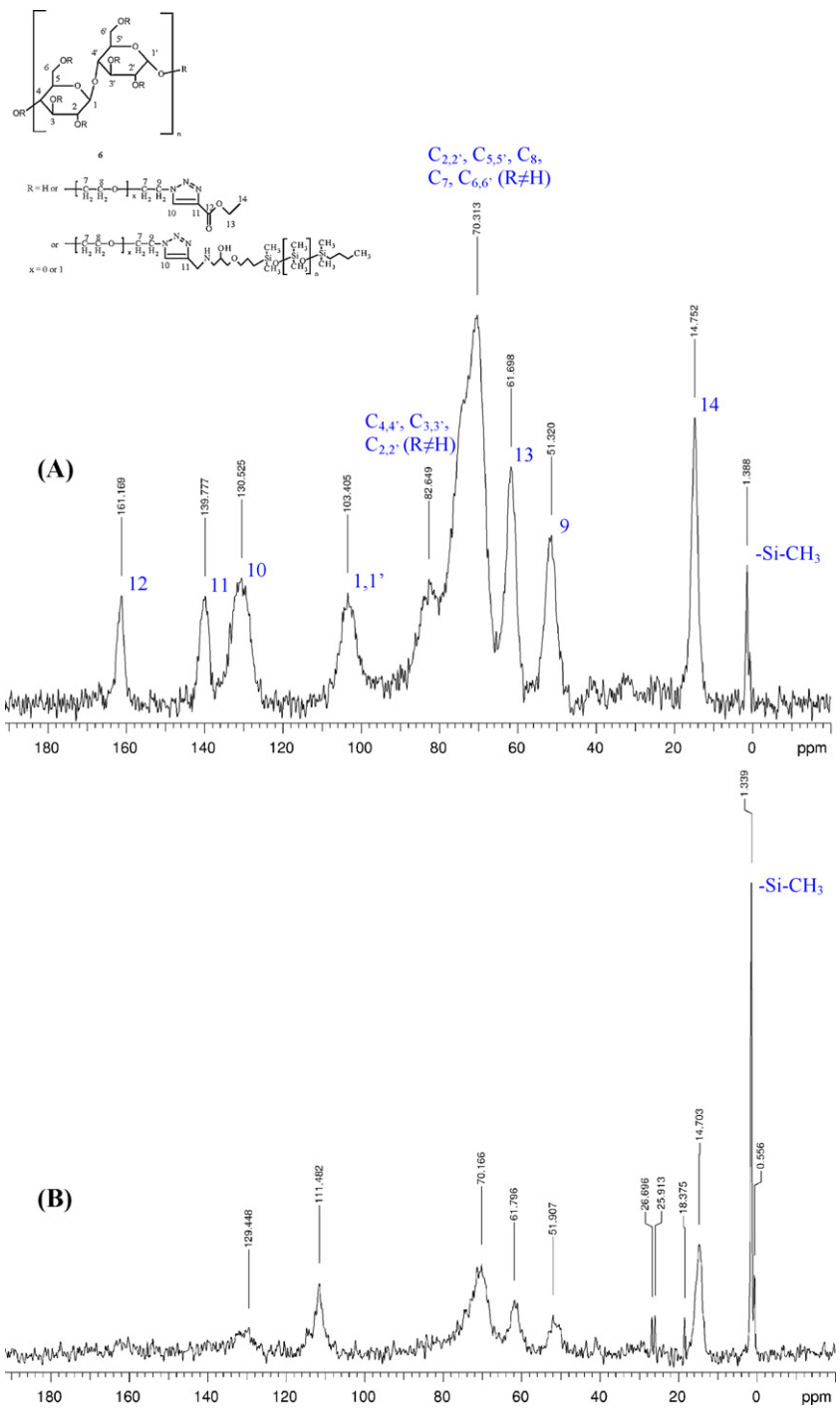


Fig. 2. Solid-state ^{13}C NMR spectra of HEC with PDMS grafts and ethylcarboxy **6** (A) CP exp. and (B) DP exp.

propiolate, Scheme 2. ^{13}C NMR spectrum of **2** (Fig. 5; supporting information) showed the appearance of two new peaks at 139.62 and 129.71 ppm, assigned to the triazole carbons (C_{11} and C_{10}). It also showed peaks due to the carbons of ethyl ester functional group (C_{12}, C_{13} and C_{14}). Moreover, the peaks due to the HEC backbone carbons were observed in the same regions and no other unassignable peaks were seen in the spectrum. The IR spectrum of **2** (Fig. 1C) compared to that of **1** (Fig. 1B) showed the complete disappearance of the azide peak at 2090 cm^{-1}, confirming the complete conversion to product **2**. It also showed appearance of a new peak at 1718 cm^{-1}, assigned to the carbonyl group of ethyl ester functionality on HEC.

3.3. HEC with ionic compositions

3.3.1. 4-(n-Butanoic acid) triazolo HEC **3**

The HEC with carboxylic acid functionality **3** was successfully synthesized *via* Click reaction between azido-deoxy HEC **1** and 5-hexynoic acid, Scheme 2. The product showed poor solubility in DMSO-d_6 and D_2O/NaOD and the addition of 2% of CD_3COOD did not greatly improve the solubility (Cimecioglu et al., 1994). Solid-state ^{13}C NMR spectrum of **3** (Fig. 7; supporting information) showed the appearance of two new peaks at 147.39 and 125.31 ppm, assigned to the triazole carbons (C_{11} and C_{10}). It also showed peaks due to the carbons of the carboxylic acid

functionality (C_{12}, C_{13}, C_{14} and C_{15}). Moreover, the peaks due to the HEC backbone carbons were observed in the same regions and no other unassignable peaks were seen in the spectrum. The IR spectra of **3** (Fig. 8B; supporting information) compared to that of **1** (Fig. 8A; supporting information) showed the complete disappearance of the azide peak at 2090 cm^{-1}, confirming the quantitative conversion to product **3**. It also showed appearance of a new peak at 1707 cm^{-1}, assigned to the carbonyl group of the carboxylic acid functionality on HEC.

3.3.2. 4-Aminomethyl triazolo HEC **4**

HEC with primary amine functionality **4** was also synthesized *via* Click reaction between azido-deoxy HEC **1** and propargyl amine, Scheme 2. Solid-state ^{13}C NMR spectrum of **4** (Fig. 10; supporting information) showed appearance of two new peaks at 144.26 and 125.46 ppm, assigned to the triazole carbons (C_{11} and C_{10}). It also showed a peak due to the carbon of the primary amine functionality (C_{12}). Moreover, the peaks due to the HEC backbone carbons were observed in the same regions. The peaks at 41.21 and 21.88 ppm are believed to be due to the bound ethanol which was used to precipitate the product. The IR spectra of **4** (Fig. 11B; supporting information) compared to that of **1** (Fig. 11A; supporting information) showed the complete disappearance of the azide peak at 2090 cm^{-1}, confirming the complete conversion to product **4**. Moreover, it showed a new peak at 1635 cm^{-1}, assigned to the primary amine functionality on HEC. The amine N—H absorption around 3000–3400 cannot be seen clearly because of the broad absorption due to OH.

Furthermore, HEC with both carboxylic acid and primary amine functionalities was successfully synthesized *via* Click reaction between azido-deoxy HEC **1** and a mixture of 5-hexynoic acid and propargyl amine (1:1 mol%).

3.4. HEC containing PDMS grafts

HEC with neutral and ionic compositions has been used for personal care products. Physical bound PDMS is usually added to enhance the delivery of certain properties (*e.g.* shininess and slipperiness). Undoubtedly, the formulations containing chemically bound compounds would offer better products and provide a diverse choice.

Over the years, it has been a challenge for the industrial sectors to bind PDMS chemically to HEC, due to the immiscibility of hydrophobic PDMS with hydrophilic HEC. Sequential Click reaction on HEC was therefore utilized to incorporate the PDMS grafts on the HEC backbone bearing other functionalities.

3.4.1. 4-Polydimethylsiloxane, 4-ethylcarboxy triazolo HEC **6**

A neutral (non-ionic) composition of HEC containing PDMS and ester functionality **6** was successfully achieved *via* sequential Click reactions. The azido-deoxy HEC **1** was subjected to Click reaction with PDMS-Alk **5** (Fig. 12; supporting information) first and then with ethyl propiolate, Scheme 3, aiming to graft ~25 wt% of HEC with PDMS. Hence, ~5 mol% (0.05 molar equivalents) of PDMS-Alk per azide groups on HEC was used. It was important to allow the Click reaction between PDMS-Alk and **1** to proceed to completion before the addition of ethyl propiolate. This was achieved by following the reaction by ^{13}C NMR.

Due to insolubility of the product, solid-state ^{13}C NMR spectroscopy was used; the cross polarization (CP) experiment which detects predominantly the rigid parts of the polymeric material (HEC backbone) and the direct polarization (DP) experiment which detects predominantly the flexible parts (grafted chains). The CP spectrum of **6** showed two new peaks at 139.78 and 130.53 ppm, assigned to the triazole ring, C_{11} and C_{10}, respectively. It also showed peaks due to the ethyl ester functionality, methyl groups of PDMS and HEC backbone (Fig. 2A). However, the DP solid-state ^{13}C NMR spectrum of **6** showed the peaks due to the methyl groups of PDMS with high intensity (Fig. 2B). The IR spectrum of **6** (Fig. 17B; supporting information) compared to that of **1** (Fig. 17A; supporting information) showed no residual peak at 2090 cm^{-1} for the azide group, confirming the complete conversion to product **6**. It also showed appearance of a new peak at 1720 cm^{-1}, assigned to the carbonyl group of the ethyl ester functionality on HEC. Furthermore, it showed two significant peaks at 1262 and 800 cm^{-1} due to the dimethyl siloxyl functionalities of PDMS chains on HEC backbone.

3.4.2. 4-Polydimethylsiloxane, 4-aminomethyl triazolo HEC **7**

PDMS grafted onto HEC bearing primary amine functionality **7** was also successfully prepared. This cationic composition was achieved by performing Click reaction between the azido-deoxy HEC **1** and the PDMS-Alk **5** followed by subsequent Click reaction between the remaining azide groups with propargyl amine, Scheme 3. The CP spectrum of **7** showed the successful Click reaction on HEC as demonstrated by appearance of two new peaks at 142.57 and 124.46 ppm, assigned to the triazole ring (Fig. 19A; supporting information). The DP spectrum of **7** showed the flexible PDMS grafts as well as the carbons of the primary amine functionality (Fig. 19B; supporting information). The IR spectrum of **7** (Fig. 20B; supporting information) compared to that of **1** (Fig. 20A; supporting information) showed no residual peak at 2090 cm^{-1} for the azide group, confirming the complete conversion to product **7**. It also showed appearance of a new peak at 1640 cm^{-1}, assigned to the primary amine functionality on HEC. Furthermore, it showed two significant peaks at 1258 and 800 cm^{-1} due to the dimethyl siloxyl functionalities of PDMS chains on HEC backbone.

3.4.3. 4-Polydimethylsiloxane, 4-(n-butanoic acid) triazolo HEC **8**

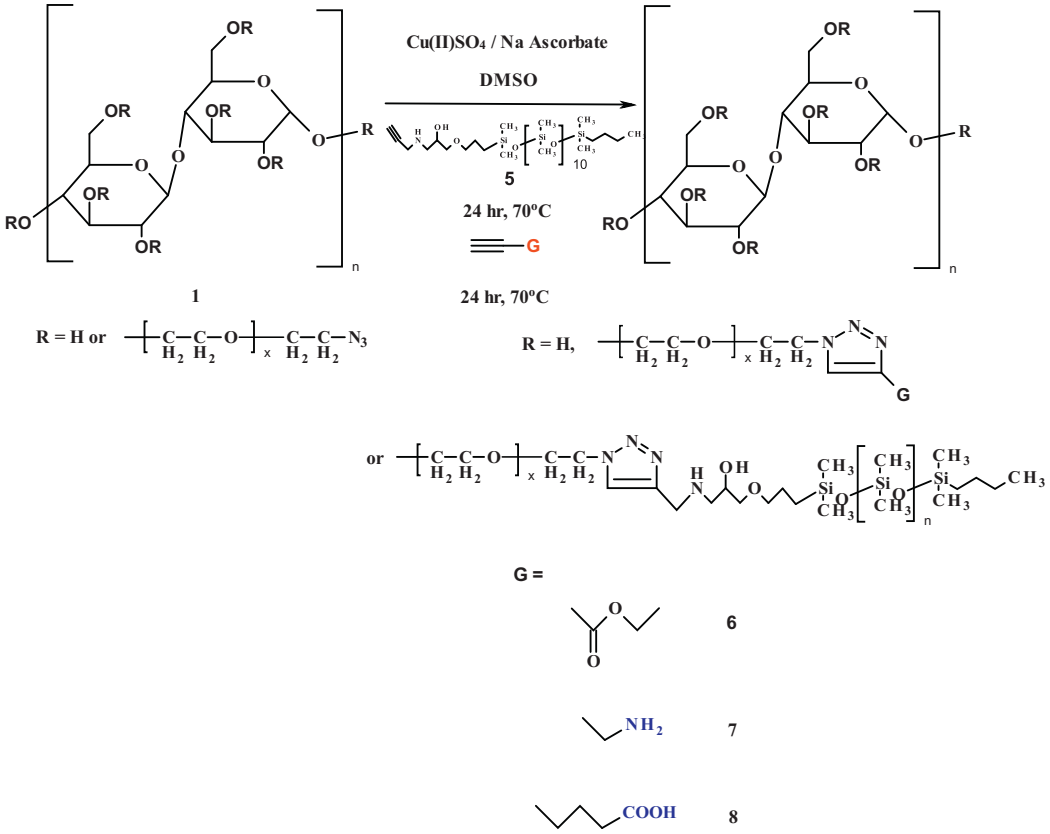
The anionic composition **8**, which involved PDMS grafted onto HEC bearing carboxylic acid functionality, was attempted by performing Click reaction between the azido-deoxy HEC **1** and the PDMS-Alk **5** followed by a subsequent Click reaction between the remaining un-clicked azide groups with 5-hexynoic acid, Scheme 3. The CP spectrum (Fig. 22A; supporting information) showed very weak peaks at the region of triazole ring and the DP spectrum (Fig. 22B; supporting information) showed the flexible grafted chains of PDMS as well as the carbons of the carboxylic acid functionality. The IR spectrum of **8** (Fig. 23B; supporting information) compared to that of **1** (Fig. 23A; supporting information) showed a considerable residual peak at 2090 cm^{-1} for the azide group, indicating that the Click reactions have not proceeded to completion. However, it showed a small peak at 1714 cm^{-1}, which is probably due to the carbonyl of the carboxylic acid functionality on HEC, as well as peaks at 1254 and 800 cm^{-1} due to the dimethyl siloxyl functionalities of PDMS chains on HEC backbone. The reaction was repeated with excess 5-hexynoic acid and the same results were obtained.

Furthermore, HEC with zwitterionic composition was prepared by performing Click reaction between the azido-deoxy HEC **1** and PDMS-Alk **5** followed by another Click reaction between the remaining azide groups on HEC and a mixture of propargyl amine and 5-hexynoic acid (1:1, mol%).

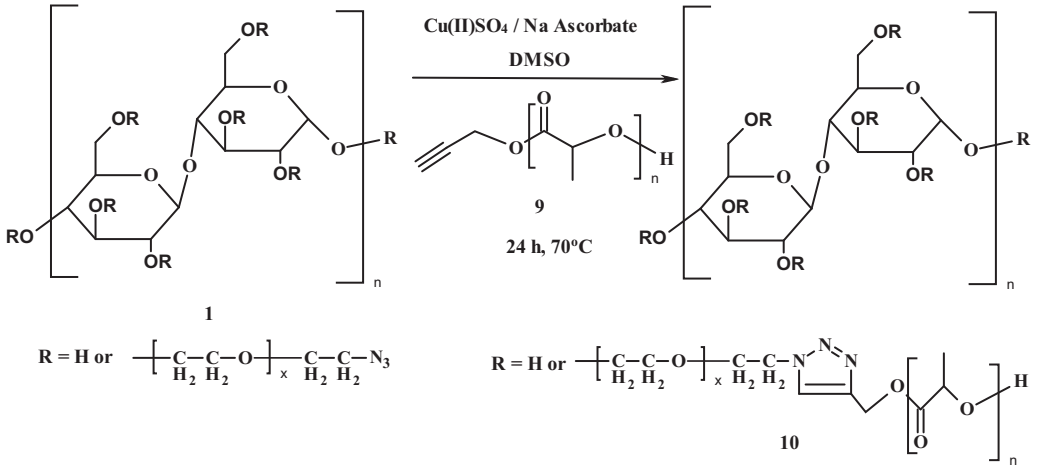
The silicon analysis of the products gave variable results due to difficulties in the accurate theoretical calculation of the Si as the commercially available HEC is not very well defined.

3.5. 4-Polylactide triazolo HEC 10

The alkyne end capped PLA **9** (Figs. 24–26; supporting information) was successfully grafted onto HEC backbone to produce HEC-g-PLA **10**, Scheme 4. The synthetic procedure was



Scheme 3. Synthesis of HEC containing PDMS grafts with neutral and ionic compositions; **6–8**.



Scheme 4. Synthesis of HEC with PLA grafts; **10**.

designed to ensure the formation of HEC with hydrophobic and biodegradable grafts/functionalities.

The CP spectrum of **10** showed the successful Click reaction on HEC as demonstrated by appearance of two new peaks at 140.41 and 130.79 ppm, assigned to the triazole ring (Fig. 28; supporting information). It also showed the peaks due to PLA grafts. The IR spectrum of **10** (Fig. 29B; supporting information) compared to that of **1** (Fig. 29A; supporting information) showed no residual peak at 2090 cm^{-1} for the azide group, confirming the complete conversion to product **10**. It also showed appearance of a new peak at 1742 cm^{-1}, assigned to the carbonyl group of the PLA grafts on HEC. Furthermore, it was observed that the intensity of the peak at ~3400 cm^{-1}, due to the OH groups (moisture and structure) was reduced.

PLA grafted HEC (HEC-g-PLA) **10** was prepared by capping all the azide functionalities on HEC with PLA, in order to increase the graft density and therefore to investigate the architecture of the resulting material. Analysis of tapping mode AFM images indicated that HEC formed uniform oval features, Fig. 3A and B. The multiple measurements of these hemi-ellipsoidal (rugby ball) features gave an average height of ~10 nm and width of ~50 nm.

AFM of HEC-g-PLA **10** revealed extended wormlike structures, Fig. 4A, which are characteristic for polymer brushes (Xia, Kornfield, & Grubbs, 2009). Measuring multiple polymer brushes gave an

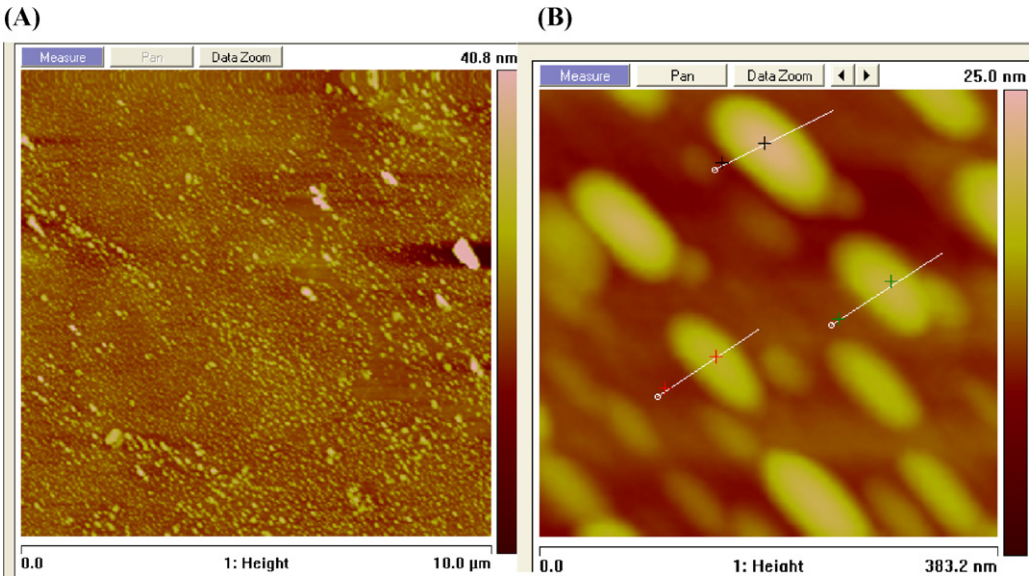


Fig. 3. Tapping mode AFM images of HEC: (A) 10 μm scale and (B) 383 nm scale with cross-sectional analysis.

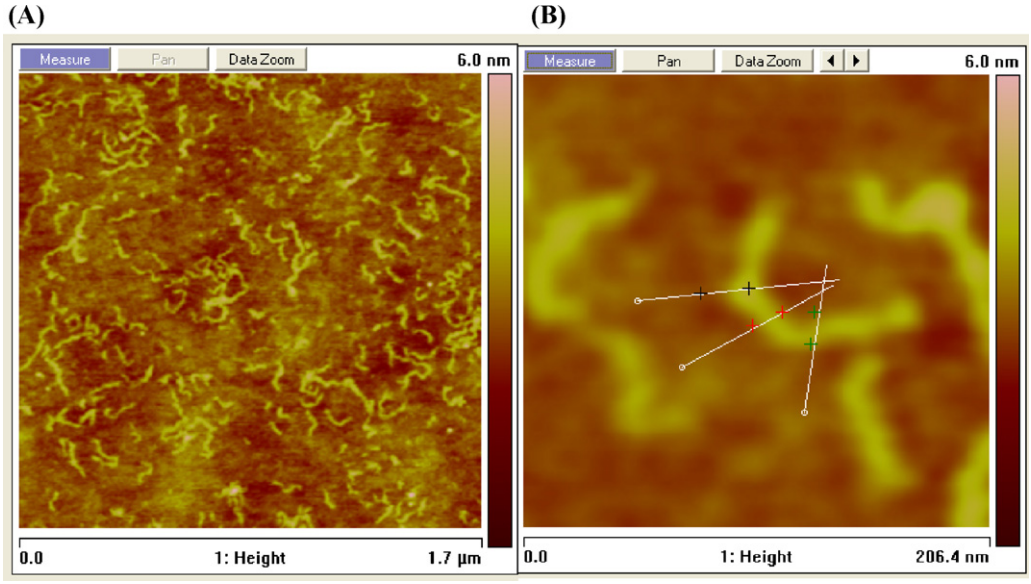


Fig. 4. Tapping mode AFM images of HEC with PLA grafts **10**: (A) 1.7 μm scale and (B) 206 nm scale with cross-sectional analysis.

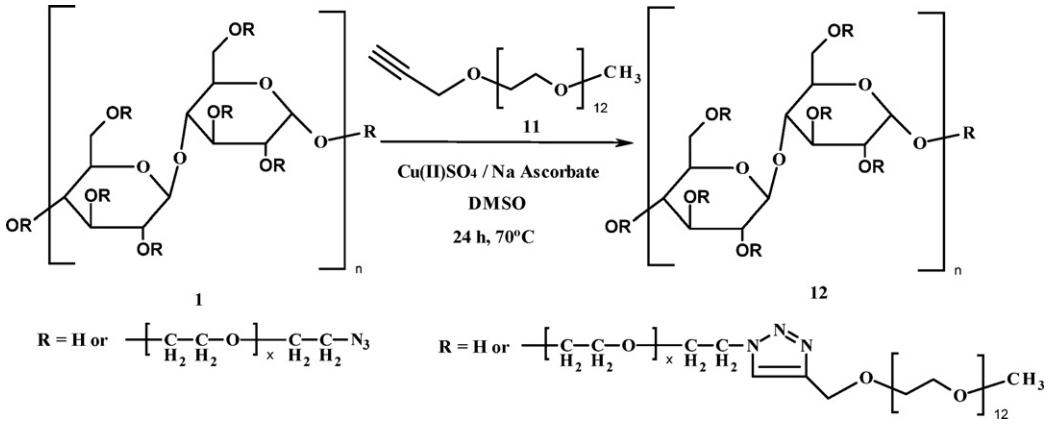
average contour height of ~2 nm and width of ~17 nm, as shown in Fig. 4B. Although, some partial hydrolysis of the PLA chain is possible but the IR clearly shows the presence of Carbonyl groups and NMR also clearly indicates the presence of PLA side chains. Therefore, the wormlike structures were anticipated to be due to the densely grafted nature of HEC-g-PLA. The formation of wormlike structures suggested that the HEC backbone exhibits an extended conformation with side chains stretched and flattened on the surface, presumably because of the steric repulsion between PLA side chains on repeating unit of the HEC backbone.

3.6. 4-Methoxypolyethyleneglycol triazolo HEC 12

The hydrophilically modified HEC was prepared *via* grafting with biocompatible PEG which was successfully grafted onto HEC backbone by Click reaction between the azido-deoxy HEC **1** and mono-alkyne terminated PEG methyl ether **11**. The synthetic procedure aimed to produce fully PEG grafted HEC (HEC-g-PEG) **12**, Scheme 5.

Mono-alkyne terminated PEG methyl ether **11** (Fig. 30; supporting information) was successfully prepared by etherification reaction between commercially available mono-hydroxyl terminated PEG methyl ether ($M_n \sim 550\,g\,mol^{-1}$) and propargyl bromide. The hydroxyl group of the mono-hydroxyl terminated PEG methyl ether was quantitatively converted into alkyne functionality to produce the alkyne terminated analogue, according to ^1H NMR spectroscopy. This was shown by the complete disappearance of the peak due to the hydroxyl groups in PEG at 2.92 ppm (Fig. 31A; supporting information). Moreover, the peaks due to the alkyne proton (H_6) at 2.40 and the CH_2 protons adjacent to the alkyne group (H_5) at 4.12 ppm, were observed (Fig. 31B; supporting information).

Grafting with PEG improved the solubility of HEC and hence it was possible to characterize the product by solution NMR in DMSO-d_6. The solution ^{13}C NMR spectrum of **12** showed clearly



Scheme 5. Synthesis of HEC with PEG grafts; **12**.

the successful Click reaction on HEC as demonstrated by appearance of two new peaks at 144.88 and 124.60 ppm, assigned to the triazole ring (Fig. 33; supporting information). It also showed the peaks due to PEG grafts (C_{13}, C_{14} and C_{15}) as well as those for HEC backbone. Moreover, there were no other unassignable peaks seen in the spectrum. The IR spectrum of **12** (Fig. 34B; supporting information) compared to that of **1** (Fig. 34A; supporting information) showed no residual peak at 2090 cm^{-1} for the azide group, confirming the complete conversion to product **12**. It also showed increase in the intensity and broadening of the peak due to OH groups at ~3500 cm^{-1}.

4. Conclusions

Click chemistry was utilized successfully on HEC to produce a new family of polysaccharide based materials. Using the coupling reaction between azido-deoxy HEC and several alkyne terminated compounds, different functionalities were introduced to the HEC backbone, yielding various neutral and ionic compositions. These included carboxylic acid and/or 1[ry] amine functionalities which are expected to dissociate in aqueous medium to generate polyelectrolytes or polyampholytes based on HEC. ^{13}C NMR spectroscopy was found to be an efficient method for quantitative determination of the azide functionalities on HEC and was used, along with FTIR, to demonstrate success of Click reactions and the conversion of azide functionalities to triazole rings. Solid state ^{13}C NMR spectroscopy was also a good characterization method for materials with poor solubility behavior.

Sequential Click reactions were also shown to be feasible on azido-deoxy HEC which enabled the preparation of novel compositions of PDMS grafted HEC. Thus, alkyne terminated PDMS was first prepared and then coupled with only about 5% of the azide functionalities on HEC. The remaining azide functionalities on HEC were then subsequently reacted with other alkyne terminated compounds. These compositions were designed, so that, HEC is chemically bonded to PDMS and also bears charged functionalities along its backbone, which are expected to find useful applications in personal care and cosmetics industries. PLA and PEG macromers were also grafted to HEC backbone using alkyne terminated precursors at different molar ratios to obtain hydrophobically and hydrophilically modified HEC materials. AFM analysis revealed that the PLA grafted HEC exhibited a brushlike architecture indicating that the HEC backbone is likely in an extended conformation with the PLA side chains stretching outward. The extended wormlike structures were not observed for other functionalized HEC prepared *via* Click reaction.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carbpol.2012.06.012.

References

Akimoto, T., Kawahara, K., Nagase, Y., & Aoyagi, T. (2000). Preparation of oligodimethylsiloxanes with sugar moiety at a terminal group as a transdermal penetration enhancer. *Macromolecular Chemistry and Physics*, *201*(18), 2729–2734 [doi:10.1002/1521-3935(20001201)201:18<2729::aid-macp2729>3.0.co;2-u]

Albertsson, A. C., & Gruvegard, M. (1995). Degradable high-molecular-weight random copolymers, based on epsilon-caprolactone and 1,5-dioxepan-2-one, with non-crystallizable units inserted in the crystalline-structure. *Polymer*, *36*(5), 1009–1016. http://dx.doi.org/10.1016/0032-3861(95)93601-h

Bombeli, T. Retrieved from <http://www.makingcosmetics.com/articles/20-polysaccharides-sugars-gums-in-cosmetics.pdf>

Brode, G. L., Kreeger, R. L., Partain, E. M., & Pavlichko, J. L. (1988). Polysaccharides for personal care applications. *Journal of the Society of Cosmetic Chemists*, *39*(1), 78.

Buschmann, H. J., & Schollmeyer, E. (2002). Applications of cyclodextrins in cosmetic products: A review [Review]. *Journal of Cosmetic Science*, *53*(3), 185–191.

Carrillo, F. V., Costello, M., Creutz, S. F. A., Deklippel, L., Henault, B., Joffre, E. J., et al. (2006). *WO2006127882. Dow Corning Corp and Genencor Int.*

Cimecioglu, A. L., Ball, D. H., Huang, S. H., & Kaplan, D. L. (1997). A direct regioselective route to 6-azido-6-deoxy polysaccharides under mild and homogeneous conditions. *Macromolecules*, *30*(1), 155–156.

Cimecioglu, A. L., Ball, D. H., Kaplan, D. L., & Huang, S. H. (1994). Preparation of amylose derivatives selectively modified at c-6–6-amino-6-deoxyamylose. *Macromolecules*, *27*(11), 2917–2922. http://dx.doi.org/10.1021/ma00089a004

Diaz, D. D., Punna, S., Holzer, P., McPherson, A. K., Sharpless, K. B., Fokin, V. V., et al. (2004). Click chemistry in materials synthesis. 1. Adhesive polymers from copper-catalyzed azide-alkyne cycloaddition. *Journal of Polymer Science Part A: Polymer Chemistry*, *42*(17), 4392–4403. http://dx.doi.org/10.1002/pola.20330

Gilding, D. K., & Reed, A. M. (1979). Biodegradable polymers for use in surgery—polyglycolic–poly(lactic acid) homopolymers and copolymers. 1. *Polymer*, *20*(12), 1459–1464. http://dx.doi.org/10.1016/0032-3861(79)90009-0

Goa, K. L., & Benfield, P. (1994). Hyaluronic-acid—a review of its pharmacology and use as a surgical aid in ophthalmology, and its therapeutic potential in joint disease and wound-healing. *Drugs*, *47*(3), 536–566.

Goddard, E. D., & Gruber, J. V. (1999). *Principles of Polymer Science and Technology Cosmetics and Personal Care*. New York: Dekker.

Hafren, J., Zou, W. B., & Cordova, A. (2006). Heterogeneous 'organoclick' derivatization of polysaccharides. *Macromolecular Rapid Communications*, *27*(16), 1362–1366. http://dx.doi.org/10.1002/marc.200600328

Halila, S., Manguian, M., Fort, S., Cottaz, S., Hamaide, T., Fleury, E., et al. (2008). Syntheses of well-defined glyco-polyorganosiloxanes by click chemistry and their surfactant properties. *Macromolecular Chemistry and Physics*, *209*(12), 1282–1290. http://dx.doi.org/10.1002/macp.200700629

Helms, B., Mynar, J. L., Hawker, C. J., & Frechet, J. M. J. (2004). Dendronized linear polymers via click chemistry. *Journal of the American Chemical Society*, *126*(46), 15020–15021. http://dx.doi.org/10.1021/ja044744e

Henkensmeier, D., Abele, B. C., Candussio, A., & Thiem, J. (2004). Synthesis and characterisation of terminal carbohydrate modified poly(dimethyl siloxane)s. *Macromolecular Chemistry and Physics*, *205*(14), 1851–1857. http://dx.doi.org/10.1002/macp.200400004

Jahn, M., Stoll, D., Warren, R. A. J., Szabo, L., Singh, P., Gilbert, H. J., et al. (2003). Expansion of the glycosynthase repertoire to produce defined manno-oligosaccharides. *Chemical Communications*, (12), 1327–1329. http://dx.doi.org/10.1039/b302380j

Joffre, E. J., Johnson, B. K., Swanton, B. J., & Starch, M. S. (2006). *WO2006127883. Dow Corning Corp and Genencor Int.*

Kobayashi, S., Uyama, H., & Kimura, S. (2001). Enzymatic polymerization. *Chemical Reviews*, *101*(12), 3793–3818. http://dx.doi.org/10.1021/cr990121l

Kolb, H. C., Finn, M. G., & Sharpless, K. B. (2001). Click chemistry: Diverse chemical function from a few good reactions. *Angewandte Chemie-International Edition*, *40*(11) [2004-+. doi: 10.1002/1521-3773(20010601)40:11<2004::aid-anie2004>3.0.co;2-5].

Krouit, M., Bras, J., & Belgacem, M. N. (2008). Cellulose surface grafting with polycaprolactone by heterogeneous click-chemistry. *European Polymer Journal*, *44*(12), 4074–4081. http://dx.doi.org/10.1016/j.eurpolymj.2008.09.016

Liebert, T., Hansch, C., & Heinze, T. (2006). Click chemistry with polysaccharides. *Macromolecular Rapid Communications*, *27*(3), 208–213. http://dx.doi.org/10.1002/marc.200500686

Lutz, J. F., Borner, H. G., & Weichenhan, K. (2005). Combining atom transfer radical polymerization and click chemistry: A versatile method for the preparation of end-functional polymers. *Macromolecular Rapid Communications*, *26*(7), 514–518. http://dx.doi.org/10.1002/marc.200500002

McAlindon, T. E., LaValley, M. P., & Felson, D. T. (2000). Efficacy of glucosamine and chondroitin for treatment of osteoarthritis—Reply. *Journal of the American Medical Association*, *284*(10), 1242.

Muzzarelli, R. A. A., & Muzzarelli, C. (2005). Chitosan chemistry: Relevance to the biomedical sciences. *Polysaccharides 1: Structure, Characterization and Use*, *186*, 151–209. http://dx.doi.org/10.1007/b136820

Nijenhuis, A. J., Grijpma, D. W., & Pennings, A. J. (1992). Lewis acid-catalyzed polymerization of l-lactide—Kinetics and mechanism of the bulk-polymerization. *Macromolecules*, *25*(24), 6419–6424. http://dx.doi.org/10.1021/ma00050a006

Quinn, K. J., & Courtney, J. M. (1988). Silicones as biomaterials. *British Polymer Journal*, *20*(1), 25–32. http://dx.doi.org/10.1002/pi.4980200106

Racles, C., & Hamaide, T. (2005). Synthesis and characterization of water soluble saccharide functionalized polysiloxanes and their use as polymer surfactants for the stabilization of polycaprolactone nanoparticles. *Macromolecular Chemistry and Physics*, *206*(17), 1757–1768. http://dx.doi.org/10.1002/macp.200500139

Racles, C., Hamaide, T., & Ioanid, A. (2006). Siloxane surfactants in polymer nanoparticles formulation. *Applied Organometallic Chemistry*, *20*(4), 235–245. http://dx.doi.org/10.1002/aoc.1051

Rinaudo, M. (2004). Role of substituents on the properties of some polysaccharides. *Biomacromolecules*, *5*(4), 1155–1165. http://dx.doi.org/10.1021/bm030077q

Rostovtsev, V. V., Green, L. G., Fokin, V. V., & Sharpless, K. B. (2002). A stepwise Huisgen cycloaddition process: copper(I)-catalyzed regioselective ligation of azides and terminal alkynes. *Angewandte Chemie-International Edition*, *41*(14), 2596–+.

Rutnakornpituk, M., Ngamdee, P., & Phinyocheep, P. (2005). Synthesis, characterization and properties of chitosan modified with poly(ethylene glycol)-polydimethylsiloxane amphiphilic block copolymers. *Polymer*, *46*(23), 9742–9752. http://dx.doi.org/10.1016/j.polymer.2005.08.051

Schulze Nahrup, J., Gao, Z. M., Mark, J. E., & Sakr, A. (2004). Poly(dimethylsiloxane) coatings for controlled drug release—polymer modifications. *International Journal of Pharmaceutics*, *270*(1-2), 199–208. http://dx.doi.org/10.1016/j.ijpharm.2003.10.007

Shao, B. M., Xu, W., Dai, H., Tu, P. F., Li, Z. J., & Gao, X. M. (2004). A study on the immune receptors for polysaccharides from the roots of Astragalus membranaceus, a Chinese medicinal herb. *Biochemical and Biophysical Research Communications*, *320*(4), 1103–1111. http://dx.doi.org/10.1016/j.bbrc.2004.06.065

Shey, J., Holtman, K. M., Wong, R. Y., Gregorski, K. S., Klamczynski, A. P., Orts, W. J., et al. (2006). The azidation of starch. *Carbohydrate Polymers*, *65*(4), 529–534. http://dx.doi.org/10.1016/j.carbpol.2006.02.009

Tsarevsky, N. V., Sumerlin, B. S., & Matyjaszewski, K. (2005). Step-growth click coupling of telechelic polymers prepared by atom transfer radical polymerization. *Macromolecules*, *38*(9), 3558–3561. http://dx.doi.org/10.1021/ma050370d

Wagner, R., Richter, L., Wersig, R., Schmaucks, G., Weiland, B., Weissmuller, J., et al. (1996). Silicon-modified carbohydrate surfactants. 1. Synthesis of siloxanyl moieties containing straight-chained glycosides and amides. *Applied Organometallic Chemistry*, *10*(6), 421–435 [doi: 10.1002/(sici)1099-0739(199608)10:6<421::aid-aoc495>3.0.co;2-c].

Wagner, R., Richter, L., Wu, Y., Weiland, B., Weissmuller, J., Reiners, J., et al. (1998). Silicon-modified carbohydrate surfactants VI: Synthesis of carbosilane, silane, polysilane and non-permethylated siloxane derivatives; the wetting behaviour of epoxy-modified precursor liquids on non-polar surfaces. *Applied Organometallic Chemistry*, *12*(1), 47–58 [doi: 10.1002/(sici)1099-0739(199801)12:1<47::aid-aoc670>3.3.co;2-1].

Witczak, Z. J., & Nieforth, K. A. (1997). *Carbohydrates in drug design*. New York: Marcel Dekker Inc.

Wu, P., Feldman, A. K., Nugent, A. K., Hawker, C. J., Scheel, A., Voit, B., et al. (2004). Efficiency and fidelity in a click-chemistry route to triazole dendrimers by the copper(I)-catalyzed ligation of azides and alkynes. *Angewandte Chemie-International Edition*, *43*(30), 3928–3932. http://dx.doi.org/10.1002/anie.200454078

Xia, Y., Kornfield, J. A., & Grubbs, R. H. (2009). Efficient synthesis of narrowly dispersed brush polymers via living ring-opening metathesis polymerization of macromonomers. *Macromolecules*, *42*(11), 3761–3766. http://dx.doi.org/10.1021/ma900280c

Zhang, W. Y., Yang, J. Y., Chen, J. P., Hou, Y. Y., & Han, X. D. (2005). Immunomodulatory and antitumour effects of an exopolysaccharide fraction from cultivated Cordyceps sinensis (Chinese caterpillar fungus) on tumour-bearing mice. *Biotechnology and Applied Biochemistry*, *42*, 9–15. http://dx.doi.org/10.1042/ba20040183