



Synthesis of a new smart temperature responsive glycopolymer via click-polymerisation

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ABSTRACT

A novel temperature responsive water-soluble glycopolymer was synthesised via copper wire-catalysed click-polymerisation. Di-hydroxyl terminated poly(ethylene glycol) was quantitatively alkyne end-capped to yield di-alkyne terminated poly(ethylene glycol) (DAT-PEG). 2,3,4,2',3',4'-hexa-*O*-acetyl-6,6'-diazido-6,6'-dideoxy- α,α -D-trehalose (HADADT) was prepared from the di hydrated α,α -D-Trehalose by tosylation/acetylation followed by azidation. Click-polymerisation reaction between DAT-PEG and HADADT was successfully carried out to produce an alternating glycopolymer with triazole rings as linkers in high yield. All the intermediates as well as the glycopolymer were fully characterised by NMR, MS, IR, SEC, TGA and DSC. The cloud point of the aqueous solution of glycopolymer was investigated by optical microscopy and UV–vis spectroscopy. The LCST was found to be within physiological range of about 39 °C, known as fever temperature.

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1. Introduction

The synthesis and development of smart polymers that can respond to external stimuli such as pH, temperature and light has been the main focus of current research [1]. Particular interests are materials that can undergo reversible conformational or phase changes in response to variations in temperature. The temperature responsive materials with low critical solution temperatures (LCST) in the physiological range (30–40 °C) attract much attention due to their potential biomedical applications and drug delivery systems [2–5].

Poly(*N*-isopropyl acrylamide) (PNIPAM) has been the most studied temperature responsive homopolymer exhibiting a soluble-insoluble changes in aqueous solutions due to its branched molecular architecture [6–8]. However, the homopolymers of PNIPAM exhibits LCST in water around 32 °C which is close to the lower end of the physiological range [9]. The efforts have been made to tune the LCST of

PNIPAM to around 37 °C by variation in hydrophilic or hydrophobic co-monomer content, for different biomedical applications [10]. Although, PNIPAM is known to be bio-compatible but strictly speaking it is not a bio-inert polymer. Indeed, the presence of multiple secondary amide functions in the molecule structure of PNIPAM may lead to the formation of cooperative H-bonding interactions with other amide containing polymers, in particular with proteins [11–12]. Therefore, the development of new classes of temperature responsive materials for *in vivo* delivery of various bioactive compounds remains a central challenge.

Recently, non-PNIPAM based materials have been developed to generate LCST materials [13–17]. Poly(ethylene glycol) (PEG) is a neutral, water soluble, biocompatible, non-toxic, non-immunogenic, FDA approved and probably the most widely used polymer in the biomedical applications [18–19]. Although, PEG undergoes a phase transition upon heating, the LCST ranges from 99 to 176 °C, depending on molecular weight [20–21]. This LCST is outside the physiological range and therefore limits its use as a temperature responsive material in medical applications [22]. However, it is possible to tune the LCST of PEG for some applications. It has been reported that the addition of addi-

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tives (such as urea, NaCl, and KH_2PO_4) affects the thermodynamic properties of aqueous PEG solutions [23]. Obviously, the applicability of this strategy to lower the LCST of PEG is limited because the use of external chemicals which are either undesirable or have to be removed for many applications.

In order to incorporate PEG in macromolecular constructions, two synthetic routes have been used. The first one is a macroinitiator approach, in which a PEG segment is transformed into an atom transfer radical polymerisation (ATRP) initiator [24–28]. The second route involves direct polymerisation of a radically polymerisable PEG macromonomer such as oligo(ethylene glycol) methacrylate (OEGMA) [29–30]. The resulting poly(oligo(ethylene glycol) methacrylate) (POEGMA) with side chains consisting of 8/9 ethylene oxide units exhibited an LCST in water around 90 °C, which is very high for medical applications [31]. Moreover, polymers of 2-(2'-methoxyethoxy)ethyl methacrylate (MEO₂MA) with only two ethylene oxide units as side groups have been reported that exhibited LCST around 26 °C [32], which is out of the physiological range and therefore, prohibits *in vivo* applications. Recently, copolymers of MEO₂MA and OEGMA have been prepared *via* ATRP with LCST in the range of 28–90 °C, depending on the composition of the copolymer [14,33–34]. It should be noticed that all temperature responsive materials mentioned above are in fact macromolecular brushes with PEG as side chains [35]. A series of linear copolymers of ethylene and ethylene oxide has been reported with LCST in the range of 7 to 70 °C in water by controlling the hydrophobic/hydrophilic balance [36–37]. The major disadvantage of all approaches discussed above is that PEG segments are attached through a hydrolysable ester and amide linkage, which is, in most cases, problematic for applications in aqueous media. Therefore, developing stable (non-hydrolysable) linkers is crucial if the range of applications for these polymers is to be expanded.

1,2,3-triazole linkers formed by click reaction, specifically the copper(I)-mediated 1,3-dipolar cycloaddition of azides and alkynes, have been reported to be extremely water soluble, making *in vivo* administration much easier. Their electronic properties are very similar to amide bonds, but they are not subject to the same hydrolysis reactions [38]. The triazoles are also stable in typical biological conditions, which tend to be aqueous and mildly reducing in nature [39]. Another advantageous property of the triazoles is that they are extremely rigid, ensuring that the two linked components are not interacting with each other [38]. Moreover, the high selectivity, reliability, and tolerance to a broad range of functional groups and reaction conditions make click reaction a powerful strategy for elaborating polymer architectures [40–41].

Recently, azide terminated PEG chains and 1-decyl azides have been grafted onto polyglycolide containing pendant acetylene groups. The result of the work in terms of LCST behaviour is unclear but it claimed that it was possible to produce biodegradable LCST materials with tunable transition temperatures in a range from 25 to 65 °C by adjusting the length and mole fraction of alkyl to PEG side chains [13]. Moreover, click chemistry has been used to couple the azide containing PNIPAM with alkyne containing PEG and alkyne-functionalised C₆₀ to produce self-assembled hybrid

nanoparticles that retained the thermoresponsiveness of PNIPAM [42]. The work involves difficult synthesis and produces materials which are exactly the same as PNIPAM in terms of their temperature responsive behaviour.

We became interested in developing a new temperature responsive material with LCST well within the physiological range, by a simple and efficient route. In the work here we demonstrate, for the first time, the use of click chemistry as a polymerisation technique to copolymerise hydrophobic and hydrophilic components based on modified trehalose and PEG to produce a linear water-soluble temperature responsive glycopolymer. The components involved in the design of our temperature responsive glycopolymer are schematically shown in Fig. 1. The design contains trehalose moiety, which is a symmetrical disaccharide found in many living organisms, including mushrooms, insects, and yeasts [43]. Its unique combination of biocompatibility and biodegradability makes it a promising monomer for the production of linear polymers [44–46]. Moreover, the free hydroxyl groups in trehalose can be protected to promote its hydrophobicity in the polymer chain. The designed material also contains PEG segments as hydrophilic and biocompatible groups. The hydrophobic (protected trehalose) and the hydrophilic (PEG) segments are linked together via the stable (non-hydrolysable) 1,2,3-triazole rings. These ideal linking groups are produced by click-polymerisation technique. In order to reduce/eliminate copper contamination, the click-polymerisation was catalysed by copper wire [47].

2. Experimental part

2.1. Materials

α,α -D-Trehalose dihydrate and poly ethylene glycol (PEG) with M_n = 200, 600, and 1000 gmol^{-1} were purchased from Sigma–Aldrich and fully characterised by NMR. All reagents used in the synthesis were also 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. Measurements

¹H-NMR spectra were recorded on a Varian Mercury 400 spectrometer at 400 MHz. Chemical shifts are quoted in ppm, relative to tetramethylsilane (TMS), as the internal reference. ¹³C-NMR spectra were recorded at 101 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 CDCl₃ (77.55 ppm). The following abbreviations are used in

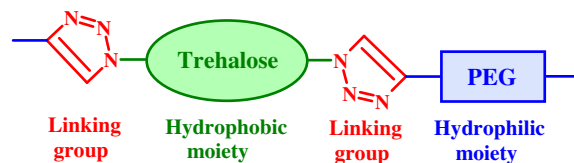


Fig. 1. Schematic presentation of the designed temperature responsive glycopolymer.

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