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The Preparation of Graft Copolymers of Cellulose and Cellulose Derivatives Using ATRP Under Homogeneous Reaction Conditions

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Abstract

In this comprehensive review, we report on the preparation of graft-copolymers of cellulose and cellulose derivatives using atom transfer radical polymerization (ATRP) under homogeneous conditions. The review is divided into four sections according to the cellulosic material that is graft-copolymerised; i) cellulose, ii) ethyl cellulose, iii) hydroxypropyl cellulose and iv) other cellulose derivatives. In each section, the grafted synthetic polymers are described as well as the methods used for ATRP macro-initiator formation and graft-copolymerisation. The physical properties of the graft-copolymers including their self-assembly in solution into nanostructures and their stimuli responsive behaviour are described. Potential applications of the self-assembled graft copolymers in areas such as nanocontainers for drug delivery are outlined.

I. Introduction

Cellulose is the most abundant biopolymer on earth as it represents about fifty per cent of biomass, with an annual production estimated to be 10^{11} tons per year[1-3]. Cellulose is

synthesised by some plants, animals, bacteria and also algae. In plants, cellulose is a major component of the rigid cell walls[4-6] . Cellulose is defined as long polymer chains of β-D-anhydroglucopyranose units (AGU units). The β-D-glucoses are covalently bonded together by the linkage between the C1 anomeric carbon and the C4 oxygen atom, providing β-1,4-glycosidic bonds[7]. The structural aspect of cellulose defines its properties. The supra-molecular aspect is mainly characterised by two hydrogen-bonding networks: the intramolecular and intermolecular H-bonding networks which are respectively between and within chains. These networks are responsible for the insolubility of cellulose in common solvents[3, 8-10]. Although cellulose is a low cost material with low density (in its unpurified state), biodegradability, high strength and high thermal stability, its applications have been mainly limited to the paper and textile industries due to its poor solubility. Cellulose has been chemically modified to impart new properties such as solubility in organic solvents, crease resistance, dimensional stability, thermoplasticity and antimicrobial properties[6, 9, 11]. The reactivity of cellulose arises from the presence of hydroxyl groups. Two secondary alcohols are present at the C2 and C3 positions and one primary alcohol at the C6 position, where the –OH reactivity follows the order: $-OH_{C6} >> -OH_{C2} > -OH_{C3}$[12, 13]. Etherification, esterification and oxidation reactions of the hydroxyl groups have been used to create a range of new cellulosic materials. These commercial derivatives include hydroxyethyl cellulose (HEC), carboxymethyl cellulose (CM Cell), ethyl cellulose (EC), hydroxypropyl cellulose (HPC) and others (Figure 1). They are defined by the degree of substitution (DS) which ranges from 0 to 3 depending on the number of hydroxyl groups in the AGU units that have been modified. Different methods, including NMR spectroscopy[14, 15] and elemental analysis[16], have been used to measure DS. For instance, DS is directly calculated from the ^{1}H NMR integral ratio of one of the protons assigned to the added functional group to a proton assigned to the cellulose backbone. Meanwhile, the content of carbon, hydrogen, nitrogen or any other

halogens present in the newly prepared derivatives can be measured by elemental analysis and the resulting elemental content permits further the estimation of the DS.

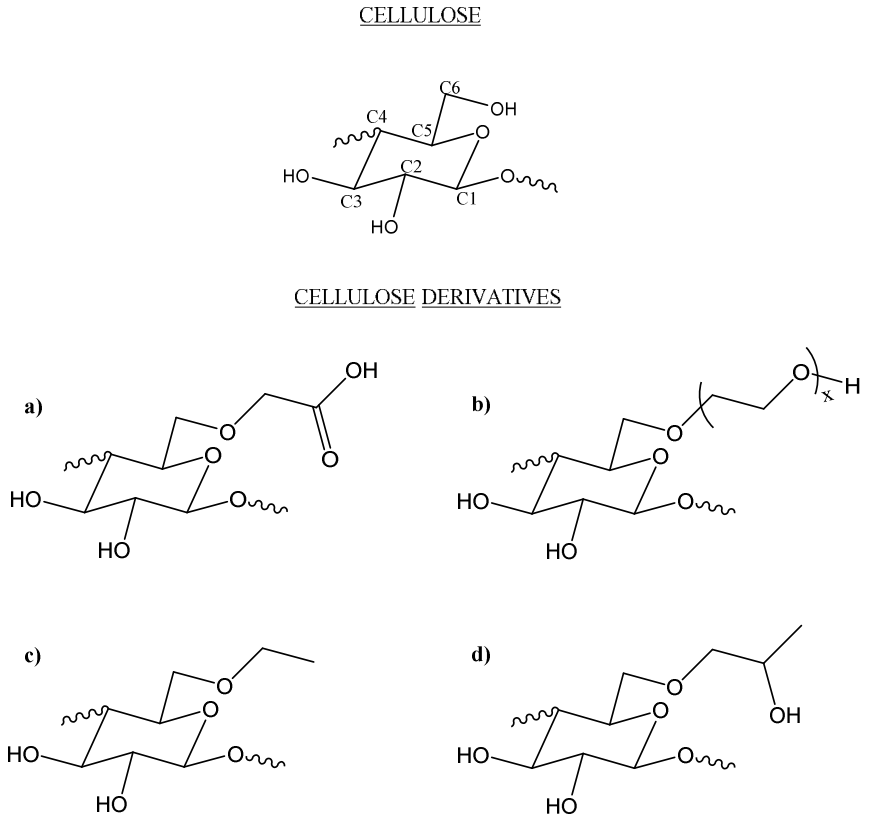

Figure 1: Molecular structure of cellulose and cellulose derivatives (considering a DS of 1 at the C6 position); a) CM Cell b) HEC c) EC and d) HPC

The chemical modification of cellulose and its derivatives has been performed under both heterogeneous and homogeneous conditions. Heterogeneous conditions refer to situations where cellulose is not dissolved in the reaction medium so the reaction occurs at the interface between the solid and liquid phases resulting in modification only at the surface. Cellulose fibers[17, 18], membranes[19, 20] and nano-whiskers[21, 22] have all been modified under heterogeneous conditions. Homogeneous conditions are defined by the dissolution or, at least, by the swelling of cellulose in the reaction medium resulting in modification of the entire cellulose molecular structure. This remains extremely challenging because of both the high

molecular weight of cellulose and the intra/inter-H bonding networks which define the cellulose solid-state structure and limit considerably its solubility in common solvents. Recently, Olsson and Westman[23] reviewed advances in methods for the dissolution of cellulose. Water swells cellulose because the water molecules interact with the cellulose backbone but do not break fully the H-bonding interactions. Cellulose is partially soluble in alkali solution where the concentration of the solution needs to be at least 10 % w/w. The addition of species including PEG, urea or thiourea enhances the solubility of cellulose in alkali solution at low temperature by limiting the aggregation of cellulose chains. Furthermore, the DMAc/LiCl system has been used commonly to dissolve cellulose. It involves interaction between the hydroxyl groups of cellulose and the Cl anion, resulting in the formation of "bridges" between cellulose and the macro-cation $[DMAc\text{-}Li]^+$. However, this process requires the prior-elimination of water which prevents its use in industry. Ionic liquids (ILs) such as BMIMCl dissolve cellulose due penetration of the anion into the cellulose structure, breaking the H- bonding networks.

Recently, chemical modification of cellulose by polymer grafting has generated much interest because it combines two polymers, one of which is a bio-polymer, in one unique material, where the combination is expected to produce new materials properties. Different grafting approaches are described in the literature[13, 24, 25]: the "grafting through" approach is characterised by the polymerisation of a macro-monomer in the presence of a low molecular weight monomer; the "grafting to" approach involves attaching a pre-synthesised polymer chain to the cellulose backbone; the "grafting from" approach involves the polymerisation of monomeric species from the backbone. The "grafting from" approach is the most popular for modifying cellulose. Free radical polymerisation is the main method used to graft synthetic polymers onto cellulose, where the backbone has been initiated by hydrogen abstraction[26, 27], single electron transfer[28], irradiation[29, 30] or other methods[13, 24, 31]. However, these methods

also result in the formation of ungrafted homopolymer chains and give no control over the density or the length of the grafts. In recent years, controlled radical polymerisation (CRP) processes have been used to create well-defined cellulose-based graft-copolymers including a narrow molecular weight distribution of the grafts. The most commonly used CRP process is Atom Transfer Radical Polymerisation (ATRP)[32, 33] because of the straightforward preparation of cellulose macro-initiators from the reaction between one of hydroxyl groups present on the cellulose backbone and commercially available acyl chlorides or bromides. Compared to other CRP techniques, ATRP produces polymers with the narrowest molecular weight distribution and the required reagents such as catalysts and ligands are commercially available at low cost. On the other hand, commercially available transfer agents for Reversible Addition Fragmentation Transfer (RAFT) polymerisation[34] can be quite expensive and may have to be synthesised for specific targets, which adds steps to the fabrication process. Furthermore, the use of RAFT polymerisation produces polymers with possibly undesirable colour and/or odour, due to the presence of sulphur from the chain transfer agent[35]. This could be a constraint in some applications. However, this problem can potentially be solved by removing RAFT agent residues from chain ends; recently, Willcock *et al*.[36] reviewed the different methods by which this can be achieved, including for instance thermal elimination, aminolysis and hetero-Diels-Alder reactions. It should be pointed out that ATRP also has some inherent disadvantages; it has to be conducted in a rigorously oxygen-free environment and the use of copper can be a problem as it can be difficult to remove. Furthermore, some solvents and vinyl monomers deactivate the catalyst resulting in unsuccessful or uncontrolled polymerisation.

The modification of cellulose and its derivatives by ATRP is reviewed in this article, with a focus on ATRP under homogeneous conditions. This has received much less attention than the alternative approach of grafting onto the surface of solid cellulosic materials (selected

relevant references are cited here [37, 38, 39]). The review is arranged into sections based on the parent cellulose derivative undergoing chemical modification. The modifications involve principally two steps. The first is the preparation of macro-initiators with a certain DS which determines the graft-density of the resulting graft-copolymer. In the second step, these macro-initiators were used to initiate the ATRP of various monomers resulting in the formation of graft-copolymers of cellulose and cellulose derivatives. The efficiency of the polymerisation has been highlighted using the monomer conversion (%) which permits a determination of the chain length, and the livingness of the polymerisation has been evaluated by measuring dispersity ($Đ_M$).

II. Graft-copolymers of cellulose

In this section, studies on the graft-copolymerisation from cellulose will be reviewed. The process of the activation of the cellulose backbone will be described, and the influence of the reaction conditions on the DS will be highlighted, for instance the choice of solvents used to dissolve the cellulose starting material. Moreover, the preparation in a controlled manner of graft-copolymers from monomers such as methyl methacrylate (MMA), N,N-dimethyl acrylamide (DMA), 3-ethyl-3-methacryloyloxy-methyloxetane (EMO), styrene (St), N-isopropyl acrylamide (NIPAAM) and N,N-dimethylamino-2-ethyl methacrylate (DMAEMA) and the characterisation of the resulting polymers will be detailed. Ring Opening Polymerisation (ROP) will be mentioned as it was used in combination with ATRP for preparing graft block copolymers from ε-caprolactone (CL) or L-lactide (LLA). The properties of these graft-copolymers including aggregation and responses to external stimuli will be discussed.

The first work related to cellulose modification using the ATRP process under homogeneous conditions was reported by Chang *et al.*[40] in 2008, who described the graft-copolymerisation of various monomers. The macro-initiator, Cl-Cell was synthesised from an excess of chloroacetyl chloride in a mixture of dimethylacetamide (DMAc)/LiCl in the presence of pyridine. The use of DMAc/LiCl enhanced the homogeneity of the reaction medium due to the interruption of the H-bonding networks of the cellulose structure, and led to a DS value of 2.1 after 10 h of reaction at room temperature. The ATRP of methyl methacrylate (MMA) or 3-ethyl-3-methacryloyloxy-methyloxetane (EMO) was performed using multidentate amines as ligands such as *N,N,N′,N′,N″*-pentamethyldiethylenetriamine (PMDETA) and tetramethylethylenediamine (TMEDA) and copper (I) bromide (CuBr) as catalyst. The influence of the solvent on the process was investigated using solvents including DMSO, anisole and DMF. DMSO and anisole were found to be less suitable than DMF for the ATRP process because they interacted with the CuBr/ligand system resulting in deactivation of the polymerisation process. Polymerisation of MMA and EMO was conducted at 130 ºC for around 20 h, long reaction times being necessary to reach the maximum yield. The ratio of initiator to catalyst, ligand and monomer ([I]/[C]/[L]/[M]) required to give maximum yield was 1/1/3/9 and 1/1/3/60 for the polymerisation of EMO and MMA respectively. The chloride at the chain end of PMMA-g-Cell and PEMO-g-Cell was used to activate the ATRP of EMO and MMA respectively to form copolymers (Figure 2), however, the ATRP of EMO onto PMMA-g-Cell was more efficient than that of MMA onto PEMO-g-Cell. The catalyst was copper (I) chloride (CuCl) for both graft-copolymerisations; TMEDA was used for graft-copolymerising EMO onto Cl-PMMA-Cell whereas PMDETA was chosen for graft-copolymerising MMA onto Cl-PEMO-Cell. For an optimum yield, a temperature of 70 °C and a ratio [I]/[C]/[L]/[M] of 1/1/3/60 were used for both polymerisations, however, the

reaction time was twice as long for graft-copolymerising EMO than MMA. The extent of control of the polymerisations was not determined.

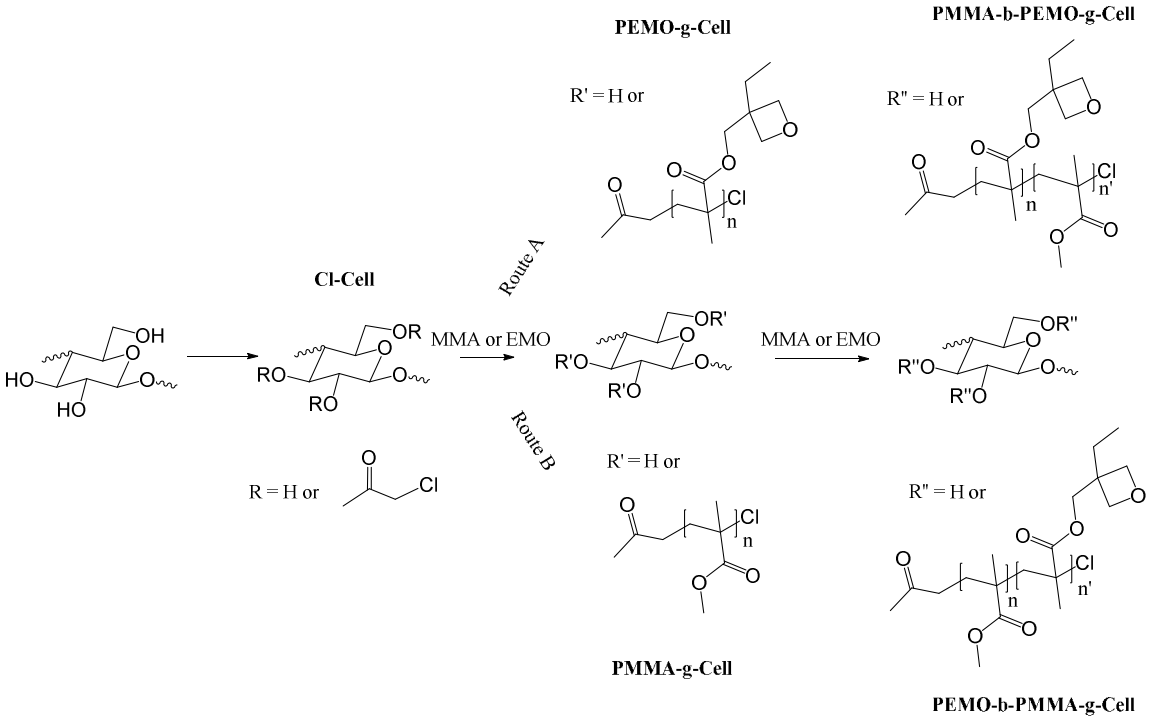

Figure 2: Preparation of graft-copolymers PMMA-b-PEMO-g-Cell (Route A) and PEMO-b-PMMA-g-Cell (Route B) from the macro-initiator, Cl-Cell.

The same authors investigated the preparation of copolymers by ROP and ATRP. The ROP of CL or LLA and ATRP of MMA or EMO were performed simultaneously by using a Cl-Cell, PMMA-g-Cell or PEMO-g-Cell initiator (Figure 3). Modification of cellulose was confirmed by Thermal Gravimetric-Differential Thermal Analysis (TG-DTA), Differential Scanning Calorimetry (DSC) and Wide-Angle X-ray Diffraction (WAXD) analyses.

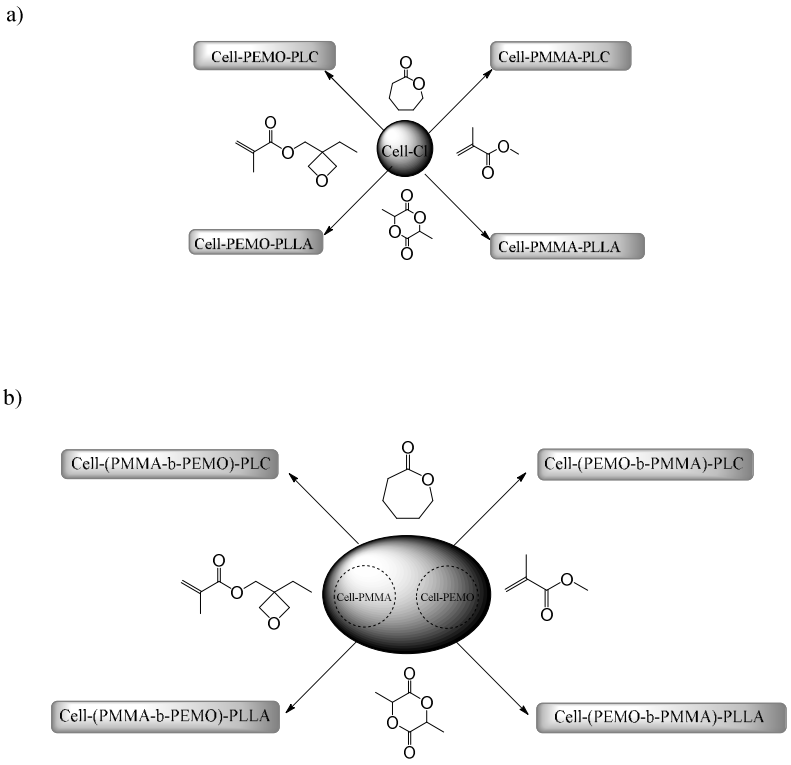

Figure 3: Preparation of graft-copolymers combining ATRP and ROP processes using macro-initiators a) Cl-Cell b) PMMA-g-Cell and PEMO-g-Cell.

Chun-xiang *et al.*[41] reported the preparation of the macro-initiator Cl-Cell (from chloroacetyl chloride) and subsequent graft-copolymerisation of MMA using an ionic liquid as the reaction medium. The DS of the macroinitiator increased when the temperature was increased, however, above 50 °C there was evidence of hydrolysis of the cellulose backbone. The highest DS reached was 1.8 which is lower than that achieved by the method of Chang *et al.*[40]. This is explained by the decrease of the amount of reactant chloroacetyl chloride compared to AGU. MMA was graft-copolymerised under mild reaction conditions, and the $Đ_M$ of the product ranged from 1.5 to 1.8, depending on the reaction conditions, which were chosen to limit the radical-radical coupling of the propagating chains. A bidentate ligand, bpy, was also used and the first time the polymerisation was conducted in an ionic liquid at 70 °C for 5 h. A maximum of 15% of monomer conversion was reached with a $Đ_M$ of 1.5 for a ratio

[I]/[C]/[L]/[M] equal to 1/1/1/300. The graft copolymers were able to form aggregates in solution.

Further work was carried out by Meng *et al.*[42] who reported the graft-copolymerisation of MMA and styrene (St) onto cellulose. The macro-initiator Br-Cell was prepared from bromoisobutyryl bromide under homogeneous conditions using 1-allyl-3-methyl-imidazolium chloride ([AMIM]Cl) and the influence of the reaction conditions on the DS were evaluated. Increases in both the molar ratio of AGU/Br and reaction time led to an increase in substitution of the hydroxyls with bromo-ester groups, and thus, the degree of functionalization, which affected the graft-copolymer solubility. The highest DS for Br-Cell was 0.72 using a ratio of AGU to Br equal to 1/5. This is lower than that reported by Ifuku *et al.*[43] because of a lower amount of reactant, a shorter reaction time and/or absence of catalyst. MMA and/or St were then graft-copolymerised from the macro-initiator by ATRP under optimised experimental conditions using bpy/CuCl, butanone as solvent, 3h reaction time, a temperature of 70 °C and a ratio [I]/[C]/[L]/[M] of 1/1/2/200. These conditions resulted in a monomer conversion of 28% and a $Đ_M$ of 1.4 as determined by GPC of the hydrolysed grafted chains, which is the lowest value of $Đ_M$ obtained for the ATRP of MMA onto cellulose under homogeneous conditions. The authors were the first to report the ATRP of styrene onto cellulose, using the same catalyst system. However, the reaction time was shorter (2 h), the temperature was higher (110 °C) and the polymerisation was conducted in dioxane as reaction medium. A relatively low monomer conversion, approximately 14%, and a $Đ_M$ of 1.5 were obtained. The authors investigated the diameter, conformation and morphology of PMMA-g-Cell aggregates using static and dynamic light scattering (SLS and DLS) and transmission electron microscopy (TEM) respectively.

In 2011 Xin *et al.*[44] prepared the graft-copolymer PMMA-g-Cell with the highest monomer conversion reported in the literature. The macro-initiator, Br-Cell with a DS of 0.7

was synthesised following the same procedure of Sui *et al.*[45] and thus ATRP of MMA onto $Br_{0.7}$-Cell was investigated in DMF. The importance of both concentration and temperature on the extent of control was demonstrated; a high dilution and low temperature limited the radical-radical coupling responsible for gel formation and enhanced the polymerisation control. However, a low temperature (50 °C) reduced the graft ratio, and thus a compromise between reaction time, temperature and concentration was required to achieve a 38% monomer conversion, a $Đ_M$ and graft ratio of 1.65. Compared to the work of Meng *et al.*[42] and Chun-xiang *et al.*[41], this increase in monomer conversion could be due to the use of a tridentate ligand which has a higher K_{ATRP}, responsible for the higher polymerisation rate. The graft-copolymer was thermally more stable than PMMA and aggregated into spheres of 500 nm and 100 nm diameters respectively in DMF and in acetone (Figure 4) as shown by TEM and Atomic Force Microscopy (AFM).

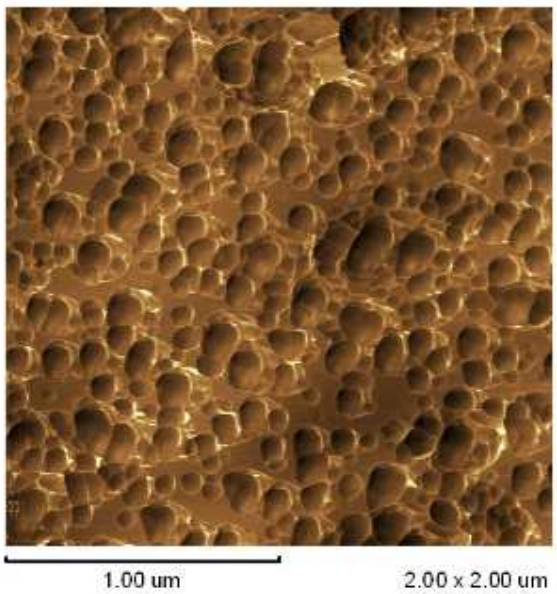

Figure 4: AFM image for the aggregates formed from PMMA-g-Cell in acetone[44].

Zhong *et al.*[46] developed a full evaporation headspace gas chromatographic (HS-GC) method [47] to analyse graft-copolymers produced from cellulosic materials by determining the

residual monomer in the graft-copolymer. In order to validate their analytical system, the homogeneous grafting of PMMA onto Cl-Cell was performed. Cl-Cell was prepared from chloroacteyl chloride in the presence of catalyst and the functionalization reaction was performed for 5 h at 50 °C in a mixture of DMAc/LiCl. The Activator Generated by Electron Transfer (AGET) ATRP process[48] was used to polymerise MMA onto cellulose and the control of the polymerisation was highlighted using the HS-GC method. Contrary to conventional ATRP, AGET ATRP uses Cu (II) and a reducing agent such as ascorbic acid to reduce Cu (II) to Cu (I). The main advantage of AGET ATRP is its ability to be carried out in the presence of air. The graft-copolymerisation was conducted in DMAc at temperatures of 50-70 °C. The authors suggested that the most efficient temperature was 50 °C as it limits MMA homopolymerisation. However, the monomer conversion was only 13% and the $Đ_M$ of the grafts was 1.4. Compared to previous work with MMA, the monomer conversion is relatively low. A plausible reason could be the low amount of catalyst, especially with TMEDA, a bidentate ligand, for which it is required to have a high concentration of catalyst to improve the rate of polymerisation.

The synthesis of PDMA-g-Cell was investigated by Yan and Tao[49], who used a DMAc/LiCl system to dissolve cellulose prior to further modifications. The macro-initiator was synthesised from 2-bromoisobutyryl bromide leading to Br-Cell of DS 0.2. The ATRP of *N,N*-dimethylacrylamide (DMA) was successfully performed using the Br-Cell macro-initiator. 2,2'-Bipyridine (bpy), a bidentate ligand, was used with CuBr and DMSO as solvent. The polymerisation was conducted at room temperature for 7 h using a ratio of [I]/[C]/[L]/[M] equal to 1/2.9/1.3/90. Compared to the work of Chang *et al.*[40], a higher amount of catalyst was used to decrease the reaction time i.e. 7 h instead of approximately 20 h. In the ATRP process, the choice of the ligand is crucial as it determines both the rate of reaction and the extent of control of the polymerisation. Compared to tetramethylethylenediamine (TMEDA)

and pentamethyldiethylenetriamine (PMDETA), bpy has a lower ATRP equilibrium constant (K_{ATRP}) which means that a greater amount of catalyst is needed to achieve the same rate of polymerisation. The DMA grafts of PDMA-g-Cell were removed by hydrolysis and were analysed by Gel Permeation Chromatography (GPC), which revealed a linear increase of molecular weight with monomer conversion, indicating a high level of polymerisation control. After 7 h of reaction, the monomer conversion reached 50% and the $Đ_M$ of PDMA was 1.5. The graft-copolymer PDMA-g-Cell was coated onto a cellulose membrane to produce a material that showed dramatically reduced protein adsorption compared to the uncoated membrane (Figure 5). This represents an improvement in the membrane hemocompatibility and therefore shows potential for use in hemodialysis.

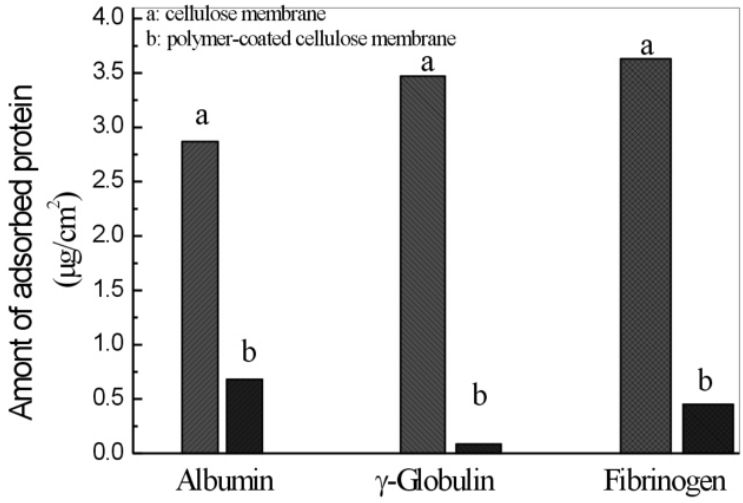

Figure 5: Adsorption of proteins onto (a) uncoated cellulose membrane and (b) cellulose membrane coated with PDMA-g-Cell[49]

In order to produce a cellulose-based stimuli-responsive material, Ifuku *et al.*[43] investigated the graft-copolymerisation of *N*-isopropylacrylamide (NIPAAM) onto cellulose (Figure 6). PNIPAAM is a thermo-responsive material with a lower critical solution temperature (LCST) of 32 °C. Below the LCST, the chains are present as unimers in solution

whereas the chains collapse above the LSCT, resulting in the precipitation of the polymer from the solution.

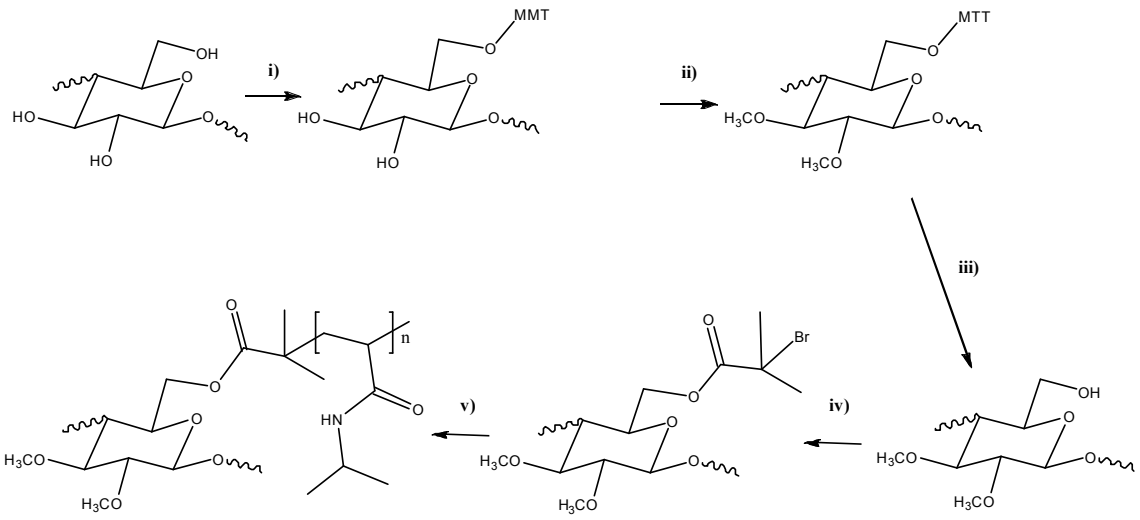

Figure 6: Reaction scheme showing the preparation of PNIPAAM-g-Cell; i) protection of the C6–OH, ii) methylation of the –OH groups at C2 and C3 positions, iii) deprotection of the OH at C6 position, iv) acylation of the OH and v) ATRP of NIPAAM; MMT= monomethoxy trityl-. [43]

The macro-initiator Br-Cell was prepared following the procedure described by Yan and Tao[49], yielding a DS of 1 indicating complete functionalization of the –OH group at the C6 position. For the ATRP of NIPAAM, a tridentate ligand, PMDETA was used to complex CuBr and a mixture DMF/H_2O was used as reaction medium. During polymerisation, both dispersity ($Đ_M$) and monomer conversion increased when the amount of ligand and catalyst were increased compared to monomer. The $Đ_M$ increase indicates a loss of polymerisation control. For a ratio [I]/[C]/[L]/[M] of 1/4/4/200 and a reaction time of 12 h at room temperature, an optimum monomer conversion of 17% and a $Đ_M$ of 2.3 were measured indicating a relatively broad molecular weight distribution. The increased degree of polymerisation (DP) led to increases in both the thermal stability and the glass transition

temperature of the product. The graft-copolymer was insoluble in water, but the PNIPAAM chains permitted the suspension of graft-copolymers in water to form a cloudy solution. Above 30 °C, the PNIPAAM chains collapsed resulting in the precipitation of the graft-copolymers, leaving the aqueous solution clear.

Further investigations were conducted to produce dually responsive materials. Sui *et al.*[45] investigated the graft-copolymerisation of 2-(dimethylamino)ethyl methacrylate (DMAEMA) onto cellulose. For the first time, the preparation of the macro-initiator was performed in an ionic liquid which enhanced the solubility of cellulose. The macro-initiator was prepared from 2-bromopropionyl bromide with a ratio of AGU to Br equal to 1/5 and the functionalization reaction led to a DS of 0.7. This DS value was obtained after a reaction time of 8 h whereas the functionalization reactions reported by Tao and Ifuku were run overnight to reach a DS of 0.2 and 1 respectively. Regarding the ATRP of DMAEMA onto cellulose, a maximum conversion of 35% and a $Đ_M$ of 2.3 were measured after one hour of reaction at 60 °C in DMF using PMDETA as ligand. These conditions were optimal for limiting radical-radical coupling, and thus preserving the "livingness" of the polymerisation. The pH- and thermo-responsive properties were comparable to the homopolymer PDMAEMA which is known to be a dually responsive material. The graft-copolymer aggregated above 42 ºC, as shown by an increase in its hydrodynamic radius (R_h). Moreover, the graft copolymer chains gradually collapsed as the pH was increased from 2 to 12.

Gupta[50] subsequently developed additional stimuli-responsive materials, by graft-copolymerisation of acrylic acid (AA) and/or dimethyl acrylamide (DMA) onto cellulose. Methyl-2-bromopropionate was used to prepare the macro-initiator Br-Cell in THF in the presence of dimethylaminopyridine (DMAP) employing a ratio of AGU to Br of 1/30. Regarding the ATRP, toluene, tris[2-(dimethylamino) ethyl] amine (Me_6TREN) and CuBr were used as solvent, ligand and catalyst respectively. The presence of AA improved the

reactivity of DMA monomers and facilitated its graft copolymerisation onto Br-Cell. Moreover, the AA monomer showed greater propensity towards graft-copolymerisation onto cellulose than DMA. The LCST of the P(AA-co-DMA)-g-Cell was lower than that of PDMA-g-Cell, and the thermal stability of the graft-copolymer increased compared to cellulose itself.

More recently, Cui *et al.*[51] prepared a PNIPAAM/Eu(III)-g-Cell complex which had both thermosensitive and fluorescence properties. NIPAAM was graft-copolymerised onto cellulose in a controlled manner. Cellulose was functionalized with chloropropionyl chloride in DMF and a DS above 1 was achieved. The ATRP of NIPAAM onto cellulose used a tetradentate ligand, Me_6TREN, which resulted in an increased monomer conversion compared to the previous work of Yan and Tao[49]. Furthermore, the use of this ligand permits a decrease of the quantity of copper in the reaction mixture which makes the ATRP process more environmentally friendly. A 1.4 value of $Đ_M$ for the grafts was measured, indicating that this polymerisation is the most successful ATRP graft polymerisation onto cellulose under homogeneous conditions. PNIPAAM-g-Cell complexed to Eu(III) was prepared via a chelation process with europium ions, and this led to an increased LCST for the complex compared to PNIPAAM-g-Cell. Furthermore, the complex showed an increase in emission intensity at 613 nm compared to that of uncomplexed Eu(III) ions (Figure 7).

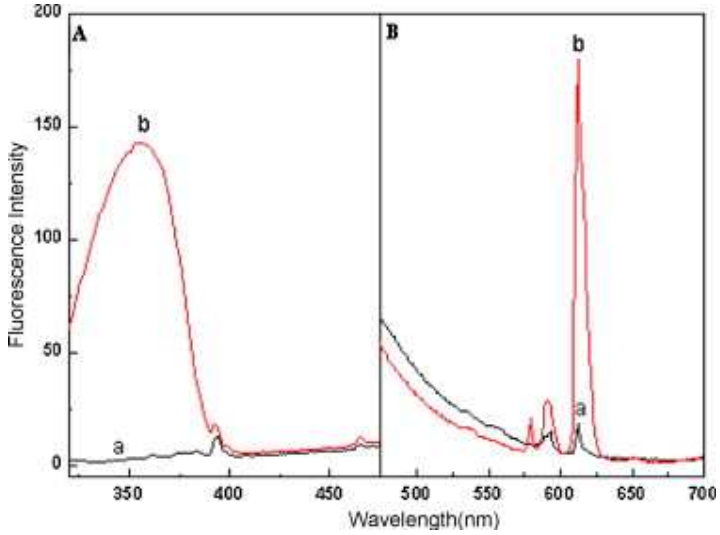

Figure 7: Excitation (A) and emission (B) spectra of (a) $EuCl_3$ and (b) PNIPAAM/Eu(III)-g-Cell[51]. Reproduced with permission, copyright Elsevier 2013.

To summarise, graft-copolymers were successfully prepared from either Cl-Cell or Br-Cell (Table S1 in ESI) in a controlled manner. The use of DMAc/LiCl or ionic liquids allowed the dissolution of the cellulose resulting in homogeneous conditions for performing ATRP. The preparation of the macro-initiators was mainly conducted at room temperature, using pyridine or dimethylaminopyridine (DMAP) as catalysts. The reaction time and the ratio of AGU to reactant were varied to determine their effect on the degree of functionalization. An increase of the amount of reactant relative to AGU and/or a longer reaction time increased the DS, while the presence of catalyst may not be necessary to reach a high DS. Different polymers have been successfully grafted onto cellulose using the ATRP method (Table S2 in ESI). The efficiency of the grafting takes into account both the monomer conversion and the control of the polymerisation. The latter was highlighted by measuring the $Đ_M$ of the grafts after removal by hydrolysis. The importance of the ligand structure on both the rate of polymerisation and the $Đ_M$ was discussed. For instance, a tetradentate ligand increased the rate of polymerisation and thus an increase of the monomer conversion was observed. The influence of the reaction parameters, including solution

concentration and choice of solvent on the success of the reaction were also investigated. Overall, the chemical modification of cellulose changed the behaviour of the raw materials. Depending on the monomers, the graft-copolymers aggregated into nanoparticles and had stimuli-responsive or dual stimuli-responsive properties which could result in potential applications in areas such as nanocontainers for drug delivery.

III. Graft-copolymer of ethyl cellulose

Ethyl cellulose (EC; Figure 1) is prepared via a Williamson etherification of cellulose with ethyl chloride. The modification takes place preferentially at the C6 and C2 position with a DS ranging from 2.1 to 2.6. The remaining free hydroxyls are therefore at positions C3 and C2, hence reactivity of EC towards further functionalisation can be low. EC is known for its thermoplasticity, chemical stability, resistance to degradation by alkali and salt, and its capability to absorb only a small amount of water. Owing to these properties, EC has been used in the formulations of paints, varnishes and lacquers and is used as an ingredient in hair sprays[6, 52]. The solubility of EC in organic solvents makes it a good candidate for graft-copolymerisation under homogeneous conditions. Due to the biocompatibility of EC and its self-assembly properties, there has been interest in possible biotechnology applications, with the formation of amphiphilic graft-copolymers being a central theme. Here, we will report the preparation of graft-copolymers from EC which have been prior-functionalized with bromo-ester bromide. Br-EC was synthesised from either 2-bromoisobutyryl bromide or 2-bromopropionyl bromide in the presence of a catalyst such triethylamine (TEA) or pyridine. The solvent commonly used was THF and the reaction was carried out at room temperature for a desired time. The importance of the reaction time and the ratio of AGU to Br on the DS of Br-EC will be discussed. Graft-copolymerisation with acrylic acid (AA), St, MMA and 2-hydroxyethyl methacrylate (HEMA) will be described and the self-assembly of the products into micelles will be discussed. The graft copolymerisation of other monomers such as methacrylate-containing azobenzene groups (MMAzo), poly(ethylene glycol) methyl ether methacrylate (PEGMA), 2-(diethylamino)ethyl methacrylate (DEAMA), and *N*,*N*-dimethylaminoethyl methacrylate (DMAEMA) onto Br-EC and the photo-, thermo- and/or pH-responsiveness properties of the products will be summarised. We will compare the

influence of the density and the length of the grafts on the behaviour of micelles produced from the self-assembly of the graft copolymers.

In 2005, Shen *et al.*[53] were the first to report the graft-copolymerisation from ethyl cellulose using ATRP. Densely grafted PSt-g-EC and PMMA-g-EC copolymers were prepared, where the macro-initiator Br-EC was synthesised under mild conditions using EC with a DS of 2.1. For a ratio of AGU to Br equal to 1/3 and a reaction time of 48 h, a maximum DS of 0.5 was obtained. This low value was explained by the low reactivity of the free –OH groups at the C2 and C3 positions. Polymerisation of St and MMA from $Br_{0.5}$-EC were performed at optimized temperatures of 110 °C and 70 °C respectively for 16 h using CuBr/PMDETA as catalyst system and toluene as reaction medium. The targeted degree of polymerisation was 300 and the ratio [I]/[C]/[L] was equal to 1/0.5/1. After 16 h of reaction, the monomer conversion was 12% and 11% for MMA and St respectively and a relatively narrow $Đ_M$ of 1.35 for both graft copolymers was measured by GPC. A rod-like shape of PSt_{30}-g-$EC_{0.5}$ in toluene was proven using light scattering and AFM experiments. Repulsion between PSt chains enhanced the extension of the EC backbone resulting in the formation of rods. Shen *et al.*[54] investigated the graft-copolymerisation of St onto EC, using macro-initiator $Br_{0.04}$-EC and $Br_{0.5}$-EC synthesised, respectively, with DS values of 0.04 and 0.5. To synthesise $Br_{0.5}$-EC, the same procedure of Shen *et al.*[53] was used, whereas to prepare $Br_{0.04}$-EC, a higher ratio of AGU to Br (1/0.2) was used. St was polymerised onto these macro-initiators resulting in various graft lengths and graft densities. The authors used the same catalyst system, solvent and temperature as reported in their previous publication[53]. However, different reaction times, targeted degrees of polymerisation and ratio of [I]/[C]/[L] were chosen depending on the DS of the Br-EC used. For $Br_{0.5}$-EC, where the authors intended to prepare graft-copolymers PSt_{60}-g-$EC_{0.5}$ of high graft density with a short graft length, a low DP of 300 was targeted using a ratio [I]/[C]/[L] equal to 1/0.5/1. A monomer conversion of

20% was reached after 21.5 h and the $Đ_M$ of the grafts was equal to 1.3 which confirmed the controlled/living nature of the polymerisation process. In order to produce longer length of grafts in a shorter reaction time, the targeted DP was increased to 6000 and the amount of catalyst was increased by a factor 2. A 10% monomer conversion and a $Đ_M$ of 1.2 were obtained resulting in the formation of the graft-copolymer PSt_{600}-g-$EC_{0.04}$. At a high concentration in acetone, the densely grafted copolymer PSt_{60}-g-$EC_{0.5}$ self-assembled into nanoparticles (Figure 8) whereas at a low concentration, graft-copolymers were present as unimers in solution. At a solution concentration of 25 μg/ml in acetone, the diameter of particles reached 200-300 nm and the size distribution was narrow. The PSt grafts are not soluble in acetone whereas EC backbone is soluble, thus PSt and EC formed the core and shell respectively of the nanoparticles.

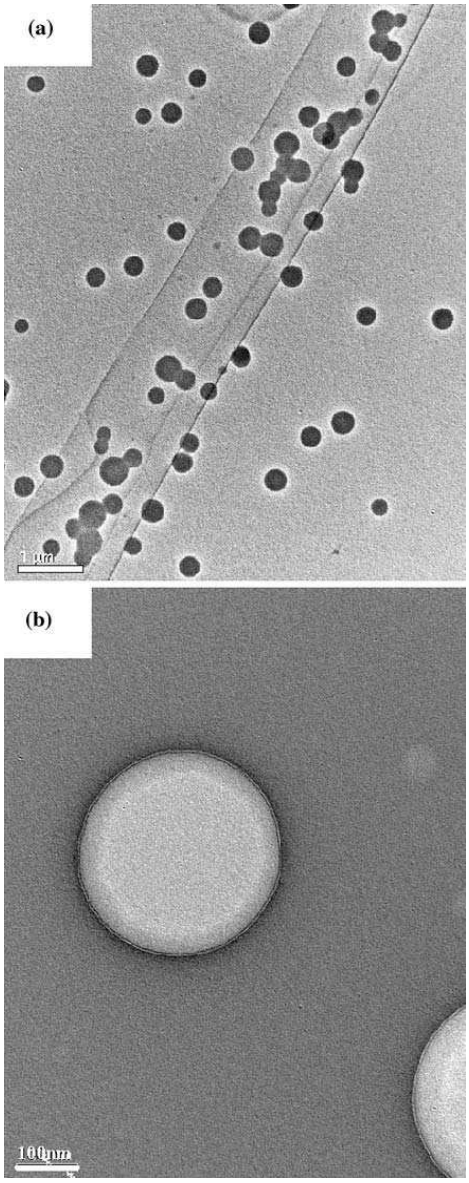

Figure 8: TEM image of spherical aggregates formed from PSt_{60}-g-$EC_{0.5}$ in acetone solution with acetone (concentration 25 μg/ml)[54]. Reproduced with permission, copyright Springer 2006.

Qinmei *et al.*[55] recently developed new graft-copolymers such as (PSt-co-PEG)-g-EC and PSt-g-PEG-g-EC combining click and ATRP processes. Two Br-EC macro-initiators with DS of 0.28 and 0.54 respectively were prepared from EC with a DS of 2.5. The variation of DS can be explained by the change of the ratio of AGU to Br; a decrease of the ratio results in

an increase of the DS of Br-EC. The ATRP procedure used to graft St onto Br-ECs was the same as that reported by Shen *et al.*[53]. Different lengths of PSt chains were achieved by varying for instance the reaction time, and/or the targeted DP.

Kang *et al.*[56] used Br-EC macro-initiators with DS of 0.04 and 0.09 to graft-polymerise 2-hydroxyethyl methacrylate (HEMA). The functionalization reaction of EC with DS of 2.1 using bromoisobutyryl bromide was carried out for 24 h in the presence of pyridine. To obtain a DS of 0.04, a ratio of AGU to Br equal to 1/1 was used whereas a lower ratio of 1/2 permitted an increase of the DS to 0.09. ATRP performed at 40 °C was found to give better control of the polymerisation process than at 30 °C. Different ratios of [I]/[C]/[L] for $Br_{0.09}$-EC and $Br_{0.04}$-EC were chosen and $CuBr_2$ was additionally used to slow down the initiating step of the polymerisation with $EC_{0.09}$-Br, helping to maintain the "livingness". The targeted DP was 510 and 1000 for $Br_{0.09}$-EC and $Br_{0.04}$-EC respectively. The length and the dispersity of the PHEMA grafts were determined using both ^{1}H NMR spectroscopy and GPC. A common $Đ_M$ of approximately 1.2 was measured indicating a narrow molecular weight distribution of the grafts and the length of the grafts was equal to 66 and 83 monomeric units of HEMA for $PHEMA_{66}$-g-$EC_{0.09}$ and $PHEMA_{83}$-g-$EC_{0.04}$ respectively. The self-assembly of similar graft-copolymers ($PHEMA_{131}$-g-$EC_{0.09}$ and $PHEMA_{10}$-g-$EC_{0.04}$), for which the synthesis was not described, was reported. These graft copolymers were self-assembled into micelles by dialysis of a solution of these graft-copolymers in DMF against water and both R_h and size distribution were determined using DLS. The average of R_h was around approximately 70 nm and a narrow size distribution was observed for a concentration of the graft-copolymers in water ranging from 5-25 μg/ml.

Amphiphilic graft-copolymers were developed by Kang *et al.*[57] who reported the graft-copolymerisation of t-butyl acrylate (t-BA) onto EC using macro-initiators (Br-EC) with DS values of 0.04 and 0.25. The reaction time used to prepare the macroinitiators was 50% lower

compared to previous work[53,54] and this could be an explanation of the low DS values. t-BA was then polymerised in a controlled manner using CuBr/PMDETA as catalyst and a mixture of toluene/cyclohexanone as solvent at 80 °C. The targeted DP was 3750 and 300 for $Br_{0.04}$-EC and $Br_{0.25}$-EC respectively. A high amount of catalyst was used for $Br_{0.04}$-EC to increase the rate of polymerisation whereas $CuBr_2$ was used in conjunction with CuBr for the polymerisation of t-BA onto $Br_{0.25}$-EC to control the rate of polymerisation by reducing the number of radicals in the reaction mixture. At the end of the polymerisation, monomer conversions were equal to 6% and 21% for $Br_{0.04}$-EC and $Br_{0.25}$-EC respectively and a common $Đ_M$ of 1.2 was measured by GPC after hydrolyzing the P(t-BA) grafts from the EC backbone. Two different graft-copolymers were produced; PSt_{63}-g-$EC_{0.25}$ with a high density of short grafts and PSt_{225}-g-$EC_{0.04}$ with low density of long grafts. Further, PAA-g-EC was successfully prepared by hydrolysis of P(t-BA) chains. The amphiphilic graft-copolymer PAA_{13}-g-$EC_{0.25}$ self-assembled in water (1.0 mg/ml), and the size of the aggregates varied from 5 to 100 nm, depending on the number of chains involved in the aggregate formation. Recently, the influence of the graft density on PAA-g-EC molecular conformation was studied by Liu *et al.*[58]; a high graft density led to a rod conformation whereas a low graft density generated a coil conformation (Figure 9).

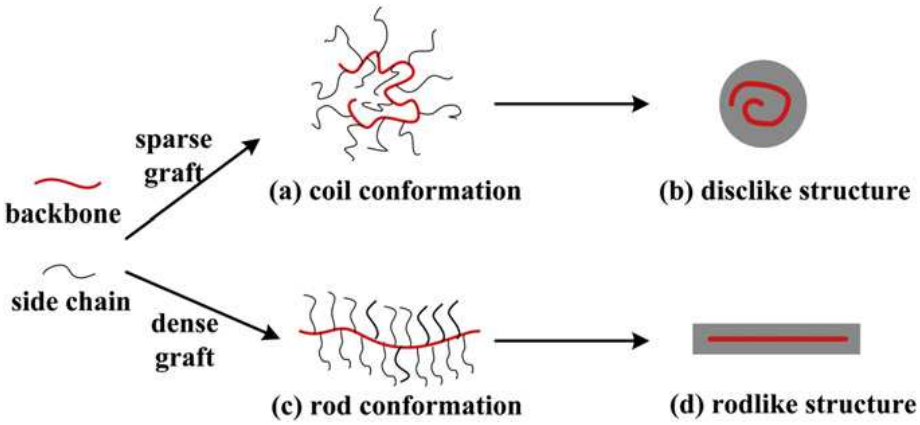

Figure 9: Molecular conformation and single chain structure of the graft copolymers[58].

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In 2007, a range of amphiphilic photo-responsive self-assembling graft-copolymers were developed by Tang *et al.*[59] by grafting an azobenzene-containing methacrylate onto EC. The monomer containing azobenzene was successfully prepared and Br-EC with a DS of 0.52 was synthesised in the presence of TEA as catalyst. The functionalization reaction of EC was performed at room temperature overnight and the ratio of AGU to Br was equal to 1/3. Compared to $Br_{0.5}$-EC prepared by Shen *et al.*[53,54], the change of catalyst from pyridine to triethylamine allowed a reduction of the reaction time to obtain the same DS. The graft-copolymerisation of azobenzene-containing methacrylate monomers onto $Br_{0.5}$-EC proceeded at 85 °C for 20 h in anisole with PMDETA/CuBr as catalyst system. [I]/[C]/[L] equal to 1/2/4 was chosen and two different DPs were targeted in order to prepare graft-copolymers with different length grafts. To highlight the grafting of PMMAzo onto $Br_{0.5}$-EC, the molecular weight (M_n) of the graft copolymers was measured by GPC. The increase of M_n indicated successful grafting and M_n was found to increase with graft length. The graft-copolymerisation gave a product with two phase transitions at 94 °C and 134 °C corresponding, respectively, to the smectic-to-nematic and nematic-to-isotropic transition

temperatures. Furthermore, a reversible trans to cis isomerisation of azobenzene groups under UV-vis light was observed by spectrophotometry.

Subsequently, in 2008, Li *et al.*[60] prepared the thermally responsive graft-copolymer PPEGMA-g-EC, using macro-initiators of DS 0.2 and 0.02 to initiate the ATRP of poly(ethylene glycol) methyl ether methacrylate (PEGMA). To avoid the radical-radical coupling responsible for gel formation, conversions were kept low; 56% and 62% with $Br_{0.2}$-EC and $Br_{0.02}$-EC respectively, using ratios of monomer to initiator of 50 and 300, respectively. The polymerisation proceeded in toluene with a 4,4'-Di-5-nonyl-2,2'-bipyridine (dNbpy)/CuCl as catalyst system at 60 °C. A common ratio of [I]/[C]/[L] equal to 1/0.75/1.5 was chosen for each polymerisation, however the polymerisation using $Br_{0.2}$-EC proceeded for a shorter time compared to that from $Br_{0.02}$-EC because of a higher possibility of radical-radical coupling in the former polymerisation. Furthermore, $CuCl_2$ was used in conjunction with CuCl for the ATRP of PEGMA onto $Br_{0.2}$-EC in order to slow down the initiation rate and maintain polymerisation control. The resulting graft-copolymers, $P(PEGMA)_{27}$-g-$EC_{0.2}$ and $P(PEGMA)_{185}$-g-$EC_{0.02}$ were dissolved in THF and dialyzed against water resulting in the formation of micellar solutions with a concentration of 1 mg/ml. The R_h of graft-copolymers $P(PEGMA)_{27}$-g-$EC_{0.2}$ and $P(PEGMA)_{185}$-g-$EC_{0.02}$ as determined by DLS was 140 nm and 73 nm respectively, which indicates that micelle size increases with the graft density but the length of the grafted chains has no influence on the micelle size. Moreover, the graft-copolymers were found to have thermo-responsive behavior defined by an LCST of 65 °C, however, the graft density and length did not influence the LCST. Above the LCST, the micelles aggregated, resulting in an increase in R_h to 180 nm and 120 nm for $P(PEGMA)_{27}$-g-$EC_{0.2}$ and $P(PEGMA)_{185}$-g-$EC_{0.02}$ respectively and solution turbidity, and these phenomena were shown to be reversible.

More recently, in 2011, Wang *et al.*[61] investigated the pH responsive graft copolymer PDEAEMA-g-EC prepared from Br-EC macro-initiators with a DS of 0.06, 0.1 and 0.2. These were used to polymerise 2-(diethylamino)ethyl methacrylate (DEAEMA), and based on ^{1}H NMR spectra, the degree of polymerisation ranged from 15 to 90, depending on the feed ratio and reaction time. The ATRP proceeded in DMF at 20 °C using bpy/CuBr as catalyst system and a common [I]/[C]/[L] ratio of 1/0.75/1.5 was chosen. The graft-copolymers were dissolved in THF and dialyzed against acidic aqueous solution to form a micelle solution of a concentration of 0.5 mg/ml. The size of the micelles was determined by DLS and their behaviour at different pH was studied (Figure 10). At a constant pH of 3.2, the critical micelle concentration (CMC) decreased when the graft length and density increased. When the pH was increased from 6 to 6.9, the R_h of the micelles decreased as the PDEAEMA chains collapsed. Above a pH of 6.9, the micelles aggregated together resulting in an increase of R_h. For instance, the size of the micelles formed by the graft-copolymer $PDEAEMA_{85}$-g-$EC_{0.1}$ was 200 nm at 3.2 of pH, when the pH increased to 6.9, R_h strongly decreased to ~75 nm because of the shrinkage of the synthetic chains and above a pH of 7, R_h slightly re-increased to ~90 nm due to the aggregation of micelles together. The authors have also studied the importance of both the graft density and the chain length on the size of the micelles. In fact, the size of the micelles formed from graft-copolymers prepared from $Br_{0.1}$-EC increased with the chain length of PDEAEMA. At a pH of 3.2, the micelle size increased from 140 nm to 200 nm when chain length was increased from 35 to 85 monomer units. However, the graft density did not affect the size of micelles for a constant chain length of 90 monomer units. Furthermore, the aggregated structure at pH above 6.9 prolonged the drug release over time compared to the structure generated at pH 6.6.

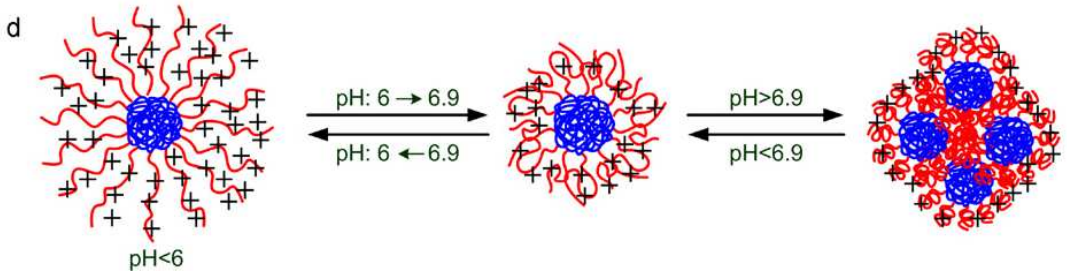

Figure 10: Proposed mechanism of the pH-responsive micelle formation from PDEAEMA-g-EC copolymers[61]. Reproduced with permission, copyright Elsevier 2011.

Yan *et al.*[62] prepared the dual graft copolymer PCL-g-PDMAEMA-g-EC by combining ATRP and ROP processes. EC was functionalized with 2-bromopropionyl bromide in presence of triethylamine for 24 h with a ratio AGU to Br equal to 1/3. After this, ROP of CL was performed then the DMAEMA was polymerised onto Br-PCL_{30}-g-EC in THF at 60 °C using PMDETA/CuBr and a [I]/[C]/[L] ratio of 1/1/1. The longest chain length was reached after 30 h of polymerisation with a monomer conversion of 23% resulting in the formation of brush-copolymer $PDMAEMA_{23}$-g-PCL_{30}-g-EC. The dual graft-copolymer displayed similar behaviour in terms of micellization, micelle structure and pH responsiveness as PDEAMA-g-EC. At low pH, the brush copolymer formed micelles of 36 nm radius whereas the size of the micelles increased to 81 nm at high pH indicating an aggregation phenomenon. Compared to $PDEAEMA_{85}$-g-$EC_{0.1}$ where the micelle size decreased when pH increased, the shrinkage of $PDMAEMA_{23}$ resulted to the formation of a micellar aggregate which was indicated by an increase of the R_h. This phenomenon can be explained by the brush structure of the graft copolymer and thus by the presence of the grafts of PCL. $PDMAEMA_{23}$-g-PCL_{30}-g-EC was also analyzed using DSC and WAXD and it proved to be amorphous because the EC and especially the PDMEAMA chains disturbed the order of the PCL.

Tang *et al.*[63] aimed to develop more complex responsive graft-copolymers, through simultaneous graft-copolymerisation of MMAzo and NIPPAM to generate a dual responsive material. Br-EC was synthesised from 2-bromosiobutyryl bromide in presence of triethylamine as catalyst because TEA had been shown to decrease the reaction time. Br-EC was then used to copolymerize NIPAAM and MMAzo monomers in a mixture of DMF/H_2O using the tetradentate ligand tris[2-(dimethylamino)ethyl]amine (Me_6TREN)/CuCl as catalyst system at 80 °C for 9 h with a ratio of [I]/[C]/[L] equal to 1/1/1. A ratio of NIPAAM to MMAZo equal to 50/1 was chosen. The grafting efficiency was not discussed and no data have been reported to confirm the formation of the graft-copolymer. However, the solubility properties of the graft-copolymer were discussed; it was found to be insoluble in water, but instead formed an emulsion. When the temperature was increased above 30 °C, the graft-copolymer side chains collapsed resulting in precipitation from the solution. Furthermore, the presence of PMMAzo chains induced changes in the solubility behavior of the graft-copolymer caused by the reversible trans/cis isomerization under UV-vis light of the azobenzene groups. Under UV light, the polarity of the graft-copolymer increased resulting in an increase of the LSCT.

In summary, amphiphilic graft-copolymers were successfully prepared from the macro-initiator Br-EC (Table S3 in ESI) for which the DS ranged from 0.06 to 0.5 depending on the reaction time, choice of catalyst and ratio of AGU to Br. For instance, the DS value was higher for a longer reaction whereas the DS decreased for a higher ratio of AGU to Br. Furthermore, the use of triethylamine as catalyst decreased the reaction time compared to the use of pyridine. The graft-copolymers of EC are listed in Table S4 (ESI) where experimental conditions and the grafting efficiency defined by the monomer conversion and/or $Đ_M$ are reported. The monomer conversion was kept low to avoid radical-radical coupling which results in the loss of livingness. Furthermore, Cu (II) was sometimes used to regulate the

production of radicals and thus enhance the control of the polymerisation. The use of a tridentate ligand such as PMDETA permitted both a reduction of the amount of catalyst and an increase of the polymerisation rate compared to the use of a bidentate ligand such as bpy. $Đ_M$ was determined after hydrolyzing the synthetic chains from the backbone and ranged from 1.1 to 1.3 which indicated a relatively good control of the polymerisation. The R_h values of graft-copolymers of EC that have been self-assembled in aqueous solution are summarized in Table S5 (ESI) and were found to range from 5 to 300 nm. For each graft-copolymer, the chain length and the graft density are indicated because of their importance for understanding of the graft copolymer structure. Graft-copolymers that had either a low graft-density with a long chain length or a high graft-density with a short chain length formed micelles in aqueous solution. However, the graft-copolymer with a low graft density and a long chain length formed larger micelles compared to graft-copolymer with a high graft-density and short chain length. Furthermore, the chain length influenced more the micelle size than the graft-density; R_h increased when the chain length increased. The use of thermo-, pH- or photo-responsive polymers such as PPEGMA, PDEAEMA and PMMAzo allowed the creation of smart self-assembled materials. Under external stimulus (temperature, pH or light) the micelles formed by the graft-copolymers collapsed together resulting in increases in R_h. All of the self-assembled graft-copolymers are potentially valuable materials as nanocontainers, and more precisely as drug delivery systems when these materials are produced from a stimuli-responsive polymer which is capable of modulating the release of a drug over time.

IV. Graft-copolymers of hydroxypropyl cellulose

Hydroxypropyl cellulose (HPC) is produced by the reaction of cellulose with propylene oxide, with reaction taking place preferentially at the C6-OH position of the glucose units to give a new hydroxyl group in addition to the propyl unit (Figure 1). This side chain can be further extended through sequential additions of propylene oxide units onto the newly formed hydroxyl group. Observed DS values range from 2.2 to 2.8, and HPC is soluble only in cold water and in most polar organic solvents[6, 64]. HPC has proven uses as an emulsion stabilizer, coating excipient, binding agent and film former in many industrial applications such as food, pharmaceuticals and personal care[65-67]. Owing to its solubility, the use of HPC supports and facilitates the preparation of graft-copolymers under homogeneous conditions. Furthermore, HPC has a lower critical solution temperature at approximately 42 °C. HPC derivatives present a strong potential in biotechnology applications such as functioning as drug nanocontainers. Thus, graft-copolymers of HPC were targeted in order to decrease the LCST to physiological temperature, and to add stimulus-responsive and self-assembly properties. In the following section, the activation of the HPC backbone will be reviewed; the strategies used to influence the DS of Br-HPC are summarised in Table S6 (ESI). We will discuss also the preparation of graft-copolymers from monomers such as DMAEMA, NIPAAM, 4-vinylpyridine (4VP) and oligo(ethylene glycol) methacrylate (OEMA). Their physical properties will be described and their responsiveness to external stimuli will be discussed. We will see that some graft-copolymers were further cross-linked to control the sizes of the micelles or to form gel particles resulting in prolonged drug release profiles.

The first reported work with HPC was by Östmark *et al.*[68] in 2007, who synthesized PMMA-g-HPCs from a conventional- and a dendronized-macro-initiator (Figure 11), Br-HPC

and Br-G1-HPC, with DS values of up to 2.26 and 0.88, respectively. The polymerisation of MMA was performed using these two macro-initiators in highly dilute solutions of toluene and PMDETA as ligand, in the presence of $CuBr_2$ with a minimum ratio $CuBr_2$/CuBr equal to 1/4. Reaction conditons of 80 °C and 19 h were chosen for the polymerisation with $Br_{2.26}$-HPC whereas the polymerisation of MMA with the dendronized macro-initiator was performed at a lower temperature, 50 °C for a shorter time, 2 h. The polymerisation of MMA onto the conventional macro-initiator $Br_{2.26}$-HPC was less controlled than that of MMA onto the dendronized macro-initiator. However, the monomer conversion was higher using $Br_{2.26}$-HPC than $Br_{0.88}$-GI-HPC with values of 39% and 18% for PMMA-g-$HPC_{2.26}$ and PMMA-g-GI-$HPC_{0.88}$ obtained respectively. Both macro-initiators were also used to polymerise hexadecyl methacrylate (HDMA), but only the polymerisation onto $Br_{0.88}$-GI-HPC was successful. $Br_{2.26}$-HPC produced a high concentration of radicals resulting in the formation of a gel due to the radical-radical coupling phenomenon between chains. The bromides at the chain end of PMMA-g-$HPC_{2.26}$ were then used to activate the polymerisation of t-BA with similar reaction conditions to those that were used for the polymerisation of PMMA onto $Br_{2.66}$-HEC. After 22 h of reaction, a low conversion of 3.5% was reached leading to a second block in a ratio of 1/0.58 MMA to t-BA. The t-butyl ester groups of P(t-BA) were then hydrolysed to form a PAA block. PHDMA-g-G1-$HPC_{0.88}$, PMMA-g-G1-$HPC_{0.88}$ and PMMA-g-$HPC_{2.26}$ formed particles in THF and their sizes were measured using DLS. D_h values of 96 and 195 nm were observed for particles from PMMA-g-$HPC_{2.26}$ and PMMA-g-G1-$HPC_{0.88}$ respectively and the particles formed from PHDMA-g-G1-$HPC_{0.88}$ were similar in size to those of PMMA-g-G1-$HPC_{0.88.}$ However, chain extension of PMMA-g-$HPC_{2.26}$ with t-BA permitted the formation of larger particles of D_h = 280 nm.

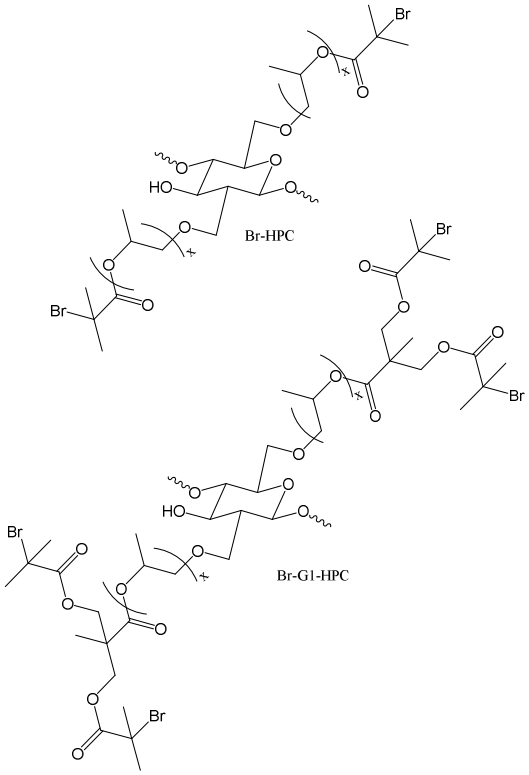

Figure 11: Molecular structure of macro-initiators Br-HPC and Br-G1-HPC

Recently (2013), Bagheri *et al.*[69] investigated the graft-copolymerisation of MMA and the simultaneous graft-copolymerisation of MMA and cholesteryl methacrylate (CMA) onto HPC. Br-HPC, the macro-initiator, with a DS of 2.04 was successfully prepared in a conventional manner and both MMA and the complex MMA/CMA were polymerized onto it in the presence of $CuBr_2$ to improve the polymerisation control. Bidentate ligand, bpy and toluene as solvent were used at a temperature of 70 °C and after 19 h of polymerisation, the monomer conversion was 25% and 30% for the ATRP of MMA and the simultaneous polymerisation of MMA and CMA respectively. Graft-copolymers (PMMA-ran-PCMA)-g-HPC were produced with graft lengths of 100 and 357, and the ratio of PMMA to PCMA was determined to be 1/0.11. The thermal stability and glass transition temperature (T_g) of each graft-copolymer were reduced compared to HPC itself, and these observations were attributed to a reduction of the crystallinity of HPC. Compared to HPC-g-MMA, the thermal stability

and T_g of (PMMA-ran-PCMA)-g-HPC graft-copolymers were also decreased. Furthermore, the T_g decreased with increased PMMA-ran-PCMA graft length, plus, the solubility behavior of the graft-copolymers was different. The (PMMA-ran-PCMA)-g-HPC formed nanoparticles of D_h below 570 nm (DLS experiments) in water/ethyl acetate solution with narrow size distribution.

Östmark *et al.*[70] investigated the preparation of the graft-copolymer PAA-b-PCL-g-HPC. The CL was polymerised onto HPC via a ROP process resulting in a degree of polymerisation (DP) of 10. The chain ends were further functionalized with bromoisobutyryl bromide using DMAP/TEA as catalyst system in DMF. After 2 h of reaction at room temperature, the Br-PCL-HPC was successfully prepared with a DS greater than 1.1 and $Br_{>1.1}$-PCL-HPC was further used for initiating the polymerisation of t-BA monomers. The chain length of P(t-BA) was controlled by varying the polymerisation time, and the monomer conversion was kept under 35% in order to maintain true living polymerisation conditions. The reaction conditions used were similar to those used for polymerising MMA onto $Br_{2.26}$-HPC and a maximum conversion of 32% was reached after 22 h of reaction. Furthermore, the t-butyl ester groups were successfully hydrolysed to form PAA-block-PCL-g-HPC. This block graft-copolymer was then cross-linked using a diamine. The three graft-copolymers self-assembled into particles in THF and their sizes were determined using DLS. The cross-linked graft-copolymers produced particles with the largest D_h of 235 nm while the size of the particles formed from PtBA-b-PCL-HPC was smaller than those from PAA-b-PCL-g-HPC (D_h of 86 and 129 nm respectively).

PAA-b-PLLA-g-HPC graft copolymers were developed by Berthier *et al.*[71] following a five step procedure (Figure 12). The macro-initiator was prepared from bromopropionyl bromide using the chain end -OH of PLLA following the ROP polymerisation of LLA onto HPC. After 2 days at room temperature in the presence of TEA, all hydroxyl group chain ends

of PLLA were functionalized to bromo-ester groups. For the first time, the ATRP was carried out without the use of solvent; instead the monomer t-BA was used as reaction medium. The polymerisation was conducted at 100 °C in the presence of PMDETA/CuBr as catalyst system. A relatively high conversion was reached after only 30 min. The reaction time had to be short to avoid gel formation from radical-radical coupling.

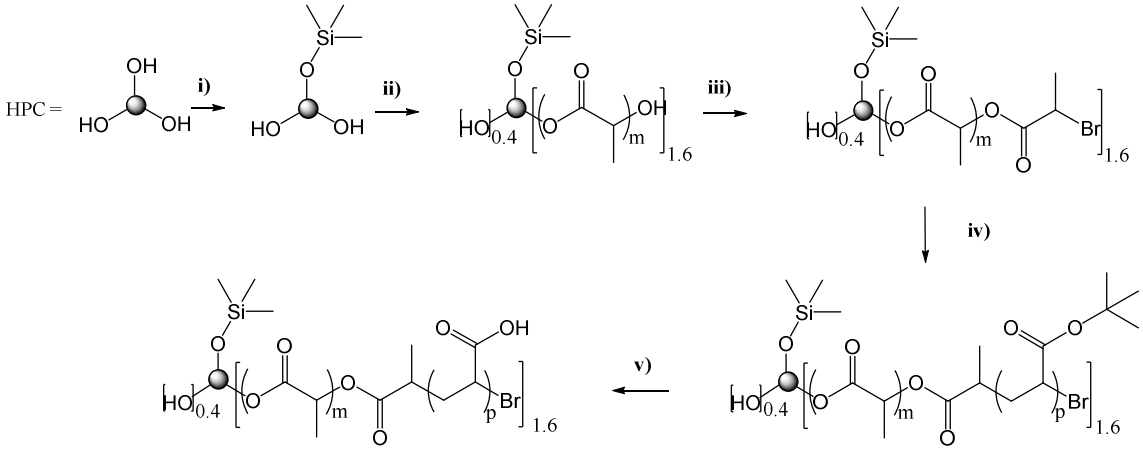

Figure 12: Preparation of the graft-copolymer PAA-b-PLLA-g-HPC: i) protection of OH via HDMS ii) ROP of LLA iii) macro-initiator preparation from chain ends of PLLA iv) ATRP of t-BA and v) deprotection of P(t-BA) to PAA. [71]

The amphiphilic graft-copolymers formed micelles of diameter approximately 64 nm in a mixture of ethanol/water, however the micelles which have been loaded with Romascone, a perfume ingredient, had an extended D_h of 203 nm and were shown to be capable of controlling the release of the volatile compound.

Stimuli-responsive graft copolymers of HPC have also been developed. Xu *et al.*[72] reported the preparation of PNIPAAM-g-HPC from $Br_{0.14}$-HPC using dioxane as reaction solvent because it is known to be a good solvent for polymerisation of NIPAAM. The graft-length was controlled via the polymerisation time and after 24 h, a high monomer conversion of 64% was achieved due to the use of tetradentate ligand. A graft efficiency ranging from 35

to 64% of PNIPAAM (LCST of 32 °C) onto HPC (LCST of 42 °C) provided a material where the LCST fell below 37 °C, and the cytotoxicity of the graft-copolymer was reduced compared to that of ungrafted PNIPAAM homopolymer. The presence of residual -OH groups permitted cross-linking of PNIPAAM-g-HPC using divinylsulfone (DVS), and this resulted in hydrogel formation. This result is significant because above a temperature of 37 °C, PNIPAAM grafts collapsed completely, releasing their payloads, whereas the hydrogel based-PNIPAAM-g-HPC showed slower, more controlled drug release than the hydrogel based on HPC (Figure 13).

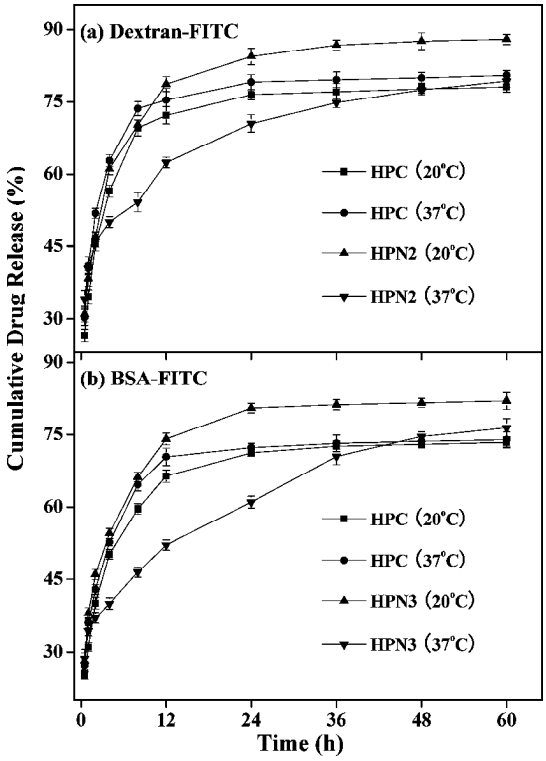

Figure 13: Release profiles of (a) dextran-FITC from HPC and HPN2 hydrogels and (b) BSA-FITC from HPC and HPN3 hydrogels at 20 and 37 °C[72]. Reproduced with permission, copyright American Chemical Society 2010.

In 2011 Porsch *et al.*[73] described the preparation of thermally responsive HPC-based graft-copolymers using a variant of ATRP known as Activators ReGenerated by Electron Transfer (ARGET) ATRP[48]. Br-HPC macro-initiators with DS values of 0.6 and 1.4 were synthesised using a procedure described above[68, 74]. Oligo(ethylene glycol) methacrylate ($OEGMA_{300}$), 2-(hydroxyethoxy)ethyl methacrylate (DEGMA) and $OEGMA_{300}$-co-DEGMA were polymerised onto Br-HPC using a bidentate ligand, bpy and $CuBr_2$/ascorbic acid as catalyst system. Polymerisation was performed at 40 °C for 4 h and anisole and methanol were used as solvent for $Br_{1.4}$-HPC and $Br_{0.6}$-HPC respectively. High dilution and low monomer conversion were maintained to limit side reactions such as cross-linking and termination reactions. Even under these conditions, $Br_{1.4}$-HPC did not give successful ARGET ATRP of $OEMA_{300}$ and $OEGMA_{300}$-co-DEGMA due to the high concentration of radical species in solution resulting in the formation of gel. At the end of polymerisation, the monomer conversion varied from 20 to 35% depending on the choice of monomer. These graft-copolymers presented both thermo-responsive and self-assembly properties. The grafting of such materials onto HPC influenced its LCST because these synthetic polymers have LCST values from 29-90 °C depending on their chain length (Figure 14). The grafting of PDEGMA onto HPC decreased the LCST to 22 °C whereas the LCST increased to 62 °C when POEGMA was grafted from HPC. However, the grafting of P($OEGMA_{52}$-co-$DEGMA_{48}$) onto HPC did not affect the LCST which remained at 42 °C. Furthermore, the graft-density of PEGMA-g-HPC did not influence the LCST as the same value was determined for both PEGMA-g-$HPC_{1.4}$ and PEGMA-g-$HPC_{0.6}$. Below their LCST, the graft-copolymers were self-assembled into micelles in water with R_h ranging from 20-40 nm. Above their LCST, the micelles aggregated resulting in an increase of R_h to 150-250 nm.

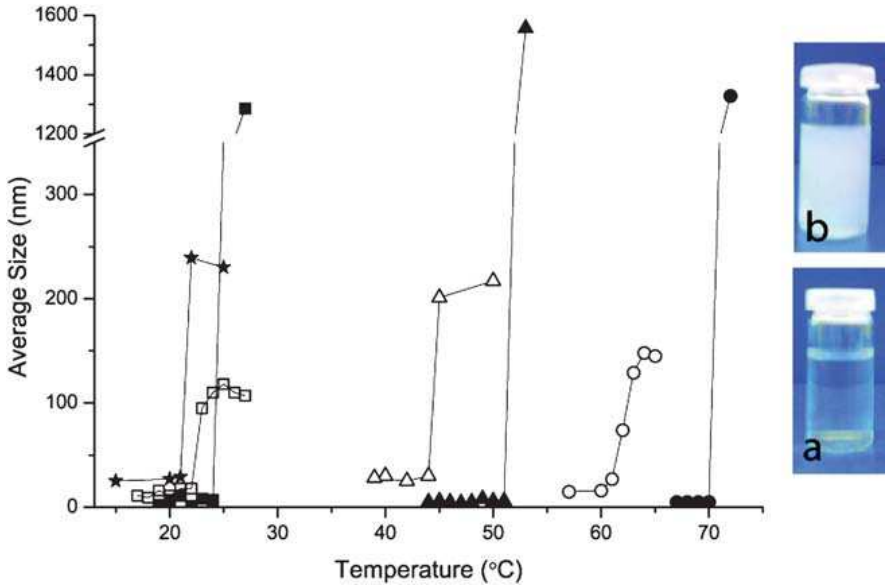

Figure 14: Size of HPC-based graft copolymers and their linear analogues as a function of temperature: PDEGMA (■),PDEGMA-g-HPC$_{1.4}$ (★),PDEGMA-g-HPC$_{0.6}$ (□), P(OEGMA$_{54}$-co-DEGMA$_{46}$) (▲),P(OEGMA$_{52}$-co-DEGMA$_{48}$)-g-HPC$_{0.6}$ (△), POEGMA (●), and POEGMA-g-HPC$_{0.6}$ (○). Insets: (a) polymer sample below LCST in aqueous solution and (b) polymer sample above LCST in aqueous solution [73].

Dually responsive materials were produced by Ma *et al.*[75] who reported the preparation of the graft-copolymer P4VP-g-HPC. The macro-initiator Br-HPC with a DS of 0.05 was synthesised from bromoisobutyryl bromide in THF using pyridine as catalyst and was used for the graft-copolymerisation of 4VP. The low DS of Br$_{0.05}$-HPC allowed the minimization of cross-linking reactions during the polymerisation while preserving the thermo-responsive properties of HPC. The authors highlighted the "livingness" of the polymerisation of 4VP onto HPC. The graft-copolymerization proceeded for 6 h at 30 °C in isopropanol and Me$_6$TREN was used as ligand. The monomer conversion was 35 % resulting in a chain length of 35 monomeric units. The resulting graft-copolymer, P4VP$_{35}$-g-HPC$_{0.05}$ was found to be dually responsive because P4VP and HPC are, respectively, pH- and thermo-

responsive materials. At pH> 6, the graft-copolymer self-assembled into micelles with R_h of 190 nm due to the collapse of the P4VP chains forming the micelle core whereas the HPC backbone formed the micelle shell. Similar behavior was observed when the temperature was raised to 45 °C, however HPC this time formed the micelle cores while P4VP provided the shell that stabilized the micelles. The cloud point of the graft-copolymers was found to depend on the graft length; 4VP of DP=3 grafted onto HPC was not insufficient to give micelle formation.

Xu *et al.*[74] reported the preparation of a quaternised PDMAEMA grafted onto HPC to produce a cationic material. In the first step, Br-HPC with a DS of approximately 0.14 was synthesised in dichloromethane (DCM). This low value can be explained by a short reaction time of 5 h and/or the absence of catalyst. 2-(Dimethylaminoethyl)methacrylate (DMAEMA) was polymerised onto the $Br_{0.14}$-HPC at room temperature in an isopropanol/water mixture using CuBr and HMTETA which is known to lead to both high monomer conversion and low $Đ_M$, but which had not been used previously in homogeneous ATRP onto cellulose or cellulose derivatives. It resulted in 62% of monomer conversion after only 8 h. The PDMAEMA grafts were then partially quaternised by treating PDMAEMA-g-HPC with 1-bromohexane. The unmodified, neutral and quaternised graft-copolymers were tested as vectors for gene delivery. The DNA and both graft-copolymers (neutral and quaternised) were complexed into nanoparticles of 150-200 nm in diameter. The neutral graft-copolymer presented a lower cytotoxicity and better gene transfection properties compared to the linear PDMAEMA polymer. Moreover, on quaternisation of the PDMAEMA portion of the graft-copolymer, improved complexation with DNA was observed.

To summarise, HPC was modified using various bromo-ester bromides to form Br-HPC with DS ranging from 0.14 to 2.04 (Table S6 in ESI). DMF, THF and DCM were the commonly used solvents and the reaction time varied from 2.5 h to 2 days. Catalysts such as

TEA, pyridine and/or DMAP were used for enhancing the degree of functionalization. A dendronized macro-initiator permitted the preparation of graft-copolymers of HPC with a high graft density. Bromoisobutyryl anhydride as the reagent for functionalizing HPC produced a macro-initiator with the highest DS of 2.26. These macro-initiators were used for graft-copolymerising various monomers; Table S7 (ESI) summarises the reaction conditions used for each graft-copolymerisation. $CuBr_2$ has been used extensively with CuBr to control the production of radicals thus enhancing the control of the polymerisation. High dilution also permitted a reduction of radical-radical coupling. Furthermore, the use of tridentate ligands such as PMDETA was favoured over bidentate ligands such as bpy because of both the enhanced polymerisation rate and the lower required amount of Cu (I). To maintain the livingness of the polymerisation, the monomer conversion was kept below 64 %. Depending on the nature of the grafted polymers, the physical properties of HPC were changed. NIPAAM, OEGMA and DEGMA were polymerised onto HPC and the resulting graft-copolymers self-assembled into particles above their LCST. The presence of PNIPAAM and PDEGMA grafts decreased the LCST of HPC to 37 °C and 22 °C respectively whereas the grafting of POEGMA increased the LCST to 62 °C. Moreover, the graft-copolymerisation of 4VP introduced pH responsiveness making the resulting HPC dually responsive with a cloud point at a temperature greater than 45 °C or a pH > 6. The grafting of a quaternised PDMAEMA to the HPC backbone extended its potential uses to that of a vector for gene delivery. The preparation of graft-block copolymers such as P(t-BA)-b-PMMA-g-HPC, PMMA-g-G1-HPC and (PMMA-ran-PCMA)-g-HPC produced micelles with different sizes. The cross-linking of NIPAAM and PAA-b-PLC-g-HPC prolonged payload release over time and increased the size of its micelles, respectively. The graft-copolymers of HPC which self-assembled into particles are summarised in Table S8 (ESI). The size of particles varied from 64 nm to 570 nm depending on the length and density of the grafts. An increase in the graft

length resulted in the formation of larger particles; however the graft density is responsible for the shapes of particles as previously discussed in the part concerning graft-copolymers.

V. Graft-copolymers of other cellulose derivatives

Other cellulose derivatives such as cellulose diacetate (CDA), cellulose acetate (CA) and hydroxyethyl cellulose (HEC) have been used for graft-copolymerisation via ATRP processes in homogeneous media. Cellulose acetate and CDA are produced by esterification with acetic anhydride where the difference resides in the DS of the hydroxyl groups (1 and 2 respectively). These cellulosics are used in the production of membranes, eyeglasses, adhesives and photography film. HEC is made by reacting cellulose with ethylene oxide, producing a DS ranging from 0.8 to 1.8[6, 64]. HEC is used as a thickener, stabilizer, binder, suspending agent and a film former in the pharmaceutical, cosmetic, adhesive, and paint industries[64, 76, 77]. In this section of the review, ATRP of these derivatives will be covered. First, we will overview the preparation of graft-copolymers from CDA. Second, the graft-copolymerisation of CA with methyl diethylene glycol methacrylate (MDEGA) will be summarised, including the influence of the graft length on the segregation state. Finally, the modification of HEC with polyacrylamide (PAM) and poly(N,N-dimethylacrylamide) (PDAM) will be described alongside the potential application of the resulting copolymer in capillary electrophoresis.

In 2004, Shen *et al.*[78] were the first researchers to use the CDA backbone for grafting MMA. A macro-initiator Br-CDA was successfully prepared from bromoisobutyryl bromide in THF in the presence of pyridine. A ratio of AGU to Br equal to 1/0.5 was chosen and almost all Br reacted with the CDA backbone at the C6 position leading to a DS of 0.43. $Br_{0.43}$-CDA was used for graft-polymerising MMA in dioxane using CuBr/PMDETA as catalyst system. A ratio monomer to initiator, catalyst and ligand ([M]/[I]/[C]/[L]) equal to 300/1/0.5/1 was chosen and the reaction was conducted at 70 °C for 8 h. Kinetic studies

highlighted the control of the MMA polymerisation, however the monomer conversion was extremely low with a value of 4 %. Cleavage of PMMA grafts from the CDA backbone using a solution of sulphuric acid confirmed the narrow molecular weight distribution with a $Đ_M$ of ~1.4. Later on, Vlček *et al.*[79] showed interest in the preparation of CDA based graft-copolymers. Macro-initiators were synthesised from 2-bromoisobutyryl bromide in dioxane or dichloroacetyl chloride in acetone using both TEA/DMAP as a catalyst system. The DS of Br-CDA and Cl-CDA were varied depending on the molar ratio of functionalizing agent to CDA. For Br-CDA, a ratio AGU to Br equal to 1/0.3 led to a DS of 0.1 whereas a decrease of the ratio AGU/Br to 1/3.1 increased the DS to 0.52. The same was observed for Cl-CDA; a 1/1 and 1/4 ratio of AGU to Cl lead to a DS of 0.1 and 0.41 respectively. The resulting Br-CDAs and Cl-CDAs macro-initiators were used for graft-copolymerising MMA, t-BA and St. For the graft-copolymerisation of MMA and St, dioxane as solvent, $CuCl/CuCl_2$ as catalyst system and principally a tetradentate ligand, HMDETA, were used. $Cl_{0.41}$-DCA and $Cl_{0.1}$-DCA were used for the polymerisation of MMA at a temperature of 75 °C or 90 °C respectively whereas Br-CDAs were used for initiating the polymerisation of St at 110 °C. For a reaction time ranging from 6.5 to 18 h, MMA has been polymerised onto $Cl_{0.41}$-CDA with a monomer conversion between 5 to 10 % whereas the ATRP of MMA onto the $Cl_{0.1}$-CDA led to higher monomer conversion (18-21 %) in a shorter reaction time (1.5-2.5h) because the use of a low DS_{Cl} reduces the radical-radical coupling which is responsible for both loss of control and gelation. Regarding the polymerisation of St, the monomer conversion of 9-14 % was similar for both macro-initiators $Br_{0.52}$-CDA and $Br_{0.12}$-CDA. These two macro-initiators, Br-CDAs were further used to graft-copolymerise t-BA in acetone using a tridentate ligand, PMDETA. As for the polymerisation of MMA onto Cl-CDAs, $Br_{0.12}$-CDA was found to be a more efficient initiator than $Br_{0.52}$-CDA, with a monomer conversion of 25 % and 15 % after respectively 5 h and 8.5 h. The alkyl halide at

the chain end of $PMMA_{69}$-g-$CDA_{0.1}$ and PSt_{25}-g-$CDA_{0.12}$ graft-copolymers was also used to polymerise t-BA producing block graft-copolymers. The reaction conditions were similar to that for the ATRP of t-BA onto Br-CDAs, except that $CuCl_2$ was omitted most probably to increase the rate of the polymerisation. After 20 h of reaction for the polymerisation of t-BA onto $Br_{0.12}$-PSt_{25}-CDA, the monomer conversion was equal to 5 % whereas after 27 h, a monomer conversion of 10 % was reached for the polymerisation of t-BA onto $Cl_{0.1}$-$PMMA_{69}$-CDA. Overall, Vlček *et al.*[79] highlighted the versatility of ATRP process onto CDA i.e. from the grafting of a single polymeric chain to the grafting of block copolymers.

Vlček *et al.*[80] continued their investigation via the preparation of brush graft-copolymers combining ATRP and ROP processes. The CDA backbone was activated as described in their previous work, via bromination forming a macro-initiator with a DS value of 0.5. Thus, PCLs with a DP of 50 and 89 were grafted onto CDA via a ROP process. Thereafter, graft-copolymers of MMA, St, or t-BA were generated by ATRP where the length of the grafts was varied by adapting the reaction conditions which were similar to that in their previous work. The monomer conversion was relatively low ranging from 6 to 10 %, but it was found to be predictable when the graft-copolymerisation was performed with a high DS of macro-initiator.

Recently, Billy *et al.*[81] chose to investigate graft-copolymerisation of methyl diethylene glycol methacrylate (MDEGMA) from CA. Br-CA macro-initiators with a DS of 0.06 and 0.01 were synthesised from bromoisobutyryl bromide in the presence of TEA in THF, and the regioselectivity of substitution at the C6 position on the CA backbone was highlighted. A ratio of AGU to Br equal to 1/0.08 was used to synthesise $Br_{0.01}$-CA, however a decrease of the ratio AGU/Br produced a higher degree of functionalization of CA with bromo-ester bromide. The graft-copolymerisation of MDEGMA onto Br-CAs proceeded in cyclopentanone using PMDETA/CuCl as catalyst system at a temperature of 40 °C. For the

most substituted macro-initiator $Br_{0.06}$-CA, the reaction time used was shorter than that for $Br_{0.01}$-CA to limit radical-radical coupling and thus prevent gelation. After 2.5 and 7 h of polymerisation onto $Br_{0.06}$-CA and $Br_{0.01}$-CA respectively, the monomer conversion was equal to 16 and 19 % respectively. Due to the difference of targeted DP, $Br_{0.06}$-CA resulted in a high number of short grafts defined by 16 monomer units with a $Đ_M$ of approximately 1.5, however, the less substituted macro-initiator $Br_{0.01}$-CA gave long PMDEGMA grafts constituting of 80 monomer units. Morphological studies showed that the PMEGMA-g-CAs with longer grafts segregated more than those with shorter grafts. Furthermore, the size of the segregated phase increased with the length of the grafts. For a DP of 98, the resulting graft-copolymer was fully segregated with sharp interfaces and a radius of gyration of 11.5 nm.

Yang and co-workers[82] described the preparation of a PAM-g-HEC graft-copolymer in a controlled manner from macro-initiator Br-HEC which had been synthesised in a mixture of DMF/THF in the presence of TEA and DMAP as catalyst system (the degree of functionalization was not given). The graft-copolymerisation of AM onto Br-HEC was also conducted in a mixture of DMF/THF at 30 °C with CuBr/$CuBr_2$ as catalyst. An unusual tetradentate ligand, Me_6[14]aneN4, was used and 40% of monomer conversion was reached after 3 days of polymerisation. Owing to its rheological behavior and its ability to suppress electroosmotic flow (EOF), the graft-copolymer found a potential application in capillary electrophoresis (CE) systems such as for DNA separation. The same group continued their investigation with the preparation of the graft-copolymer, PDMA-g-HEC[83] by polymerisation of DMA onto Br-HEC. The reaction conditions were similar, however, a mixture of DMF/toluene was used. A monomer conversion of 62% and a $Đ_M$ of 4.2 were measured after 6 h of polymerisation suggesting a loss of polymerisation control. The graft-copolymer was

coated onto capillaries to investigate protein separation, and the results showed efficient protein separations at pH 2.2, 4.6 and 6.0 (Figure 15).

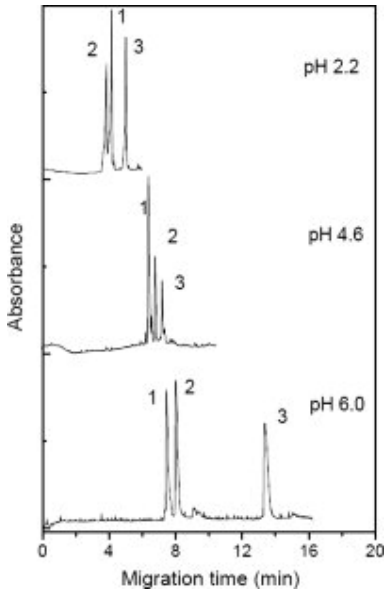

Figure 15: Effect of buffer pH on the separation of common proteins. Separation buffer: phosphate-citrate of pH 2.2, pH 4.6 and pH 6.0, separations were conducted in a PDMA-g-HEC coated capillary. Conditions: separation voltage, 20 kV; temperature, 25°C; detection, UV 214 nm; injection, 0.5 psi for 5 s; polymer concentration, 0.2% w/v. Sample: 0.5 mg/mL protein mixture, peak identification: 1, lysozyme; 2, cytochrome *c*; 3, ribonuclease A. Capillary, bare fused-silica of 40 cm total length (30 cm to the detector) ×75 μm id [83].

To summarise, CDA, CA and HEC have been successfully combined with synthetic polymers via graft-copolymerisation by ATRP. These derivatives were prior-functionalized using either bromoisobutyryl bromide or dichloroacteyl chloride and DS ranged from 0.1 to 0.52 depending in both the number of free hydroxyl groups and the ratio AGU to alkyl halide. Further details regarding the preparation of the macro-initiators are summarised in Table S9 (ESI). Regarding the graft-copolymerisation, PMMA, PSt and P(t-BA) were grafted on CDA and PMMA-g-CDA and PSt-g-CDA were further used to polymerise t-BA to form block

graft-copolymers. Combining ROP and ATRP processes, a brush graft-copolymer from PCL was also obtained. CA was graft-copolymerised with MDEGMA, however, CA systems remain sparsely investigated. The resulting graft-copolymer phase-segregated depending on the lengths of the grafts. HEC was modified with DAM and PDAM and the resulting products showed potential for applications in capillary electrophoresis. The reaction conditions for all graft-copolymerisations described in this section are summarised in Table S10 (ESI). In the case of CDA, dioxane was used as solvent and principally tetradentate ligands were used for the graft-polymerisation of both MMA and St whereas acetone and tridentate ligand was used as reaction media and ligand respectively for polymerizing t-BA onto CDA. Furthermore, the DS of the backbone seemed to affect the monomer conversion; higher conversion was obtained from lower DS macro-initiator and vice versa, potentially explained by a higher concentration of radicals for higher DS macro-initiator leading to gelation at too high monomer conversion.

VI. Conclusions

Grafting synthetic polymers onto solid cellulosic substrates such as membranes and fibers has been described extensively, however, chemical modification of cellulose and cellulose derivatives with polymers under homogeneous conditions is less well explored. The use of ATRP processes to graft polymers onto cellulose and its derivatives is highly attractive because they permit grafting in a controlled manner to produce designed bio-based hybrid materials. Despite this, the area has been the subject of study only for the last ten years. Cellulose, ethyl cellulose and hydroxypropyl cellulose have received most attention as materials for the graft-copolymerisation of various monomers, including methyl methacrylate, N-isopropylacrylamide and styrene. In this review we have described the synthetic polymers which have been grafted onto cellulose and its derivatives, and these are summarized chronologically in Figure 16 and by cellulose backbone type in Table 1. The main purpose of the grafting was to create amphiphilic hybrid materials which could self-assemble into nanoscale species and/or which possess stimuli-responsive properties. These materials are being considered for applications in biotechnology given their cost effectiveness and their largely renewable origin.

Figure 16: Graft-copolymers of cellulose and cellulose derivatives arranged in chronological order of date of publication.

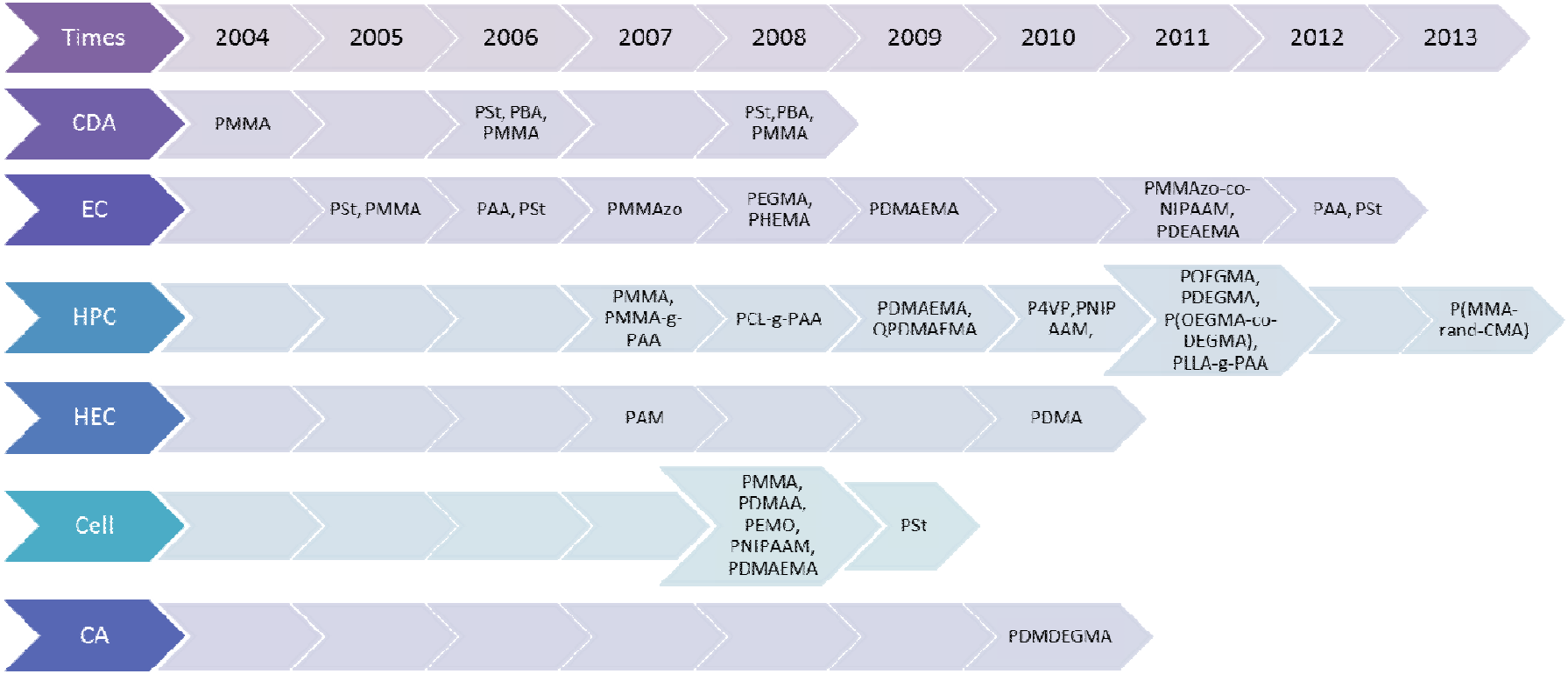

Table 1: Summary of the polymers grafted onto cellulose or its derivatives using ATRP under homogeneous conditions

From cellulose	From cellulose derivatives						
PMMA [40-42, 44, 46] PDMA [49, 50] PEMO [40] PNIPAAM [43, 51] PDMAEMA [45] PSt [42]	EC		HPC		Others		
	Assembly	Smart-assembly	Single Brush	Brush copolymer	CDA	HEC	CA
	PAA [57] PSt [53-54] PMMA [53] PHEMA [56]	MMAzo [59] PEGMA [60] PDEAEMA [61] PDMAEMA [62] PMMAzo-co-NIPAAM [63]	POEGMA [73] PDEGMA [73] P4VP [75] PMMA [68, 69] PDMAEMA [74] QPDMAEMA [74] NIPAAM [72]	PMMA-g-PAA [68] P(OEGMA-co-DEGMA) [73] P(MMA-ran-CMA) [69] PLLA-g-PAA [71] PCL-g-PAA [70]	PSt [80] PBuA [80] PMMA [80] PSt [79] P(t-BA) [79] PMMA [79] PMMA [78]	PAm [82] PDMA [83]	PMDEGMA [81]

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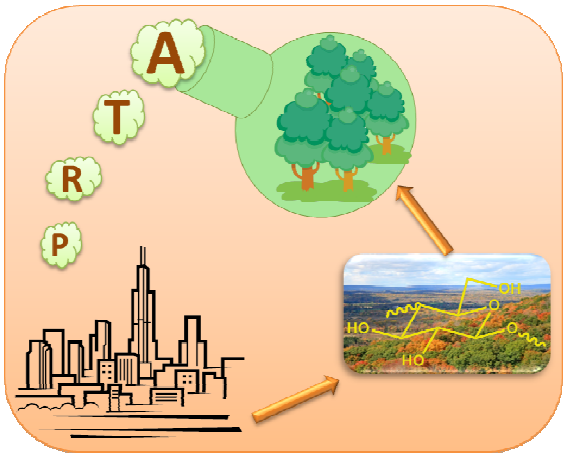
Graphical Abstract



Atom transfer radical polymerisation (ATRP) is used to modify cellulose and cellulose derivatives under homogeneous conditions, yielding novel materials for application in areas such as drug delivery.

Fanny Joubert graduated from Polytech Montpellier, France, in 2011, then moved to England where she is currently undertaking her PhD studies under the supervision of Prof. Neil Cameron and Dr David Hodgson at Durham University. Her research interests are focussed on the chemical modification of polysaccharides to prepare novel hybrid materials.

David Hodgson read Natural Sciences followed by a PhD at the University of Cambridge. He did post-doctoral work at the University of Toronto, then at SUNY Buffalo as a Royal Society-Fulbright post-doctoral fellow. David returned to the UK as a lecturer in Durham University in 2003 and was promoted to senior lecturer in 2013. Research in the DRWH group lies within the areas of physical organic and biological chemistry, with specific focus on nucleosides, nucleotides, bioconjugation, biopolymers and aqueous chemistry.

Dr. Osama M. Musa earned two Master of Science degrees in organic chemistry (heterocyclic) and polymer chemistry and a Doctorate in organic chemistry from Wayne State University, Michigan, USA under Prof. Martin Newcomb, with whom he also completed a post doctoral fellowship. He joined National Starch/ICI Company, New Jersey, USA in 1998 where he was the Reactive Chemistry and

Polymer Modification Pillar Leader. He is now the vice president of Global Technology & Innovation at Ashland Specialty Ingredients. Dr. Musa's current interests are novel monomers, oligomers, synthetic and natural polymers, and crosslinkers for use in a variety of industries including Personal Care, Pharmaceutical, Energy, Adhesives, Construction and Coatings.

Neil Cameron undertook his BSc and PhD at the University of Strathclyde in Glasgow. Following two post-doctoral periods, first in Eindhoven then at Heriot Watt University, he was appointed as a Lecturer (Assistant Professor) at Durham University in 1997. In 2005 he was promoted to Reader (Associate Professor) and in October 2008 he took up the position of Professor of Bioactive Chemistry in the same department. His research is focused on the preparation of novel polymeric materials, with particular emphasis on scaffolds for 3D in vitro cell culture and tissue engineering, self-assembling polypeptides, peptide-synthetic polymer hybrids and sugar-containing polymers (glycopolymers).