Review article

Graft modification of chitosan, cellulose and alginate using reversible deactivation radical polymerization (RDRP)

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ABSTRACT

This perspective covers the most recent literature on the graft-modification of the natural polymers celluloses, chitosan and alginate through reversible deactivation radical polymerization (NMP, ATRP and RAFT). The different routes to obtain well-defined polysaccharide-based hybrids including “grafting from” and “grafting to” approaches, and their applications as composite, stimuli-responsive, and biomaterials are discussed.

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1. Introduction

Natural polymers have received increasing attention in the past few decades due to concerns about the depletion of fossil fuel reserves and their potential to replace petroleum-based feed stocks. The major challenge for the manufacture of “green” materials however is to attain physicochemical properties similar or preferably superior to their counterparts derived from petroleum resources. Polysaccharides may be desirable for a variety of reasons, including their lower cost, biodegradability and biocompatibility, renewability, and abundance. While these features sound very promising, their physicochemical properties often represent challenges in the overall processing scheme for many materials. For example, cellulose and its derivatives are hydrophilic in nature and not compatible with hydrophobic polymer matrices, while alginate exhibits low stability against depolymerization in its native form and difficulties in processing.

Graft modification via reversible deactivation radical polymerization (RDRP) has become one of the most studied and reliable techniques to introduce new, or improve existing physicochemical properties of polysaccharides, such as mechanical strength, flexibility, water or oil repellence, adhesion, biocompatibility, stimuli-responsiveness, and a number of other properties, dramatically enhancing their value and potential utilization in the field of advanced, composite or biomaterials.[1–3] In this mini-review, we highlight the most recent achievements in the field of graft modification via RDRP of a select few polysaccharides of high current interest that have emerged during the past three years.

2. Reversible deactivation radical polymerization (RDRP)

The use of RDRP methodologies has opened the door for the development of a new class of highly functional materials. RDRP, formerly known as controlled/living radical polymerization (CLRP), is a powerful tool for the preparation of well-defined (co)polymers with precise control over molecular weight distribution, chain-end functionalities, and polymer architectural design. The main RDRP techniques include atom transfer radical polymerization (ATRP), from which many other related techniques are derived such as SARA ATRP (or SET-LRP), AGAT, or ARGET[3–5], nitroxide-mediated polymerization (NMP)[6,7], and reversible addition fragmentation chain transfer (RAFT)[8], all of which rely on the concept of employing a mediating agent (X) capable of reversibly deactivating
active chains (i.e. propagating radicals $P_n$) such that the majority of living chains are maintained in dormant form ($P_n\cdot X$) (Fig. 1). The control agent that caps the radical in ATRP is a halide atom originating from a transition-metal complex ($X\cdot M^{n+}$), whereas a nitroxide in NMP mediates the radical polymerization. In RAFT, thioacrylonitrile compounds (RAFT or chain transfer agent, CTA) form an intermediate carbon-centered radical with the propagating species, which undergo $\beta$-scission to either liberate a new carbon-centered radical (R-group), or regenerate the propagating radical.

3. Grafting techniques

Polysaccharides are generally very amenable to graft modification, due to their reactive groups (hydroxyl, amino or carboxyl). Essentially, grafting can be performed using three approaches: “grafting from”, in which polymer chains are grown from initiating sites on the surface, “grafting to”, whereby a pre-formed polymer with a reactive end-group is coupled with the functional group located on the surface, and “grafting through”, in which unsaturated units are immobilized on the surface and built into the polymer chains growing in solution. To our knowledge, there are only few reports on “grafting to” procedures involving polysaccharides, presumably because this approach has been shown to result in low graft densities and polymer loadings [9]. Polymer chains already bound to the surface in the “grafting to” approach may shield other reactive sites, thereby hindering the diffusion of subsequent chains, whereas chain-growth in the “grafting from” approach is only limited by the diffusion of small organic compounds, i.e. monomer molecules. However, this should not be generalized, as each substrate surface has to be individually considered, especially with respect to its morphology.
When performing “grafting from” reactions, the preliminary step is to convert the functional groups on the polysaccharide backbone into a haloester (ATRP), alkoxyamine (NMP), or thio-carbonyl thiol derivative (RAFT). Anchoring a haloester is usually done in one step through esterification with BiBB, for instance. In NMP, the functional groups are first converted into suitable moieties, for example acrylate, acrylamide or glycidyl methacrylate (GMA), which are then converted into the alkoxyamine by intramolecular radical 1,2-addition (IRA). The RAFT agent can be covalently bound to the surface either through a link at its R-group or Z-group. The R-approach usually leads to higher graft densities and better control over the reaction, as the grafts grow from the polysaccharide backbone and shielding effects and bi-radical brush-brush coupling can be avoided. Common RAFT agents bearing carboxylic acid functions are particularly useful, since they can easily react with the surface hydroxyl groups of the polysaccharide.

**4. Chitosan**

Chitosan (CS) is a biodegradable copolymer of N-acetyl-D-glucosamine and D-glucosamine, and obtained from chitin, which is the second most abundant polymer in the world after cellulose. The presence of hydroxyl, amino, and acetamido functional groups (Fig. 2) makes it an ideal starting material for applications in biochemistry, medicine, agriculture, as well as wastewater treatment [2]. In addition to its biodegradability, and nontoxicity, chitosan is known for its potential to adsorb contaminants such as dyes, metals, ions, phenols, drugs, or pesticides [13]. Chitosan can be dissolved in aqueous acidic media, following protonation of its amino groups. Its insolubility in common organic solvents however makes its functionalization quite challenging. Some studies have been reported where the NH2 groups were functionalized [14–17], for example to graft MAA from chitosan beads by ATRP to enhance cell adhesion and proliferation rate of human endothelial cells [14], or to remove Cd(II) ions from aqueous solution (Table 1) [15]. With NMP, acryloyl chloride can be used to functionalize the amino groups followed by IRA of the SG1-based BlocBuilder alkoxyamine to obtain chitosan-SG1 macroinitiators, and graft OEGMA, MEO2MA, and AN to obtain thermoresponsive chitosan with antimicrobial properties [16], or MMA, AN and sodium 4-styrenesulfonate (SS), yielding a hybrid material with potential application as a biocompatibilizer [17].

However, since some of the valuable bioproperties of chitosan are attributed to the presence of the amino group, preserving this functional group may be crucial for bio-related applications. Hence, several studies have focused on protecting the amino groups (e.g. by phthaloylation), before linking the RDRP agent to the OH groups [18,19]. Using pNIPAAm, pH- and T-responsive comb-shaped CS-g-pNIPAAm was prepared via ATRP, which self-assembled into micelles above LCST, and could have potential application in stimuli-responsive drug delivery [18]. For similar purposes, NIPAAm and AA block copolymers were grafted from chitosan via RAFT employing BPATT as CTA [19]. An interesting approach was reported for NMP using a Br-OH-TEMPO salt under acidic conditions, circumventing the necessity of a protecting group [20]. CS-TEMPO acted as macroinitiator and controller to graft styrene (S) and maleic anhydride (MA) with 90% conversion. To enable a homogeneous graft polymerization, which provides both more uniform grafting and higher grafting efficiency, the OH groups can be functionalized under acidic conditions with GMA [21], or GMA reversibly protected with sodium dodecylbenzenesulfonate (SDBS) to yield CS-g-GMA or CS-SDBS-g-GMA (Fig. 2) [10,22]. CS-SDBS-g-GMA can then be functionalized with a TIPNO-based, or SG1-based (BlocBuilder) alkoxyamine to graft S and nBA from the CS backbone under homogeneous conditions [10,22]. The SG1 and TIPNO nitroxides are more versatile and allow a wider selection of monomers to be grafted than TEMPO. Furthermore, they require lower reaction temperatures compared to TEMPO, which may be a concern for some natural polymers where exposure to temperatures above 120 °C for several hours may lead to degradation.

![Chitosan, Cellulose, Sodium Alginate](image-url)
Table 1
Examples of the graft modification of chitosan, cellulose derivatives and alginate using RDRP.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>RDRP</th>
<th>Pre-functionalized material (targeted group)</th>
<th>RDRP agents</th>
<th>Grafting approach</th>
<th>Grafted polymer</th>
<th>Reported properties; potential application</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chitosan beads</td>
<td>ATRP</td>
<td>CS-Br (OH, NH₂)</td>
<td>CuBr/CuBr₂/PMDETA</td>
<td>from</td>
<td>pMAA</td>
<td>Human cell carrier, in vitro prevascularization</td>
<td>[14]</td>
</tr>
<tr>
<td>Chitosan</td>
<td>NMP</td>
<td>CS-SG₁ (NH₂)</td>
<td>BlocBuilder</td>
<td>from</td>
<td>p(MMA-co-AN)/pSS</td>
<td>Hybrid material for biocompatibilizers</td>
<td>[15]</td>
</tr>
<tr>
<td></td>
<td>NMP</td>
<td>CS-SG₁ (OH)</td>
<td>BlocBuilder, SG₁</td>
<td>from</td>
<td>pOEEMA/pMEO₂MA/pAN</td>
<td>T-responsive, tunable LCST</td>
<td>[16]</td>
</tr>
<tr>
<td></td>
<td>ATRP</td>
<td>CS-Br (OH)</td>
<td>CuCl/bpy</td>
<td>from (R)</td>
<td>p(NIPAAm-b-AA)</td>
<td>pH/T-responsive, tunable LCST; drug carrier</td>
<td>[18]</td>
</tr>
<tr>
<td></td>
<td>RAFT</td>
<td>CS</td>
<td>BPATT</td>
<td>from</td>
<td>p(S-co-MA)</td>
<td>Improved thermal stability, NMP in scCO₂; controlled drug release</td>
<td>[19]</td>
</tr>
<tr>
<td></td>
<td>NMP</td>
<td>CS-TEMPO (OH)</td>
<td>Br–OH-TEMPO salt</td>
<td>from</td>
<td>to and from</td>
<td>Enhanced solubility in water and organic solvents, improved biocompatibility</td>
<td>[20]</td>
</tr>
<tr>
<td></td>
<td>NMP</td>
<td>CS-g-GMA and CS-g-GMA-NBB (OH)</td>
<td>NHS-BlocBuilder, SG₁</td>
<td>from</td>
<td>to</td>
<td>Soluble in DMSO, NMP in homogeneous media</td>
<td>[21]</td>
</tr>
<tr>
<td></td>
<td>NMP</td>
<td>CS-g-GMA (OH)</td>
<td>TIPNO-based “Universal Alkoxysamine” or BlocBuilder, SG₁</td>
<td>from</td>
<td>to</td>
<td>Biomedical, wastewater treatment, biopharmaceutics, agriculture</td>
<td>[22]</td>
</tr>
<tr>
<td>Cell</td>
<td>SARA ATRP</td>
<td>Cell-Br</td>
<td>Cu(0) wire/CuBr₂/ Me₆TREN PMDETA, dnpy, or bpy</td>
<td>from</td>
<td>p(isoprene)</td>
<td>Rigid, flexible, hydrophobic, hydrophilic, various Tg, material and biomedical applications</td>
<td>[25]</td>
</tr>
<tr>
<td>MCC</td>
<td>ARGET ATRP</td>
<td>MCC-Br</td>
<td>CuBr₂/PMDETA/AsAc</td>
<td>from</td>
<td>p(isoprene)</td>
<td>High strain, tensile strength; high resilient elastomers</td>
<td>[26]</td>
</tr>
<tr>
<td>Cell-Ac</td>
<td>NMP</td>
<td>Cell-Acryl</td>
<td>BlocBuilder, SG₁</td>
<td>from</td>
<td>pS</td>
<td>Hydrophobic, first report on RAFT and grafting from cellulose in ILS</td>
<td>[31]</td>
</tr>
<tr>
<td>Cell (cotton linters)</td>
<td>RAFT</td>
<td>Cell-Cl</td>
<td>Bis(thiobenzoyl) disulphide</td>
<td>from (R)</td>
<td>pNIPAAm/pDEAAm</td>
<td>T-responsive, tunable LCST; T-responsive delivery systems</td>
<td>[11]</td>
</tr>
<tr>
<td>Cell (filter paper)</td>
<td>RAFT</td>
<td>Cell-Cl</td>
<td>Methyl-3-mercaptopropionate, Cs₂</td>
<td>from (R)</td>
<td>pNIPAAm/pDEAAm</td>
<td>T-responsive, tunable LCST; T-responsive delivery systems</td>
<td>[11]</td>
</tr>
<tr>
<td>Cell (filter paper)</td>
<td>RAFT</td>
<td>Cell</td>
<td>Cumyl dithiobenzoate</td>
<td>from (R)</td>
<td>pHEMA</td>
<td>Hydrophobic; biomedical applications</td>
<td>[36]</td>
</tr>
<tr>
<td>Cell (wood pulp)</td>
<td>ATRP</td>
<td>Cell-Br</td>
<td>CuBr/PMDETA</td>
<td>from</td>
<td>p(BA-co-DAEMA)/p(LMA-co-DAEMA)</td>
<td>Various Tg, high elasticity, hydrophobic, thermal stability; thermoplastic elastomers</td>
<td>[32]</td>
</tr>
<tr>
<td>EC</td>
<td>ATRP</td>
<td>EC-Br</td>
<td>CuBr/PMDETA</td>
<td>from</td>
<td>pMAEDA/pEDDA/pMAHDA</td>
<td>Tunable Tg, hydrophobic, thermal stability; UV-absorbent coating materials</td>
<td>[33]</td>
</tr>
<tr>
<td>EC</td>
<td>ATRP</td>
<td>EC-Br</td>
<td>CuBr/PMDETA</td>
<td>from</td>
<td>pDMAEMA/p(MEO₂MA-co-DMAEMA)</td>
<td>T-responsive, CO₂-triggered LCST and drug release, micelle formation; stimuli-responsive drug delivery</td>
<td>[47]</td>
</tr>
<tr>
<td>BC</td>
<td>ATRP</td>
<td>BC-Br</td>
<td>CuBr/PMDETA</td>
<td>from</td>
<td>pMAA/pBA</td>
<td>Tunable hydrophobicity, improved thermal and mechanical properties; controlled drug release</td>
<td>[29]</td>
</tr>
<tr>
<td>CNC</td>
<td>ATRP</td>
<td>CNC-Br</td>
<td>CuBr/HMTETA</td>
<td>from</td>
<td>p(DMAEMA-co-NpMA)</td>
<td>Rapid hydrogel recovery and sol-gel transition, high storage modulus; advanced dynamic materials</td>
<td>[27]</td>
</tr>
<tr>
<td></td>
<td>ATRP</td>
<td>CNC-Br</td>
<td>CuBr/CuBr₂/PMDETA</td>
<td>from</td>
<td>pOEEMA/p(NIPAAm-co-EAN)</td>
<td>T-responsive, tunable LCST; Fluorescent, T-responsive; drug carriers, sensors</td>
<td>[28]</td>
</tr>
<tr>
<td></td>
<td>SET-LRP</td>
<td>CNC-Br</td>
<td>CuBr/PMDETA</td>
<td>from</td>
<td>pAEAm/pAEAm</td>
<td>Non-cytotoxic, immunogenic and non-immunogenic; adjuvant for vaccination, drug and DNA delivery</td>
<td>[41,42]</td>
</tr>
<tr>
<td></td>
<td>ATRP</td>
<td>CNC-Br</td>
<td>CuBr/HMTETA</td>
<td>from</td>
<td>pDMAEMA</td>
<td>T- and redox-responsive, virus binding, viral delivery</td>
<td>[43]</td>
</tr>
<tr>
<td></td>
<td>ATRP</td>
<td>CNC-Br</td>
<td>CuBr/bpy</td>
<td>from</td>
<td>pDMAEMA</td>
<td>Redox-responsive, transfection efficient, low cytotoxicity; gene therapy, drug delivery</td>
<td>[44]</td>
</tr>
<tr>
<td>RAFT, ATRP</td>
<td>CNC-Br</td>
<td>to and from</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[45]</td>
</tr>
</tbody>
</table>
Employing the precursors CS-g-GMA [21] and CS-SDBS-g-GMA [22], it is also possible to perform the "grafting to" approach. PEGylation of CS-g-GMA in water was performed using "grafting from" and "to", which can enhance the solubility of CS in water and organic solvents, and possibly improve biocompatibility [21]. In addition, homo, random and block (co)polymers of S, nBA, and AA were grafted to CS-SDBS-g-GMA in homogeneous media [22]. In both cases, SG1-end-capped ("living") polymers were grafted to GMA modified CS by simple reaction of the GMA double bond and the macroradical originating from thermal activation of SG1. "Grafting to" allows a precise control over the molecular weight of the grafted polymer, thereby allowing tailoring of the properties of the final product. The "grafting from" approach allows for higher polymer loadings and graft densities, however to characterize the grafted chains, an appropriate cleaving procedure has yet to be developed, which with natural polymers is often a challenge. In summary, NMP has become a frequently employed method over the past few years, possibly because of its facile and straightforward implementation, and the absence of impurities in the final product, which is advantageous, especially for applications in the biomedical sector. NMP usually does not require a catalyst, thus avoiding additional purification steps for catalyst removal. Rigorous exclusion of air and moisture, or removal of residual metallic atoms is also not required, as with conventional ATRP [4,5].

5. Cellulose and cellulose derivatives

Cellulose is the most abundantly present renewable biopolymer, produced by plants, animals, and bacteria. Cellulose is composed of repetitive D-glucose units linked through $\beta(1 \rightarrow 4)$-glycosidic bonds (Fig. 2), and available in different forms depending on the functionalization (e.g. ethyl cellulose (EC), or hydroxypropyl cellulose (HPC)), shape, size and degree of crystallinity (e.g. micro- or nanocrystalline cellulose). "Nanocellulose" refers tocellulosic extracts or processed materials with nano-scale dimensions, namely cellulose nanocrystals (CNCs), nanofibrillated cellulose (NFC), also referred to as cellulose nanofibrils (CNF); and bacterial cellulose (BC). Nanocelluloses are drawing a tremendous level of attention related to their exceptional properties such as high tensile strength, aspect ratios, surface area, low toxicity and biodegradability [23]. Potential applications of nanocellulose are envisioned in a wide range of areas including the paper, packaging or composite industries, medical and hygiene products, the food industry, and many others [23]. Hence, the past few years have witnessed increasing efforts toward the large-scale production of especially CNC, due to easy access to cellulose-rich sources and the potential development of cost-efficient production processes [24].

Graft modification of cellulose and its derivative with synthetic polymers has been extensively studied to improve thermal and mechanical properties, compatibility with hydrophobic nanocomposites, and dispersibility [1]. For instance, flexible polyisoprene can be grafted from stiff cellulose (MCC) to combine rigidity, flexibility, hydrophobicity and hydrophilicity in one material [25], or to prepare high resilient cellulose elastomers with high strain, and reasonable tensile strength [26]. Self-healing hydrogels can be prepared by grafting DMAEMA/naphthyl-functionalized methacrylate (NpMA) copolymers from CNC, which exhibit rapid sol–gel transition and high storage modulus [27]. Further modification of CNC includes the introduction of LCST by grafted OEGMA [28]. Regarding BC, there is only one report available where pMMA or pBA was grown from BiBB functionalized BC-membranes [29]. All of these studies are based on ATRP, which is the most frequently used RDRP technique for cellulose. To our knowledge, there are only two studies in which NMP was employed. pS and pAM were grafted from the backbone of Barton ester-modified MCC and HPC under homogeneous conditions using 2-mercaptopyridine N-oxide and TEMPO, respectively [30]. More recently, BlocBuilder was linked to acrylated cellulose acetate to graft pS in the presence of 5 mol\% free SG1 [31]. In both reports, the pS grafts were isolated by hydrolysis of the cellulose backbone for polymer characterization, which confirmed moderate control over the polymerization.

Besides synthetic polymers, biopolymers from natural rosin or fatty acids can be grafted from cellulose to prepare thermoplastic elastomer materials [32]. Using ATRP, copolymers of DAEMA (derived from rosin), and LMA (derived from fatty acids) can be grafted to synthesize cell-g-p(BA-co-DAEMA) and cell-g-p(LMA-co-DAEMA) with varying glass transition temperatures $T_g$ and remarkable elasticity [32]. Similarly, four different rosin-based monomers were graft-copolymerized from an ethyl cellulose backbone to increase thermal stability and introduce tunable $T_g$, film forming and UV-adsorption properties [33].

In the last decade, ionic liquids (ILs) have emerged as alternatives to volatile organic compounds, due to their low vapor pressure, recyclability, high thermal and chemical stability, nonflammability and miscibility with other solvent systems. Moreover, they show an enhanced ability to dissolve polysaccharides such as starch or native cellulose [34]. Two reports exist on "grafting from" cellulose in ILs via RAFT [35,11], in which chloride moieties were first introduced onto the cellulose backbone, followed by conversion into the RAFT agent and grafting of MMA [35] or DEAAm and NIPAm for potential use as temperature-responsive delivery systems (Fig. 2) [11]. In addition, γ-radiation as an alternative to thermal initiation can be used to conduct RAFT under mild conditions, and has been applied to graft HEMA from cellulose fibers using cumyl dithiobenzoate (CDB) as CTA [36].

The first application of fluorescent CNC for bioimaging [37]
provided strong impetus for the exploration of nanocellulose in drug and gene delivery systems, enzyme/protein immobilization scaffolds, bioimaging, and tissue engineering [38,39]. For instance, thermo-enhanced fluorescent CNC can be prepared by grafting NIPAAm and fluorescent dye EANi via AGET ATRP [40]. Cationic pAEM and pAEMA were grafted via SET-LLRP [41]. Neither unmodified CNC nor polyacationic CNC decreased cell viability in mouse macrophage (J774A.1) or human breast adenocarcinoma (MCF-7) cell lines [41]. Further investigations suggested that one of the CNC-g-pAEMA hybrids possessed immunogenic properties, whereas CNC-g-pAEM did not show any immunogenic activity, making it potentially useful for drug and DNA delivery [42]. Cationic pDMAEMA grafted CNCs prepared via ATRP with pH-responsive and redox-responsive properties were also employed for viral [43], and non-viral gene delivery [44,45]. The needle-like shape of CNC seems to play a crucial role on enhancing transfection efficiency, whereas CNC-based polyion carriers show good activity in suppressing the growth of cancer cells and tumors [44]. Based on this study, a bi-functional CNC-based macroinitiator was prepared to graft pPEGEEMA and pDMAEMA individually via RAFT and ATRP [45]. Cationic pDMAEMA chains not only bind pDNA efficiently, but can also be used as reducing and protective agents to form Au nanoparticles for in vitro CT imaging, wherein charged pPEGEEMA brushes reduce cytotoxicity and improve the transfection performance [45]. Furthermore, CNFs were used to produce bioactive films by grafting AEM-co-HEMA via SI-RAFT and conjugating a short peptide to the modified CNF [46]. The resulting bioactive peptide-CNPs showed high binding capability toward human IgG, while maintaining very good nonspecific protein resistance, and may offer a new platform for low cost and disposable CNF-based hIgC sensors and other sustainable bioactive materials [46]. DMAEMA and MEO2MA were also grafted from ethyl cellulose (EC) via SI-ATRP to obtain temperature- and CO2-responsive EC-g-pDMAEMA and EC-g-p(MEO2MA-co-DMAEMA), which self-assembled into micelles with a hydrophobic EC core [47]. The LCST could be adjusted by bubbling CO2/Ar, whereas the hydrodynamic radius (R0) of the micelles increased with temperature, allowing the controlled drug release of doxorubicin by changing the temperature and alternatively bubbling CO2/Ar [47].

6. Alginate

Alginate is an anionic polysaccharide typically extracted by the alkali treatment of seaweed. It is obtained as a water-soluble block-copolymer, containing blocks of (1,4)-linked β-d-mannuronic (M) and α-l-guluronic (G), which are arranged irregularly as MM, GM, and GG regions (Fig. 2). Alginate has been extensively studied and used for biomedical applications, due to its biocompatibility, relatively low cost, and ability to bind multivalent cations and form insoluble hydrogels [48,49]. Alginate can be chemically modified by reactions of the hydroxyl or carboxyl groups. Recently, the first case of living radical polymerization from alginate using SET-LLRP was reported [12]. Native sodium alginate was depolymerized into molecular weight fragments (~12 000 g/mol) and then modified with tetrabutylammonium to enable 11-carboxylmethylidazole (CDI) activated anhydrous esterification of the alginate hydroxyl groups with bromoisobutyric acid (Fig. 2). Hydrophobic pMMA was then grafted from the macroinitiator in a highly controlled manner, which resulted in polymerization induced self-assembly (PISA) of the amphiphilic graft-copolymers. Micelles containing alginate as the outer-shell with preserved carbonate moieties are expected to find application in the area of controlled and targeted delivery, with the possibility for postpolymerization conjugation of drugs and signal molecules from the alginate backbone and possible cross-linking of micelles to produce hybrid nanohydrogel systems [12].

7. Conclusions and outlook

RDRP techniques are promising ways to incorporate desired characteristics and functionalities into polysaccharides in a precisely-controlled manner. The overall manufacture of these composite hybrids however may involve time consuming, multi-step and/or expensive procedures, such as synthesis of the nitroxide or RAFT agent, functionalization with initiating groups, or removal of the catalyst, thereby increasing costs and reducing economic viability. Therefore, potential applications are mainly expected in niches and specialty markets, such as flexible electronics, optical devices, diagnostics, tissue engineering, or drug delivery. The use of especially alginate and nanocellulose as biomaterials is still in its infancy. Given the non-biocompatibility and toxic effects of traditional nanomaterials like carbon nanotubes or metal nanoparticles, the next few years are expected to see a surge in activity expanding the use of polysaccharides as biomaterials, along with further development of RDRP techniques.

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