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Self-assembled cellulose materials for biomedicine: A review

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Highlights

- Modification of cellulose and its derivatives.
- Stimuli-responsive cellulose-based materials.
- Application of self-assembled cellulose-based materials.

Abstract: Cellulose-based materials have reached a growing interest for the improvement of biomedicine, due to their good biocompatibility, biodegradability, and low toxicity. Self-assembly is a spontaneous process by which organized structures with particular functions and properties could be obtained without additional complicated processing steps. This article describes the modifications, properties and applications of cellulose and its derivatives, which including a detailed review of representative types of solvents such as NMMO, DMAc/LiCl, some molten salt hydrates, some aqueous solutions of metal complexes, ionic liquids and NaOH-water system etc. The modifications were frequently performed by esterification, etherification, ATRP, RAFT, ROP and other novel methods.

Stimuli-responsive cellulose-based materials, such as temperature-, pH-, light- and redox-responsive, were synthesized for their superior performance. Additionally, the applications of cellulose-based materials which can self-assemble into micelles, vesicles and other aggregates, for drug/gene delivery, bioimaging, biosensor, are also discussed.

KeyWords: Cellulose; Self-assemble; Modification; Stimuli-responsive; Biomedicine

1. Introduction

Self-assembly is well-known as one of the most promising strategies to achieve micelles from amphiphilic polymers (Yang, & Nan, 2012; Zuo, Liu, & Han, 2014). While there are both hydrophilic groups and hydrophobic groups in backbone of molecule chain, amphiphilic block copolymers in solution can self-assemble into a variety of nanoscale structures such as micelle and vesicle (Li & Guo, 2013; Palao-Suay, Gómez-Mascaraque, Aguilar, Vázquez-Lasa, & Román, 2016). And polymer micelles have vast potential applications in the field of biomedicine, such as drug or gene delivery, biosensor and bioimaging (Branco, & Schneider, 2009; Park et al., 2008; Rösler, Vandermeulen, & Klok, 2012). However, the large-scale application of many synthetic block polymers is limited by their high prices and potential biotoxicity. Therefore, there has been a growing interest in developing amphiphilic polymers from natural polysaccharides (Yang, & Pan, 2012), due to their outstanding merits such as abundant, cheap, safe, non-toxic, biocompatible, and biodegradable (Chang, & Zhang, 2010; Hassani, Hendra, & Bouchemal 2012; Liu, Jiao, Wang, Zhou, & Zhang, 2008; Yang, & Yang, 2013).

Cellulose is a kind of polysaccharides which can be derived from tress, cotton, straw and other higher plant cell walls since it could be formed by plants through photosynthesis (Mutwil, Debolt, & Persson, 2008; Yu, Liu, Qiu, & Huang, 2007). It is

one of the most abundant natural polymer organic compounds on earth which consists of β -(1-4)-linked anhydroglucose repeating unit $((C_6H_{10}O_5)_n, n=10000 \text{ to } 15000$, where n is depended on the cellulose source material) (Liu, Yu, & Huang, 2005; Moon Martini, Nairn, Simonsen, & Youngblood, 2011). There are many kinds of cellulose derivatives used frequently, such as cellulose acetate (CA), methylcellulose (MC), ethylcellulose (EC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), sodium carboxymethylcellulose (CMC) and others. In addition, cellulose and its derivatives have been demonstrated to be nontoxic in both animal and humans which make it ideal material for biomedicine (Habibi, Lucia, & Rojas, 2010).

In the meantime, the rich functional groups in cellulose molecule provide the opportunity for modification of cellulose and its derivatives to obtain the product which could self-assemble. Recently, an increasing number of publications demonstrate that self-assembly as a feasible and effective strategy to prepare cellulose-based materials has been deeply studied (Tsiptsias, Stefopoulos, Kokkinomalis, Papadopoulou, & Panayiotou, 2008). During the self-assembly of cellulose-based materials, molecules associate into well-defined, functional geometries through simple interactions with each other. The self-assembly process of cellulose and its derivatives is similar to many other biological molecules, like DNA and proteins, that could proceed in water phase under normal conditions to generate materials with superior properties and functions (O'SULLIVAN, 1997).

Till now, cellulose-based materials which could self-assemble have been demonstrated tremendous potential for applications in the field of biomedicine. Here, we reviewed the recent advancement of self-assembled cellulose materials in biomedicine. Firstly, we focused on the dissolution and modification of cellulose and its derivatives. In the meantime, self-assembly of cellulose-based materials were

summarized concisely. Subsequently, cellulose-based materials with different stimuli-responsive, such as temperature-, pH-, light- and redox-responsive were emphasized. Finally, we further discussed the application of self-assembled cellulose materials in biomedicine, such as drug/gene delivery, bioimaging, biosensor and other fields. By presenting self-assembled cellulose materials from theory to application, we wish that this review will provide a broad overview of this promising new material in biomedicine.

2. Modification of cellulose and its derivatives

2.1 Dissolution of cellulose

Natural cellulose, with strong inter- and intra-molecular hydrogen bonding caused by the hydroxy groups, is high crystalloid, which makes it insoluble in water and common organic solvents (Roy, Semsarilar, Guthrie, & Perrier, 2009). These properties limit their development and utilization. Hence, the dissolution of cellulose or its derivatives is the most urgent problem what should be dissolved. Therefore, in recent years, increasing attentions have been attracted to the studies on the dissolution of cellulose and the homogeneous derivatives and their modification. Since the first attempts to dissolve cellulose or its derivatives, a variety of cellulose solvent systems have been developed, including N-methylmorpholine oxide (NMMO) (Dogan, & Hilmioglu, 2009; Rosenau et al., 2002; Rosenau Potthast, Sixta, & Kosma, 2001), N,N-dimethylacetamide/lithium chloride (DMAc/LiCl) (Edgar, Arnold, Blount, Lawniczak, & Lowman, 1995; Tosh, Saikia, & Dass, 2000), 1,3-dimethyl-2-imidazolidinone/lithium chloride (DMI)/LiCl (Fischer, Leipner, Thümmeler, Brendler, & Peters, 2003), N,N-dimethylformamide/nitrous tetroxide (DMF/N₂O₄) (Wagenknecht, Nehls, & Philipp, 1993), dimethyl sulfoxide/tetrabutyl-ammonium fluoride (DMSO/TBAF) (Ass, Frollini, & Heinze, 2004;

Liebert, & Heinze, 2001), some molten salt hydrates, such as $\text{LiClO}_4 \cdot 3\text{H}_2\text{O}$ (Fischer, Thümmeler, Pfeiffer, Liebert, & Heinze, 2002), $\text{LiSCN} \cdot 2\text{H}_2\text{O}$ (Fischer, Leipner, Thümmeler, Brendler, & Peters, 2003), and some aqueous solutions of metal complexes (Saalwächter et al., 2000).

In recent years, the comprehensive utilization of cellulose resources has drawn much attention from the researchers, and there is an increasing demand to obtain and dissolve cellulose. Many solvents have been developed for the dissolution of cellulose, but they all suffer from drawbacks, such as cost is high, environmental pollution and solubility is insufficient. Thus, new solvents of cellulose to be developed is necessary to overcome the drawbacks of traditional solvents.

In the last decade, ionic liquids(ILs) have emerged as effective and green solvent, mainly due to their high thermal and chemical stability, nonflammable nature, and miscibility with many other solvent systems (Mecerreyes, 2015). Rogers et al. (2002) found that cellulose could be dissolved in IL 1-butyl-3-methyl imidazole chloride ($[\text{C4mim}]\text{Cl}$), which opened up a new way for the development of a class of cellulose solvent systems. Subsequently, 1-Butyl-3-methylimidazolium chloride (BMIMCl), 1-ethyl-3-methylimidazolium acetate (EMIMAc) and 1-allyl-3- methylimidazolium chloride (AMIMCl) have been used for dissolving cellulose and performing homogeneous esterification of cellulose as well (Heinze, Schwikal, & Barthel, 2005; Kosan, Michels, & Meister, 2008; Turner, Spear, Holbrey, & Rogers, 2004; Wendler, Todi, & Meister, 2012). It is thought that both anions and cations are involved in the dissolution process (Pinkert, Marsh, Pang, & Staiger, 2009). Scheme 1 shows the proposed dissolution mechanism of cellulose in ionic liquids.

And many other ILs which can dissolve cellulose have been reported, as shown in table 1. We can see that the ILs with moderate amount of water which can dissolve

cellulose and its derivatives at lower temperature with less time. Moreover, it can be easily regenerated through the addition of water or other poor solvents. In addition, used ILs can be easily recycled by the removal of water. In the recent decade, lots of cellulose and its derivatives were modified in ILs. A series of microcrystalline cellulose-graft-Poly(L-lactide) (MCC-g-PLA) with various molecular factors were synthesized in IL BMIMCl by Guo et al.(2012). In 2013, they synthesized self-associating cellulose-graft-poly (ϵ -caprolactone) (cellulose-g-PCL) copolymers via homogeneous ring-opening polymerization (ROP) of ϵ -CL onto softwood dissolved pulp substrate in IL BMIMCl (Guo, Wang, Shen, Shu, & Sun, 2013). In 2015, cellulose acetate was synthesized in an IL, 1,5-diazabicyclo(4.3.0)non-5-enium acetate [HDBN][OAc] (Jogunola et al., 2016). Although significant progress has been achieved in this field, there are still many disadvantages including high dissolution temperature, slow dissolution rate, high solution viscosity and high cost.

The last major cellulose solvent family is based on aqueous sodium hydroxide solutions. Preparing cellulose solutions in NaOH-water system is very attractive. It is rather simple, with reagents that are easy to obtain and cheap, and the solvent itself is well known and widely used in the industry (Budtova & Navard, 2016).

The dissolution and regeneration of cellulose in NaOH-water system which consisted of NaOH, urea and thiourea, such as aqueous NaOH, NaOH/urea aqueous, NaOH/thiourea, has been extensively studied over the past decades (Isogai & Atalla, 1998; Li, Wang, Lu, & Zhang, 2015; Qi, Chang, & Zhang, 2008; Xiong, Zhao, Hu, Zhang, & Cheng, 2014; Yang et al., 2011; Zhao et al., 2013; Zhang, Li, Yu, & Hsieh, 2010). A series of derivatives were synthesized in NaOH-water system. Qi et al. (2012), synthesized 3-Allyloxy-2-hydroxypropylcelluloses (AHP-celluloses) by the reaction of cellulose with allyl glycidylether (AGE) in NaOH/urea aqueous solution.

In 2016, graphene oxide reinforced regenerated cellulose/polyvinyl alcohol (GO-RCE/PVA) ternary hydrogels were successfully prepared via a repeated freezing and thawing method in NaOH/urea aqueous solution (Xie et al., 2016). For alkali/urea aqueous systems, urea is not directly interacting with NaOH or with cellulose, but by another indirect way. It can be that the role of urea is to trap the free water that is present in solution, preventing cellulose chain to interact with other cellulose chains and associate via hydrogen bond formation (Egal, Budtova, & Navard, 2008). Cellulose was dissolved rapidly in 9.5 wt% NaOH/4.5 wt% thiourea aqueous solution pre-cooled to -5 °C, the viscosity of the cellulose solution increased slowly with an increase in the temperature at 0-40 °C (Ruan, Lue, & Zhang, 2008). We can find that cellulose can be dissolved at low temperature; Furthermore, the NaOH and thiourea is cheap and can be obtained easily.

In recent years, a lot of effort has been done for dissolution of cellulose, and many new solvents with different merits, such as high solubility, lower solution temperature or easy regeneration etc., have been developed for dissolution of cellulose. A new all-aqueous process of the dissolution/regeneration of cellulose was developed. Cellulose was completely dissolved in the 54-60 wt% lithium bromide aqueous solutions in the temperature range of 110-130 °C within a dissolution time of 1 h (Yang et al., 2014). Then, the cellulose was directly regenerated from the solution by cooling down to approximately 70 °C and removing the salts with water, yielding a translucent gel. In 2015, cold phosphoric acid was used to dissolve cellulose in order to convert crystalline cellulose into its molecular form (Hao et al., 2015). More efficient solvents, tetrabutylammonium acetate (TBAA)/DMSO (Kang et al., 2006), DMSO/1-ethyl-3-methylimidazolium acetate([C₂mim][CH₃COO])(Sun, Miao, Yu, & Zhang, 2015), 1-butyl-3-methylimidazolium acetate (BmimAc)/DMSO (Li et al.,

2016) and tetra-butylammoniumhydroxide (TBAH)/urea (Yamamoto & Miyake, 2017), were used to dissolve cellulose.

2.2 Strategies of modification

In aqueous solution, amphiphilic polymers spontaneously self-assemble into 3D supramolecular structures with different morphologies such as spherical micelle, wormlike micelle, layered micelle and vesicle etc. Particularly, in the core-shell organization, the inner core which is surrounded by a hydrophilic shell is composed of the hydrophobic part of the amphiphilic polymer, it can serve as a container of poor soluble substance. Therefore, the choice of appropriate monomers, macromolecular architecture and hydrophobic/hydrophilic balance will be crucial in the design of self-assembly systems.

As we all know, the molecular which is amphiphilic can self-assemble into various aggregates in solutions under appropriate condition. It means that the cellulose and its derivatives which are equipped with both hydrophilic and hydrophobic groups can spontaneously self-assemble into supramolecular structures. As discussed above, the chemical structure of cellulose includes abundant of functional groups, -OH group. The chemical modifications of cellulose considered here are esterification, etherification and grafting of the backbone. Esterification is one of the most traditional methods for modification of cellulose. For example, commercial rayon grade cellulose was esterified with acetic anhydride in the lithium chloride-N,N-dimethylacetamide (LiCl-DMAc) solvent system (Tosh, Saikia, & Dass, 2000). And a series of cellulose esters (CEs) with high degrees of substitution have been obtained by linking aliphatic acid chlorides (from C8 to C18) onto cellulose backbone, in a homogeneous LiCl/DMAc medium (Crépy, Miri, Joly, Martin, & Lefebvre, 2011). Cao et al. (2011) synthesized cellulose mixed-esters containing

acetyl and butyryl without any catalyst in the ionic liquid AmimCl. Cao et al. (2013) found that DMSO/aqueous NaOH (or KOH) is a highly suitable system for the production of CEs. The little time required for the synthesis of cellulose acetate, cellulose propionate, and cellulose butyrate via the transesterification reaction with vinyl ester. And in 2014, they developed a novel transesterification system to rapidly synthesize cellulose aliphatic esters (Cao et al., 2014). This method involved the transesterification of cellulose with vinyl esters (from C4 to C14) in DMSO under the catalysis of aqueous NaOH. And the results confirmed that CEs could be synthesized at 100 °C within 5 min. High water content or excessive amounts of NaOH were detrimental to the synthesis of CEs.

The use of etherification reactions provides another important way of modifying the structure of cellulose chemically. Song et al. (2011) introduced hydrophobic hexadecyl groups to the hydroxyl groups of cellulose via etherification reaction to synthesize amphiphilic cationic cellulose derivatives (HMQC). The amphiphilic cellulose derivatives in aqueous solution were able to self-assemble into nano-scaled polymeric micelles with spherical shape. E.S. Abdel-Halim (2014) used cellulose extracted from sugarcane bagasse to prepare hydroxyethyl cellulose through reaction with ethylene oxide in alkaline medium.

Many other methods used for the modification of cellulose and its derivatives, such as ring opening polymerisation (ROP), atom transfer radical polymerization (ATRP), reversible addition-fragmentation chain transfer (RAFT) etc., have been reported. And the cellulose graft copolymers is usually achieved by modifying the cellulose molecules through the creation of branches (grafts) of synthetic polymers that impart specific properties onto the cellulose substrate, without destroying its intrinsic properties. (Roy, Semsarilar, Guthrie, & Perrier, 2009) The synthesis of

cellulose graft copolymers marked the first departure from the traditional means of modifying cellulose. ROP is a well-established technique to polymerize cyclic monomers such as lactones and lactides. An alcohol (or hydroxyl group) is generally used as the initiator for ROP which makes it especially interesting to utilise ROP of cyclic monomers for the polymer modification of cellulose or cellulose derivatives (Jérôme & Lecomte, 2008). There is a report in the literature reported that cellulose-based amphiphilic copolymers can be synthesized by ROP, with Tin(II) 2-ethylhexanoate ($\text{Sn}(\text{Oct})_2$) as the catalyst (Carlmark, Larsson, & Malmström, 2012).

A series of biodegradable amphiphilic cellulose-g-PCL copolymers with varying molecular factors were synthesized via homogeneous ROP of ϵ -CL onto cellulose backbone in IL [Bmim]Cl. Yuan et al. (2007) prepared a series of novel EC-g-PCL graft copolymers and EC-g-PCL-b-PLLA graft-block copolymers by ROP.

Among the methods to prepare cellulose graft copolymers, ATRP is popular for synthesizing cellulosic graft copolymer. Carlmark et al. (2001) reported on the ATRP of methyl acrylate from initiators immobilized on cellulose fibers, which is the first time that an organic substrate has been employed for surface grafting by controlled radical techniques. Since that, various polymer chains, such as poly (2-hydroxyethyl methacrylate) (PHEMA) (Kang, Liu, Liu, & Huang, 2008), poly(butyl acrylate) (PBA) (Li, Xiao, Zheng, & Xiao, 2011), 6-[4-(4-methoxyphenylazo)phenoxy] hexyl methacrylate(MMAzo) (Tang, Gao, Fan, & Zhou, 2007), poly (methyl methacrylate)(PMMA) (Chang, Yamabuki, Onimura, & Oishi, 2008; Zhong, Chai, & Fu, 2012), poly(N,N-dimethylamino-2-ethyl methacrylate) (PDMAEMA) (Sui et al., 2008), have been grafted to the cellulose backbone. Cellulose derivatives are widely applied in many fields due to their dissolution in common organic solvents. Environmental responsive cellulosic materials can be prepared via ATRP from

cellulose derivatives. In 2009, Yan and his group prepared pH-sensitive cellulose-based dual graft molecular brushes, composed of ethyl cellulose-graft-poly(N,N-dimethylaminoethyl methacrylate)-graft-poly(ϵ -caprolactone) (EC-g-PDMAEMA-g-PCL) by ROP and ATRP (Yan et al., 2009). The process is shown in Figure 1. They also studied and found that these kinds of biocompatible copolymer could self-assemble to micelles in aqueous solution.

Thermosensitive ethyl cellulose graft poly (poly(ethylene glycol) methyl ether methacrylate) (EC-g-P(PEGMA)) amphiphilic copolymers were synthesized via ATRP (Li et al., 2008). Redox-sensitive and thermo-responsive cellulose derivatives, hydroxypropyl cellulose-graft-poly (2-acryloyloxyethyl ferrocenecarboxylate) (HPC-g-PAEFC), were synthesized via atom transfer radical polymerization. The obtained HPC-g-PAEFC graft copolymers have the unique redox-responsivity of ferrocene and the biodegradability, non-toxicity and biocompatibility of cellulose, which may be used in redox-responsive drug delivery (Li et al., 2015).

RAFT polymerization is another promising living radical method for synthesizing well-defined graft polymers. Such as, ethyl acrylate (EA) and N-isopropylacrylamide (NIPAAm) were grafted onto the hydroxypropylcellulose backbone by RAFT (Semsarilar, Ladmiraal, & Perrier, 2010). And methylmethacrylate (MMA) was grafted onto cellulose by RAFT in a typical IL (BMIMCl) (Lin et al., 2013). In recent years, RAFT polymerization has been successfully used for the graft of various monomers onto the cellulose backbone, as shown in table 2.

In recent years, many other methods for modification of cellulose and its derivatives have been developed. Water-soluble cellulose-graft-PDMAAm copolymers were prepared by single-electron-transfer living radical polymerization (SET-LRP) (Hiltunen, Siirilä, Aseyev, & Maunu, 2012). And beta-cyclodextrin (β -CD)

functionalized cellulose acetate (CA) nanofibers have been successfully prepared by combining electrospinning and “click” reaction (Celebioglu, Demirci, & Uyar, 2014). In 2016, Sirviö et al. (Sirviö, Visanko, Laitinen, Ämmälä, & Liimatainen, 2016) Introduced methyl-, ethyl-, n-propyl-, n-butyl-, n-pentylamine, and n-hexylamine into a cellulose backbone using combined periodate oxidation and reductive amination in an aqueous environment. Linear amines with increasing chain length were used to adjust the hydrophobicity of amphiphilic cellulose nanocrystals (CNCs).

2.3 Self-assembly method

Polymers, with specific molecular architectures, can self-assemble into different forms of aggregates, like polymeric micelles and vesicles. Self-assembly is an procedure generally in aqueous and does not require any harsh reaction condition or solvent (Yang, Han, Zheng, Dong, & Liu, 2015). The self-assembly could be driven by the hydrophobic interactions and the electrostatic interactions (Chen, Liu, & Guo, 2009). In both cases, van der Waals forces and hydrogen bonds may take part in the self-assembly process, but would not take the major role (Yuan, Zhang, Zou, Shen, & Ren, 2012). The self-assembling systems exhibit unique structural characteristics, such as unusual rheological features, a nanoscale hydrodynamic radius with core-shell structure, and thermo-dynamic stability (Kim et al., 2005; Park, Han, & Kim, 2001; Tae, Kornfield, Hubbell, & Lal, 2002; Zhang et al., 2015). This kind of self-assembling systems can be used for trapping hydrophobic substances, such as hydrophobic drug, fluorescent probes and biomolecule. Amphiphilic cellulose materials can self-assemble into various aggregates in solutions under appropriate condition. Dissolution induced method is one of the most extensively used methods to get the self-assembled polymer micelles. Guo et al. (2013) dissolved cellulose-g-PCL in DMSO, then the solution was slowly dropped into ultrapure water under vigorous

stirring and dialyzed against plenty of deionized water to prepared self-assembled micelles with the size is approximately 20-100 nm). In 2011, novel amphiphilic cationic cellulose (HMQC) derivatives self-assembled into cationic micelles in distilled water with the average hydrodynamic radius of 320-430 nm (Song et al., 2011). For stimuli-responsive cellulose-based materials, in appropriate solvent, they can self-assemble into various aggregates introduced by appropriate conditions, such as temperature (Bai et al., 2012), pH (Li, Yin , Zhang, & Zhang, 2009), light (Wang, Chen, Yang, Yang, & Liu, 2014), redox (Ritter, Knudsen, Mondrzik, Branscheid, & Kolb, 2012), etc. In 2006, amphiphilic ethyl cellulose (EC)-g-poly (acrylic acid) (PAA) copolymers were synthesized, and they were self-assembled to micelles or particles with diameters of 5 nm and 100 nm in water (pH=10) when the concentration was 1.0 mg/mL (Kang et al., 2006).

3. Stimuli-responsive cellulose-based materials

Stimuli-responsive self-assembled materials are equipped with environmental sensitive modalities within their structures. These materials can release their encapsulated cargos in response to specific environmental stimuli and surprisingly provide a new horizon for the development of nanoformulations. Due to their potential applications in nano-smart materials and biomedical field, such as bioimaging, biosensor and drug/gene delivery system. Various structures and properties of stimuli-responsive polymers can be finely tuned by altering the molecular structure parameters or environmental conditions, such as temperature, pH, light, redox, etc.

3.1 pH-responsive cellulose-based materials

Among the different types of stimuli, pH sensitive system has been most widely used to design sensitive nano-systems for biomedicine. It is well known that pH

values vary significantly in different tissues or organs, such as stomach and liver, and in disease states, such as ischemia, infection, inflammation, and tumorigenesis (Liu et al., 2014).

Copolymers of HEC-g-PAA have been synthesized, which could self-assemble in water. And it was demonstrated that their micellization and the transition between micelles and hollow spheres were found to be pH-dependent and reversible. The resultant spheres are characterized by large hydrophilic cavities and have an on-off character: open at $\text{pH} > 3$ but closed at $\text{pH} < 3$. Such a unique micelle is expected to be useful in broad application fields (Dou et al., 2003).

As a kind of pH-responsive side chains for cellulose graft copolymers, poly(2-(diethylamino) ethyl methacrylate) (PDEAEMA) has the properties of pH-stimuli-responsibility. In aqueous media with $\text{pH} < 6.5$, the tertiary amine groups on PDEAEMA chain are in protonated state and PDEAEMA is soluble. If $\text{pH} > 6.5$, PDEAEMA will coagulate due to the deprotonation of the tertiary amine groups (Liu, Billingham, & Armes, 2001). Wang et al. (2011) synthesized pH-responsive ethyl cellulose graft poly(2-(diethylamino) ethyl methacrylate) (EC-g-PDEAEMA). The graft copolymers can form micelles in acid aqueous medium. The micelles have the reversible pH sensitivity which start to shrink at $\text{pH} 6.0$ and aggregate at $\text{pH} > 6.9$, as shown in Figure 2. The loading and controlled release of drugs in the micelles was investigated by using rifampicin (RIF). It was found that the cumulative release of RIF in the buffer solution at $\text{pH} 6.6$ is higher than that at $\text{pH} 7.4$.

Synthetic EC-g-PDMAEMA-g-PCL could self-assemble to micelles in aqueous solution. And upon pH change, the single micelles further assembled into micellar aggregates. As a result, the micelles in aqueous media could act as excellent drug

nanocarriers for controlled drug release (Yan et al., 2009).^[85]

3.2 Redox-responsive cellulose-based materials

In recent years, redox-sensitive micelles self-assembled from amphiphilic copolymers have been paid extensive attentions. Redox-active moieties such as quinone derivatives, ferrocene and its derivatives, and osmium complex are generally used in biosensors to establish efficient electron transfer between electrodes and the target solution species for the detection of H_2O_2 , glucose etc.

Li et al. (2016) utilized hydroxypropyl cellulose to synthesize a series of redox-active cellulose derivatives, ferrocene functionalized HPC (HPC-Fc). HPC-Fc and horseradish peroxidase (HRP) were coated on a platinized carbon electrode to prepare an amperometric biosensor for hydrogen peroxide (H_2O_2) detection. The novel biosensor exhibits a fast linear response toward H_2O_2 in the range of 0.1-8 μM with sensitivity of 4.21 nA/ μM . They confirmed that HPC-Fc exhibits an excellent reversible redox activity and could establish amazing electron transfer ability between enzyme and electrode. And, Li et al. (2014) synthesized redox-sensitive graft copolymers, hydroxypropylcellulose-graft-poly (2-acryloyloxyethyl ferrocenecarboxylate) (HPC-g-PAEFC) which can self-assemble into spherical micelles in aqueous solution, with a hydrodynamic radius $\langle R_h \rangle$ in the range 70-130 nm depending on length of the graft chains. They investigated the redox-responsive behaviors of the graft copolymers with H_2O_2 and sodium ascorbate as oxidant and reductant. The results show that the electrostatic repulsion between the side chains results in a swollen core and a larger micelle size when the micelles are oxidized with H_2O_2 , and the size of the micelles can recover to some extent when they are reduced with sodium ascorbate. And the reversibility of the redox process of the HPC-g-PAEFC copolymers gradually becomes weaker with an increase of the graft

chains as the side chains become more difficult to be oxidized.

Cellulose graft copolymers hydroxypropylcellulose-g-poly(4-vinylpyridine)-Os (bipyridine) were synthesized by Kang et al(2012). The electrochemical properties of the redox-functionalized cellulose graft copolymer modified electrode were studied by cyclic voltammetry. The results indicate that the cyclic voltammograms are the reversible electrochemical process at low potential scan rates. Further immobilization of the glucose oxidase (GOx) on the cellulose graft copolymer electrode can be used as glucose detection sensor.

3.3 Thermo-responsive cellulose-based materials

Many synthetic thermal sensitive polymers, such as poly(N-isopropylacrylamide) (PNIPAM), poly(ethylene glycol) (PEG), and poly(oligo (ethylene glycol) methacrylate) have been reported and investigated extensively (Jin, Kang, Liu, & Huang, 2013). The most popular thermal sensitive polymer is PNIPAM, which has a lower critical solution temperature (LCST) in water around 32 °C (He et al., 2011) and has been studied extensively in both of its phase transition behaviors(sol-to-gel) and bio-applications (Gorey & Escobar, 2011; Ifuku & Kadla, 2008; Vasile, Bumbu, Dumitriu, & Staikos, 2004). Yang et al. (2015) synthesized a series of cellulose-g-PNIPAM copolymers, and the copolymers with relatively high content of PNIPAM segments (molar substitution of PNIPAM ≥ 18.3) were soluble in water at room temperature. Furthermore, aqueous solutions of cellulose-g-PNIPAM copolymers exhibited clear temperature-sensitive behavior (sol-to-gel phase transition). Spherical particles of cellulose-g-PNIPAM copolymers formed at temperatures above LCST. And when the temperature was raised up from 25 °C to 50 °C the size of spherical particles increased and the solution turned into opaque. And This process is reversible with the temperature decreasing. Two polyacrylamides,

PDEAAm and PNIPAM, were grafted from the cellulose backbone. The synthesized cellulose-copolymers are thermor-esponsive and show LCST behavior in water, which is very sensitive toward the molecular weight of the side chains (Hufendiek, Trouillet, Meier, & Barner-Kowollik, 2014). Poly (oligo (ethylene glycol) methacrylate), also, present good thermo-responsive properties and biocompatibility (García-Juan et al., 2016). Porsch et al. (2011) synthesized linear homo- and copolymers of oligo (ethylene glycol) methyl ether methacrylate (OEGMA₃₀₀) and di(ethylene glycol) methyl ether methacrylate (DEGMA). Furthermore, this group of thermo-responsive polymers was grafted from hydroxypropyl cellulose, resulting in complex macromolecular comb architectures. In the fully soluble state, below the LCST of the grafts, the comb polymers formed self-assemblies with sizes in the range 20-40 nm. Moreover, at the LCST the comb polymers show the distinct and instant increase in size, resulting in a collapse and the formation of micellar aggregates. In recent years, novel thermal sensitive cellulose-based polymers were synthesized, such as 2-hydroxy-3-butoxypropyl hydroxyethyl cellulose (HBPEC) (Tian, Ju, Zhang, & Hou, 2016) and polymer (PNMN) which was synthesized through the polymerization of N-isopropylmethacrylamide (NIPMA) with methyl acrylate and N-(Hydroxymethyl) acrylamide (Ding, Zheng, Li, & Cao, 2016).

3.4 Light-responsive cellulose-based materials

From different stimuli, light is a very appealing one because it can be accurately operated in time and space. Azobenzene, coumaric acid, and cinnamic acid derivatives have been used as light-responsive compounds in the control over the formation and disruption of threadlike micelles (Takahashi, Kishimoto, & Kondo, 2016).

In 2012, photoactive derivatives of cellulose were prepared by a mild esterification of the biopolymer with 2-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]acetic

acid. And preliminary experiments about photo-control of solution properties were carried out. The relative viscosity of a solution of photoactive derivatives in aqueous NaCl solution was measured. They found that the solution was irradiated with UV light (333 nm) for 120 min, the relative viscosity decreases from 720 to 490 mL/g (Wondraczek, Pfeifer, & Heinze, 2012).

Huang et al. (2013) Synthesized photosensitive azobenzene functionalized hydroxypropyl cellulose derivatives (azo-HPCs) with different degrees of substitution with azobenzene moieties. The azobenzene groups in the azo-HPCs undergo the reversible cis-trans isomerization transition under irradiation by UV and visible light both in solution and a solid film. In 2014, amphiphilic EC-g-PHEMA-g-PSPMA was prepared using ATRP approach, which exhibited reversible micellization induced by light change (Wang, Chen, Yang, Yang, & Liu, 2014). The graft polymers can self-assemble into spherical micelles with an average diameter of approximately 100 nm in aqueous solution. The micelle diameter can be controlled by UV and visible light. The hydrophobic side chain of PSPMA became hydrophilic under UV light, which decreased the average size of the micelles. Additionally, the diameters of the micelles can be recovered when subsequently irradiated with visible light.

3.5 Multiple stimuli-responsive nanocarriers

Compared with the single responsive polymer, multiple stimuli-responsive cellulose-based materials, with more merits have drawn greater attentions. There are many stimuli-responsive cellulose-based materials have been synthesized and investigated (Bai et al., 2012; Chang, He, Zhou, & Zhang, 2011). Among of them, thermo- and pH-sensitive cellulose-based materials have drew the most attention.

The thermo- or pH-sensitivity hydroxypropyl cellulose-graft-poly (4-vinyl pyridine) (HPC-g-P4VP), which could be micellized, were synthesized (Ma, Kang,

Liu, & Huang, 2010). For the pH-induced micelles, the P4VP side chains collapsed to form the core of the micelles when the pH raised above the pK_a of P4VP side chains and the HPC backbones were in the shell to stabilize the micelles. In the thermoinduced micelles, HPC backbone collapsed to form the core of the micelles upon heating, and the P4VP side chains stabilized the micelles as the shell. The cloud point of the HPC-g-P4VP copolymers in the aqueous solution also depends on the length of the side chains at the same graft density.

Wen et al. (2015) reported the synthesis of monodisperse dual temperature/acidic pH-responsive bionanogels (DuR-BNGs) by aqueous crosslinking polymerization through temperature-induced self-association method. And the DuR-BNGs have prolonged colloidal stability and negligible non-specific interactions with proteins. In response to acidic pH at higher temperature, they exhibit synergistic release of anticancer drugs as a consequence of both acidic pH-sensitivity of carboxymethyl cellulose and temperature-induced volume change of grafted thermoresponsive copolymers (**Figure 3**).

Some of pH-sensitivity materials could be stimulated and responded by CO₂ which is “green”, reversible and non-toxic. Poly (N,N-dimethylaminoethyl methacrylate) (PDMAEMA) could react with CO₂ in water to form protonated PDMAEMA without functionalization with amidine, and the protonation of PDMAEMA would lead to the increase of its lower critical solution temperature (LCST) drastically (Han et al., 2012; Han et al., 2013; Han, Tong Boissière, & Zhao, 2012). Yuan et al. (2016) synthesized amphiphilic ethyl cellulose-graft-poly (N,N-dimethylaminoethyl methacrylate) (EC-g-PDMAEMA) and ethyl cellulose-graft-poly (2-(2-methoxyethoxy) ethyl methacrylate-co-

N,N-dimethylaminoethyl methacrylate) (EC-g-P(MEO₂MA-co-DMAEMA)) graft copolymers. They demonstrated that the micelles self-assembled from the copolymer presented switchable temperature-CO₂ dually responsive properties. Moreover, the temperature-CO₂ dually responsive properties of the copolymer were reversible and could be accomplished through altering the temperature and bubbling CO₂/Ar as depicted in Figure 4.

Other multiple stimuli-responsive cellulose-based materials were designed and synthesized in recent years. Rahimian et al. (2015) synthesized HPC-g-P(HMssEt-co-OEOMA) graft copolymers exhibiting dual reduction and temperature responses. They studied about the polymers, and the results suggested that HPC-g-P(HMssEt-co-OEOMA) form small aggregates in aqueous solution at temperature below the LCST. When the temperature was constant, the diameters of the aggregates were changed with the in-situ disulfide crosslinking and the reduction-responsive cleavage of disulfide crosslinkages to the corresponding thiols.

4. Application of self-assembled cellulose-based materials

Cellulose-based materials which could self-assemble have been widely adapted for using in biomedical engineering, such as drug delivery vehicles, biomarkers or sensors, gene vectors.

4.1 Application in the drug delivery field

Presently, drug delivery has been a very popular research area. Cellulose self-assembly materials have good biocompatibility, biodegradability, low toxicity; And stimuli-responsive self-assembled cellulose materials could make the drug trapped in release under control. The concept of using cellulose materials for drug delivery is pretty new and shows great promise.

The graft copolymer, hydroxypropyl methyl cellulose grafted with

polyacrylamide (HPMC-g-PAM) was synthesized (Das & Pal, 2013). And it was evaluated *in vitro* as a potential carrier for controlled release of 5-amino salicylic acid (5-ASA). It was demonstrated that the drug release study was performed at various pH values akin to the condition of gastrointestinal tract, which indicates that the release is controlled by a combination of polymer relaxation or erosion of the matrix and diffusion of the drug from the swollen matrix.

The graft copolymer, hydroxypropyl methyl cellulose grafted with Aminated-glycidylmethacrylate grafted cellulose-grafted polymethacrylic acid-succinyl cyclodextrin(Cell-g-(GMA/en)-PMA-SCD) was synthesized for the controlled release of 5-Fluorouracil(5-FU), an anticancer drug (Anirudhan, Nima, & Divya, 2015). Cytotoxicity studies revealed that the drug delivery systems(DDS) did not show any cytotoxicity, but 5-FU-DDS showed significant cytotoxicity lesser than that of 5-FU confirming the controlled release of 5-FU from the carrier to the targeted site. The results indicated that Cell-g-(GMA/en)-PMA-SCD may be a potential material for drug loading and sustained release of 5-FU. Bielska et al. (2013) synthesized cationic and anionic derivatives of hydroxypropyl cellulose, which were thoroughly characterized and were found to be thermo-responsive. They studied and found that those derivatives could self-assemble into nanoparticulate systems. And those nanospheres could be used as carriers for curcumin since the encapsulation efficiency and loading are satisfactory. Furthermore, the curcumin release was found to be temperature-dependent in the physiologically relevant range of temperatures. A nanogel which is obtained by self-assembly of low density lipoproteins (LDL) and sodium carboxymethyl cellulose (CMC) could be used to deliver doxorubicin (DOX) to cancer cells (He et al., 2015). In the meantime, the *in vitro* studies demonstrated that DOX release from LDL/CMC nanogels was pH-dependent. Furthermore, studies

showed that DOX-loaded LDL/CMC nanogels reduced endocytosis in HepG2 cells (Figure 5). So the activity in inhibiting the growth of HeLa and HepG2 cells by the DOX-loaded LDL/CMC nanogels was weaker comparable to that of free DOX. Hence, such excellent LDL/CMC nanogels provide a favorable platform to construct drug delivery systems (DDS) for cancer therapy.x

In recent years, the cgraphene oxide has drawn much attention from the researchers. The unique structure of graphene oxide leads to its wide application in anticancer drugs delivery. In 2017, Biodegradable carboxymethyl cellulose/graphene oxide (CMC/GO) nanocomposite hydrogel beads as a drug delivery system were prepared via physically crosslinking with $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ for controlled release of anticancer drug doxorubicin (DOX) (Rasoulzadeh & Namazi, 2017).

4.2 Application in biosensor

A novel fluorescent amphiphilic cellulose nanoaggregates sensing system is designed and applied in detecting explosives in aqueous solution by Wang et al. (2012). Due to the maximized interaction between sensing material and analyte within the cellulose-based nanoaggregates, significantly enhanced sensitivity with 50-fold higher quenching efficiency is obtained. A material based on cellulose acetate (CA) and the room temperature ionic liquid 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ($\text{BMI} \cdot \text{N}(\text{Tf})_2$) was developed for incorporation in a biosensor. Under optimized conditions, the biosensor shows a wide linear range of 34.8-370.3 μM and adetection limit of 5.5 μM . Moreover, this sensor showed an acceptable level of accuracy for methyldopa determination inpharmaceutical samples (Moccelini, Franzoi, Vieira, Dupont, & Scheeren, 2011). Cellulose self-assembly materials can make the detection performed in aqueous solution by sensing material, and significantly enhance the sensitivity.

4.3 Application in other fields

A nanocarriers were first attained by the self-assembly of microcrystalline cellulose-graft-poly(p-dioxanone) copolymers(Cell-g-PPDO) in aqueous solution and followed by fluorescent conjugated polymers (FCPs) loading via sonication. The FCPs-loaded micelles were well-distributed spherical structures with diameters ranging from 20 nm to 120 nm. Compared to FCPs in water, FCPs-loaded micelles presented lower cytotoxicity in cell culture and improved intracellular uptake efficiency. Furthermore, in live cells intracellular imaging, significantly stronger fluorescence was observed in the cytoplasm of both Hep3B and MAD-231 cells treated with FCPs-loaded micelles compared to those treated with FCPs in water. The micellar aqueous dispersion of FCPs would be a potential tool for live tumor cell imaging (Guo et al., 2015).

Well-defined comb-shaped cationic copolymers (HPDs) composed of long biocompatible hydroxypropyl cellulose (HPC) backbones and short poly((2-dimethyl amino)ethyl methacrylate) (P(DMAEMA)) side chains were prepared. The P(DMAEMA) side chains can be further partially quaternized to produce the quaternary ammonium HPDs (QHPDs). It was found that HPDs and QHPDs as gene carriers can effectively bind pDNA to form nanoparticle complexes of 150 to 200 nm in size. Thus, structural tailoring of functional comb-shaped cationic copolymers provides a unique and versatile means for designing novel gene carriers (Xu et al., 2009).

Additionally, cellulose-based core/shell composite materials with the core is catalyst solid particles and the shell is cellulose or its derivatives can be used in green synthesis (Maleki & Kamalzare, 2014). This kind of nanocatalyst can be recovered and reused several times without significant loss of catalytic activity (Maleki, Jafari,

& Yousefi, 2017). A new magnetic cellulose/Ag BNC catalyst was prepared and was used to synthesize 5-methyl-7-aryl-4,7-dihydro-1H-tetrazolo[1,5-a]pyrimidine-6-carboxylic ester derivatives. This ecofriendly catalyst has remarkable magnetic property, and can be easily separated from the reaction mixture without considering loss of catalytic activity (Maleki, Ravaghi, Aghaei, & Movahed, 2017). An efficient magnetic cellulose/Ag nanobiocomposite was prepared with the particles were about 20–25 nm. And was used as catalyst for synthesis (Maleki, Movahed, & Ravaghi, 2017).

5. Conclusions and perspectives

Cellulose is the most abundant, renewable biomass energy. And it has been demonstrated that amphiphilic cellulose-based materials could self-assemble into a variety of 3D structures with tremendous potential in applications. All kinds of effective solvents of cellulose and feasible methods for modification of cellulose provide the possibility for obtaining more kinds of functional cellulose-based materials with many merits. These cellulose-based polymers with the specific functionality and equilibrated balance of hydrophobic and hydrophilic components offers exceptional possibilities for the preparation of self-assembled materials which could be used in biomedicine and other fields. And the ultimate goal is that the cellulose-based materials which could self-assemble can be used in clinical practice.

However, some barriers exist in the commercialization of cellulose-based materials which could self-assemble. Further researches need to be done to deal with the dissolution problem of cellulose. In the meantime, more effective methods of modification of cellulose need to be developed. Moreover, majority of the studies performed so far are in vitro, thus more in vivo studies need to be carried out. Process optimization and scale-up from the laboratory to pilot plant are yet to be undertaken. Therefore, more investigations are required to resolve these challenging problems. We

anticipate that the future advancements will affect future biomedicine field.

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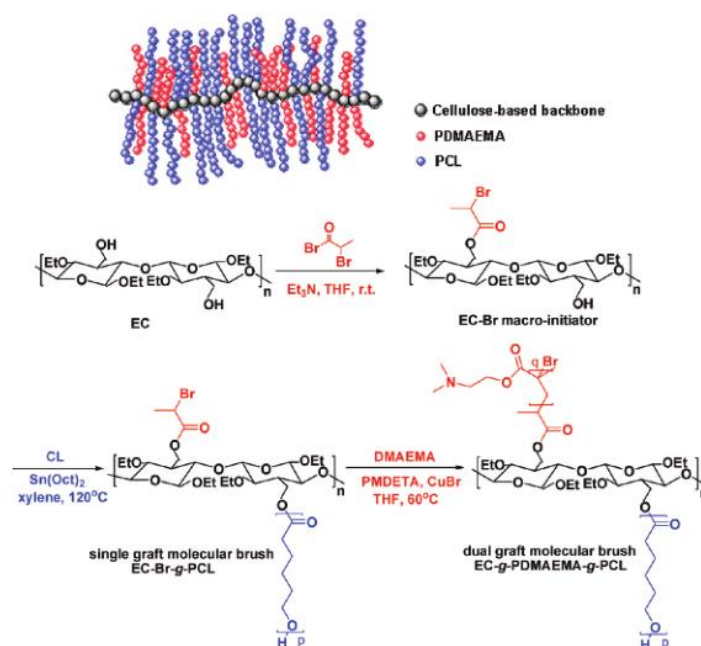


Figure 1. Synthesis of Dual Graft Molecular Brush EC-g-PDMAEMA-g-PCL via ROP and ATRP (Yan et al., 2009)

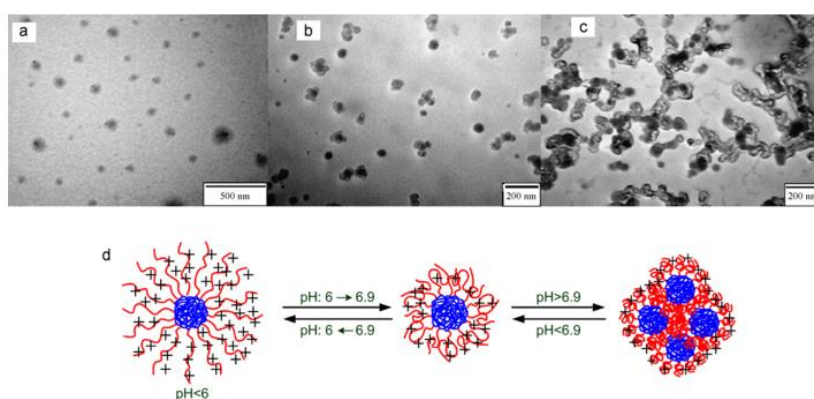


Figure 2. TEM images of graft copolymer EC_{0.1}-g-PDEAEMA₈₅ micelle nanoparticles at pH of (a) 3.2, (b) 6.5, and (c) pH 7.3 at c=0.1mg/mL. (d) The schematically mechanism of the pH-responsive micelles prepared from EC-g-PDEAEMA copolymers (Wang et al., 2011).

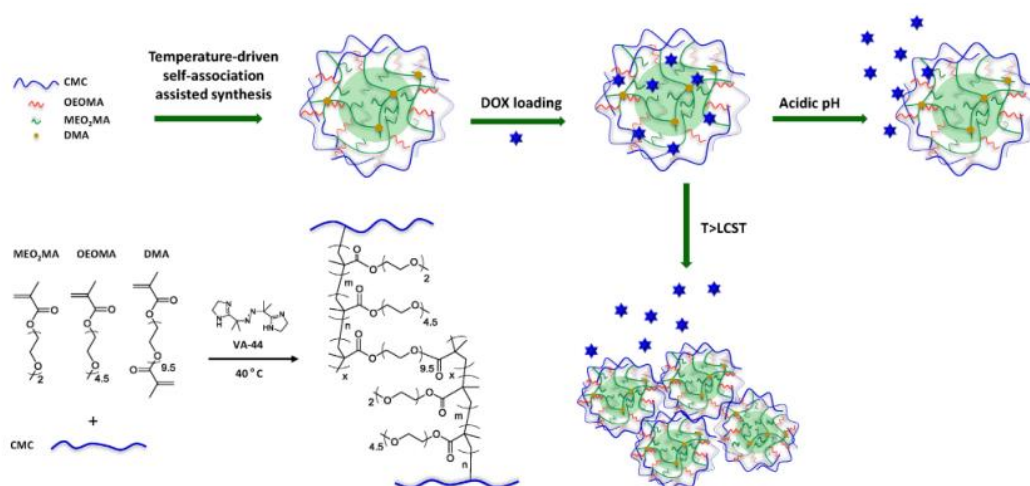


Figure 3. Synthesis of dual temperature/acidic pH-responsive DuR-BNGs via temperature-driven self-association method and their dual stimuli-responsive DOX release (Wen et al., 2015).

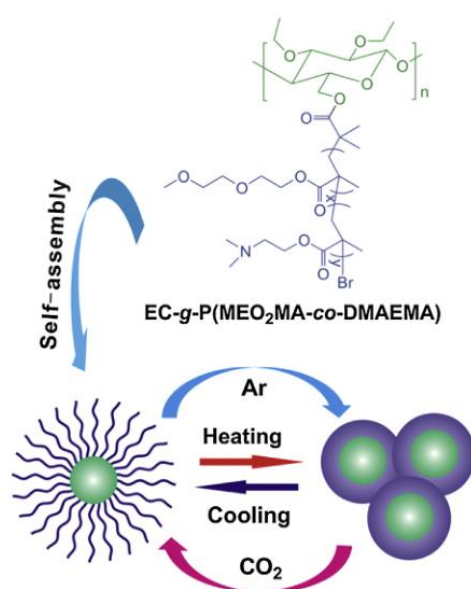


Figure 4. The schematic self-assembly process of EC-g-P(MEO₂MA-co-DMAEMA) and the CO₂-temperature dual responses of the micelles (Yuan et al., 2016).

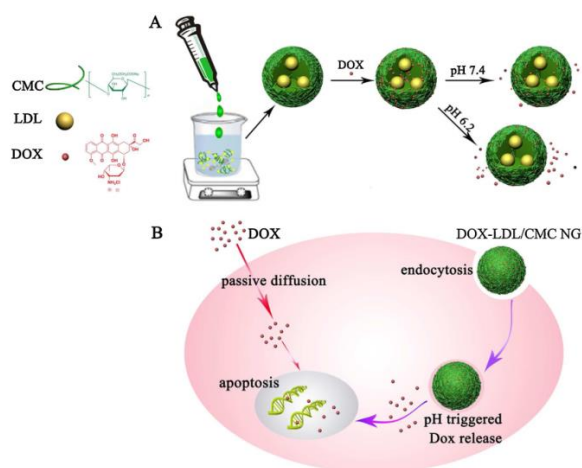
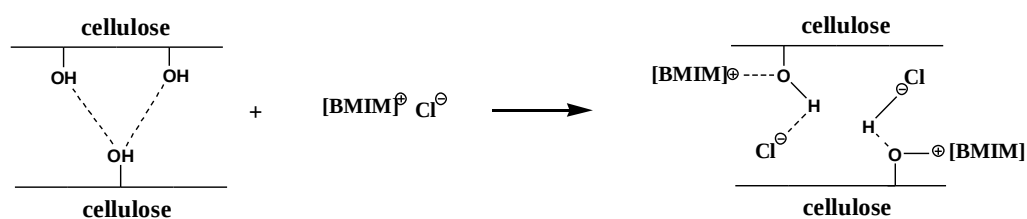


Figure 5. (A) Illustration of the synthesis and structures of LDL/CMC nanogels, DOX loading, and pH-dependent drug release. (B) Schematic diagram showing the proposed model for intracellular delivery processing of DOX-loaded LDL/CMC nanogels in tumor cells (He et al., 2015).



Scheme 1. Proposed dissolution mechanism of cellulose in [BMIM]Cl (redrawn from Pinkert et al., 2009)

Table1. Dissolution of cellulose in ILs.

Original cellulose	Solvent	Dissolution temperature (°C)	Dissolution time (min)	Article cited
Cellulose pulp or cotton	1-allyl-3-methylimidazolium chloride	110-1130	40-240	Zhang et al. (2005)
Microcrystalline cellulose	[N-ethyl-N9-methylimidazolium] [dimethylphosphate]	45	30	Fukaya et al. (2008)
Cellulose pulp	1-Butyl-3-methylimidazolium chloride	116	/	Righi, Morfino, et al. (2011)
Microcrystalline cellulose	methylimidazolium /methylmorpholium with [CH ₃ COO] ⁻ anion	25-65	/	Lu et al. (2014)
Cellulose pulp	1-ethyl-3-methylimidazolium acetate, 1-butyl-3-methylpyridinium chloride, benzyl(tetradecyl)dimethylammonium chloride	above 180	Over 400	Dorn et al. (2008)
Avicel cellulose	1-ethyl-3-methylimidazolium diethyl phosphate	100	60	Vitz et al. (2009)
Microcrystalline cellulose	Tetrabutylphosphonium hydroxide containing 30-50wt% water	25	/	Abe et al. (2012)
Cellulose	1-butyl-3-methylimidazolium chloride	40-90	/	Moulthrop et al. (2005)
Microcrystalline cellulose	1-ethyl-3-methylimidazolium acetate (0-20% water)	10-60	/	Le et al. (2012)
α -cellulose(7% water)	1,3-dimethylimidazolium dimethylphosphate	30	/	Mazza et al. (2009)
	1-Butyl-3-methylimidazolium chloride	95	/	
Microcrystalline cellulose	1-ethyl-3-methylimidazolium acetate 1-Butyl-3-methylimidazolium chloride	80	1440	Sescousse et al. (2010)

Table2. The graft copolymerization of cellulose synthesized by RAFT

Start material	Monomer	Article cited
cellulosic filter paper	2-(Dimethylamino)ethyl methacrylate	Roy et al. (2008)
ethyl hydroxyethyl cellulose	acrylamide	Hiltunen et al. (2009)
wood fiber	vinyl acetate, styrene, n-butyl acrylate and 4-vinylbenzyl chloride-styrene	Tastet, Save, et al. (2011)
Cellulose	Glycidyl methacrylate	Barsbay et al. (2014)
Cellulose	styrene	Roy et al. (2005)
ramie fiber	methyl methacrylate, methyl acrylate	Chen et al. (2009)
ramie fiber	2,2,2-trifluoroethyl methacrylate	Liu et al. (2010)
cellulose acetate	(ar-vinylbenzyl)trimethylammonium chloride)	Demirci et al. (2014)
cellulose membrane	N,N-dimethyl-(methacryloylethyl)-ammonium propanesulfonate	Yuan et al. (2013)
Cellulose	2-(dimethylamino)ethyl methacrylate	Roy et al. (2008)
Cellulose	N,N-diethylacrylamide, N-isopropylacrylamide	Hufendiek et al. (2014)