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Review

Chitosan Derivatives: Introducing New Functionalities with a Controlled Molecular Architecture for Innovative Materials †

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† Dedicated to the memory of the late Prof. Ruth D. Henríques, who introduced me to research on chitin [WMAM]

Abstract: The functionalization of polymeric substances is of great interest for the development of innovative materials for advanced applications. For many decades, the functionalization of chitosan has been a convenient way to improve its properties with the aim to prepare new materials with specialized characteristics. In the present article, we summarize the latest methods for the modification and derivatization of chitin and chitosan, trying to introduce specific functional groups under experimental conditions, which allow a control over the macromolecular architecture. This is motivated because an understanding of the interdependence between chemical structure and properties is an important condition for proposing innovative materials. New advances in methods and strategies of functionalization such as click chemistry approach, *grafting onto* copolymerization, coupling with cyclodextrins and reactions in ionic liquids are discussed.

Keywords: chitin; chitosan; derivatization; controlled functionalization, click chemistry; graft copolymer; cyclodextrin; dendrimer; ionic liquids

1. Introduction

Polysaccharides are widely found in the biosphere fulfilling various important functions in living organisms, such as energy storage and structural materials, among others. Cellulose and chitin are the most abundant natural polymers in nature. However, chitin has very few applications compared to cellulose. This has several reasons including, scarce natural structures of chitin available to be used with low processing and the poor solubility properties of this polysaccharide. Therefore, most of the obtained chitin is processed by extensive alkaline deacetylation to obtain chitosan. This amino-polysaccharide is composed of β(1→4) linked units of N-acetyl-D-glucosamine and D-glucosamine (Figure 1). Due to its key properties such as biodegradability, biocompatibility, mucoadhesive and non-toxic, chitosan is of great interest in many applications such as biomedicine, pharmacy, biotechnology, food industry, nanotechnology, etc. [1,2].

One constant topic in materials research is the modification of natural polymers, which results in the development of new derivatives with unique properties. There is a great variety of methods to modify polysaccharides. Chitosan is prone to chemical modification at free amino groups from the deacetylated units at C-2, and hydroxyl groups at C-3 and C-6 positions [2]. Commonly, the chemical derivatization of chitosan is carried out to improve some specific characteristics, such as

solubility, hydrophilic character, gelling properties, affinity toward bioactive molecules, among others [3].

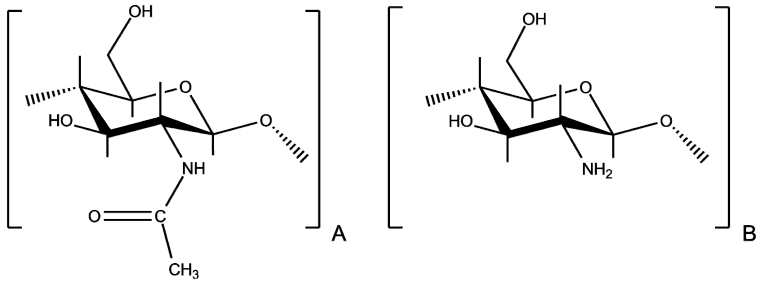

Figure 1. Chemical structure of chitosan composed of β(1→4) linked units of (**A**) N-acetyl-D-glucosamine and (**B**) D-glucosamine.

Chemical modification of chitosan is usually done in bulk, randomly reacting its units. When specific new functionalities are pursued, other approaches are preferred where the reactions could be controlled stoichiometrically. In this scenario, polymer science is taking advantage of diverse strategies to design new polymer-based hydrogels, drug and gene delivery systems, scaffolds for tissue engineering, toxic substance and mineral chelation, and materials for the electronic and aerospace industry, among others. For example, introducing lipophilic or hydrophilic molecules to chitosan may result in altering or improving its properties like its solubility in acidic solutions and organic solvents, and its thermal and mechanical properties [4].

There are previous reviews covering important and specific aspects of the chemical modification of chitin and chitosan [5–7]. In the present paper, we aim to review and analyze recent developments found on literature dealing with the chemical modification of chitin and chitosan, with emphasis on proposed methods to obtain chitosan derivatives with a controlled macromolecular architecture. An understanding of the interdependence between chemical structure and properties is an important condition for proposing innovative materials. Some aspects of the chemistry of these polysaccharides (and their modification conditions) could have an impact on the properties of the products and should be taken into account:

1. Chitin and chitosan are in fact a family of polymers, differing in terms of not only the molecular weight and extent of acetylation, but also in the dispersion of the degree of polymerization and the distribution of the acetylated and deacetylated units along the polymer chain. All these parameters will depend mainly on the natural source and isolation processes. Therefore, it is very important to know these intrinsic characteristics, as far as they shall affect the properties of the derivatives.
2. Due to their insolubility in certain solvents (particularly chitin), some chemical reactions are carried out under heterogeneous conditions. This will have a determinant influence on the structure of the obtained derivatives. Using words from Kurita, "reactions under heterogeneous conditions are usually accompanied by problems including poor extents of reaction, difficulty in regioselective substitution, structurally ununiformly products, and partial degradation due to severe reaction conditions" [1]. Nowadays, these drawbacks could be circumvented using some novel solvent systems like ionic liquids. This topic will be revised herein as well.
3. Usually, non-selective chemical derivatization could lead to the development of products with an irregular distribution and uncontrolled growth of the substituent groups in the main chain, or undesired depolymerization of the polysaccharide.
4. Although chitosan presents valuable functional groups for derivatization reactions, often it is necessary to obtain some precursors to facilitate subsequent reactions or, in other cases, to protect the reactive amine in order to favor the chemoselectivity of the modification. Due to

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their frequent use in chitosan functionalization processes, we will first refer to those reactions whose use is more or less recurrent under diverse experimental conditions.

1.1. Chitosan precursors with protected amino groups

Due to the high reactivity of the amino groups, these should be protected in order to promote the functionalization reaction to take place through the hydroxyl groups. Several methods have been proposed, but until now, the most frequent is the *N*-phthaloylation of chitosan [8–10].

With this purpose, typically, amino groups of chitosan could be protected from unwanted reactions by means of phthalic anhydride, whose derivative, *N*-phthaloyl chitosan, protects the amine moieties for further chemical modifications. *N*-phthaloylation should be carried out in DMF/water (95/5), in order to avoid *O*-phthaloyl substitution [9]. At the end of the chemical modification, the phthaloyl protection must be removed from the polymer by reaction with hydrazine monohydrate to regenerate the free amino groups. Nevertheless, this strategy has two drawbacks:

- the *N*-phthaloylation of chitosan affects the solubility of chitosan in aqueous solutions. It is only soluble in aprotic polar organic solvents, which had been attributed to certain crystallinity [9,10]. Obviously, the solubility of the precursor in some organic solvents could be advantageous when the *O*-substitution reaction needs to be carried out in the later.
- the unblocking reaction with hydrazine monohydrate severely depolymerize chitosan chain with the consequent weakening of its mechanical properties [11,12]

Nonetheless, it is one of the best ways to protect the amine moieties in the chitosan polymer chains.

Dissolving chitosan in methanesulfonic acid has been also used for the protection of amino groups [13–16]. As it should be expected, there is an important degradation of chitosan polymer chain due to the strong acidic conditions used to dissolve chitosan [13,14].

1.2. Some frequent reactions in chitosan chemistry

There is a group of organic reactions, whose use in chitin chemistry is recurrent, due to their experimental simplicity, and because their products could be used as a kind of wildcards during other chemical modification strategies. These reactions provide the researcher with valuable tools for specificity control and regioselectivity of the functionalization, with minimal possibilities of side reactions or chain degradation. Herein, we will only make a brief summary of them, and the reader could get more details in other excellent reviews and compilations [1,5,17–20].

Among these reactions, the following will be frequently used: *i*) *formation of Schiff bases (and reductive amination)*. It refers to the formation of imine products between amine and carbonilic (aldehydes and ketones) groups. This reaction is very simple, and takes place under mild conditions. The imine could be easily reduced with a suitable reducing agent like sodium borohydride (or, preferably, sodium cyanoborohydride) giving selectively *N*-alkyl derivatives; *ii*) *carbodiimide-mediated amidation*. There is a group of activators for the amidation of amines with carboxylic groups. When using these agents, the amidation is straightforward, usually takes place under mild conditions, at ambient temperatures. Most frequently used activators are: N,N'-dicyclohexylcarbodiimide (**DCC**); 1-ethyl-3-(3-(dimethylamino)propyl) carbodiimide (**EDC**); and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (**DMTMM**). In order to increase yields and decrease side reactions *N*-hydroxysuccinimide (**NHS**) is often added.

2. Click chemistry reactions

Among the different approaches developed to produce new chitin and chitosan derivatives, the polymer scientist should take into account the way to reduce cost, time consumption during the experiment, undesired byproducts of reactions, and reduce the possible pollution to minimum. Under the concept of "click chemistry" are recognized a few number of nearly perfect reactions, in

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which two functional groups exclusively react with each other. They are quick reactions and exhibit high yields; they are carried out under mild temperature conditions (25-37°C), in a wide range of hydrogen potential (pH 4-12); they are insensitive to water and oxygen. They must generate highly regioselective products that need no complicated purification processes. An important characteristic is that they are modular reactions resembling biochemical processes in nature. Among these reactions, it could be mentioned [21,22]:

- cycloaddition reactions, including those from the 1,3-dipolar family (like Huisgen reaction), and hetero-Diels-Alder reactions,
- nucleophilic ring-opening reactions in strained heterocyclic electrophiles,
- carbonyl chemistry of the non-aldol type, and
- additions to carbon-carbon multiple bonds.

Among the reactions that are considered as click chemistry, cycloadditions are the most used reactions in chitosan derivatization. On the one hand, the Huisgen's reaction is a cycloaddition between alkynes and azides yielding two regioisomer triazoles [23]. It could be carried out with or without Cu(I) as catalyst, as could be appreciated in Figure 2. This is one of the most investigated chemoselective "click" reactions, which takes place in aqueous medium at room temperature, and is almost instantaneous. On the other hand, the Diels-Alder is a [4+2] cycloaddition between a diene and a dienophile, giving products with an unsaturated six-membered ring (Figure 3). This is also an important click reaction, with the peculiarity that it is thermodynamically reversible, depending on the reactants, but the reaction product is absolutely stable [24–26].

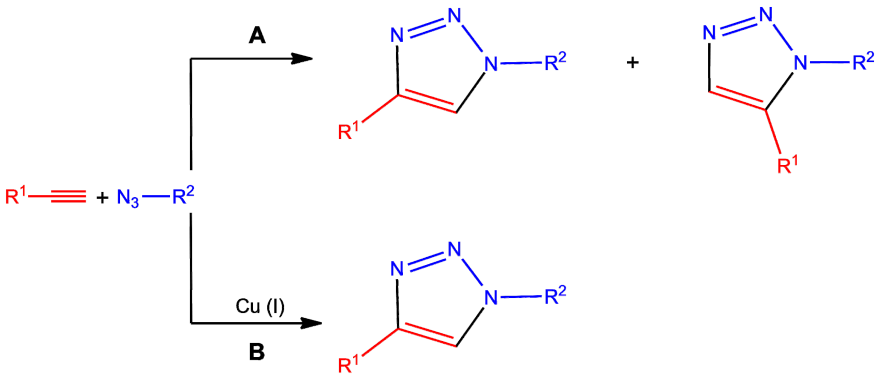

Figure 2. Huisgen cycloaddition reactions in absence (A) or presence (B) of Cu(I) catalyst.

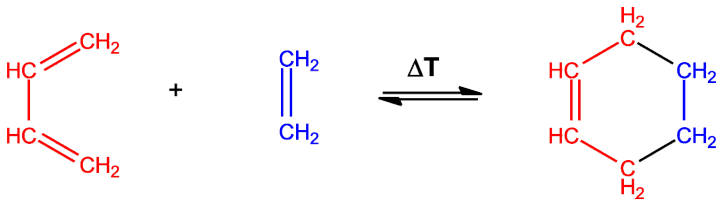

Figure 3. Diels-Alder reaction between a diene and a dienophile.

The use of "click chemistry" has expanded the possibilities to produce new materials with outstanding properties [27–31]. Chitosan derivatives synthesized by click chemistry have shown tunable thermosensitive characteristics, photochromic behaviors, pH-sensitivity macromolecular networks and highly soluble chemoselective properties [32–35].

The main application of click chemistry on chitosan derivatization seems to be in the preparation of grafting copolymers. Due to the chemoselectivity of these reactions it was possible to obtain *N*- [36,37] or *O*-grafted [38,39] chitosan-*g*-poly(ethylene glycol). Other homopolymers grafted onto the chitosan backbone are: poly(*N*-isopropyl acrylamide) [40,41], β-cyclodextrin (on O-6 position [42] or in the amine [43]), poly(caprolactone) [44,45] and others [46,47].

An interesting example of what it could be prepared with this powerful tool is the study of Jung *et al*. in which chitosan-poly(ethylene glycol) hybrid hydrogel microparticles are prepared and then conjugated with single-stranded DNAs via Cu-free click chemistry [48]. Authors consider that this strategy is an example of a robust biomolecular assembly platform that could be replicated as biomolecular targets and therapeutic applications.

Furthermore, there are other chitosan derivatives developed via click chemistry reactions [33,49–59], some of which exhibit diverse properties like antimicrobial, antifungal, enhanced solubility in acidic and basic conditions, as well as an antigen detection system initiated by click chemistry, etc. Other materials synthesized are a cellulose-click-chitosan material [60], click-coupled graphene sheet with chitosan [61] and chitosan functionalized multiwalled carbon nanotubes [62].

The use of the Diels-Alder cycloaddition, gives the materials properties that can vary depending on the temperature, a characteristic that Huisgen's cycloaddition does not possess. In this sense, it is very premonitory to combine the properties of chitosan with the potential capacity of furans for the development of Diels-Alder reactions. The structure of the furan gives it a markedly dienic character, very suitable for the development of this type of reactions [63]. This feature opens up opportunities to investigate the potentialities of the Diels-Alder cycloaddition between furan-chitosan derivatives and dienophiles such as maleimides. This approach has been used to obtain a novel chitosan hydrogel with interesting drug-carrier characteristics suitable for the development of novel biotechnological and biomedical materials (Figure 4) [64].

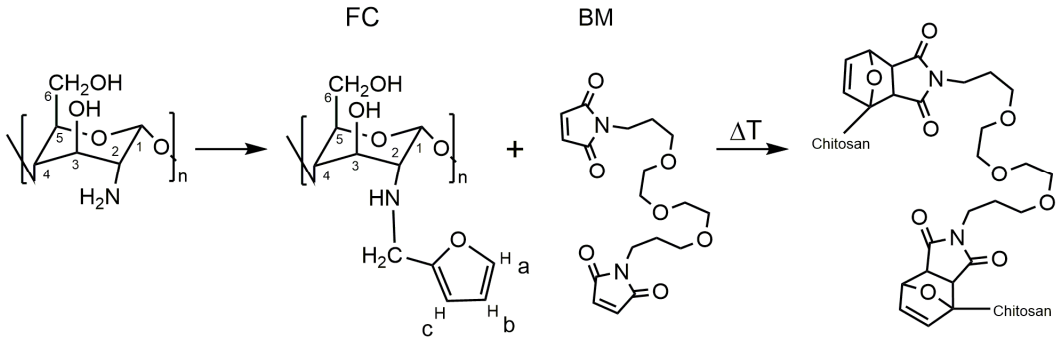

Figure 4. Synthetic scheme for the preparation of N-(furfural) chitosan by reductive amination, FC, and Diels–Alder cycloaddition with a bismaleimide giving chitosan hydrogel.

The number of reports about the use of click chemistry to modify chitosan is growing. However, the application of click chemistry in the controlled modification of chitosan is only in its early stages, and we should expect its use to have an even greater momentum in the coming years. The real possibilities of click chemistry are to be revealed in the coming years, and new materials with advanced properties for specific applications will surely appear. This is undoubtedly due to the simplicity of the reactions and especially to the excellent opportunities offered by these tools to introduce chemical modifications with a high control of the molecular architecture.

3. Graft copolymerization

Among the strategies of chitin and chitosan derivatization, grafting procedures are a strong chemical tool in order to develop innovative materials [6]. The structure of a typical *graft*-copolymer consists of a long sequence of the backbone polymer chain (chitin or chitosan in this case), containing one or more side polymer chain of distinct chemical nature [65]. The properties of this kind of copolymer are widely dependent on the molecular characteristics of the grafted side chains, such as molecular structure, length of the chain, as well as the degree of grafting [66].

There are three main techniques for the grafting copolymerization: *grafting from*, *grafting onto* and *grafting through*. As far as in this case the polysaccharide backbone chain is already formed, only the two former methods are of interest. On the one hand, the *grafting from* method involves the *in situ*

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polymerization of the grafting monomer (Figure 5a). This reaction is initiated directly from the main chain, but its free homopolymerization could not be discarded as well. This procedure is usually accomplished by one-step, but no control over the macromolecular structure is possible. On the other hand, the *grafting onto* method is carried through the reaction between pendant functional groups of the backbone chain and end-functional groups of previously synthesized polymer chains (Figure 5b) [65]. This procedure allows the elaboration of polymer systems with a well-defined structure. This technique affords the preparation of versatile macromolecular materials from chitin and chitosan, allowing the development of novel hybrid materials with specific properties for advanced applications in several fields as food processing, biotechnology, water treatment, biomedicine, among others.

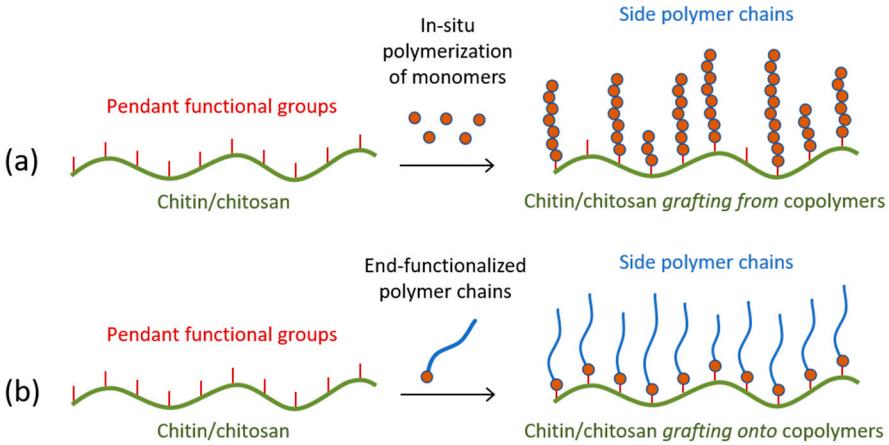

Figure 5. Schematic representation of the (a) *grafting from*, and (b) *grafting onto* methods for graft copolymerization.

3.1. Chitin "grafting from" copolymers

The type of polymerization to be selected depends obviously on the type of monomer to be grafted, in most cases, radical polymerization has been used [67–74], although there is also a report of anionic ring-opening polymerization [75]. Acrylic monomers (especially acrylic acid) are among the most frequently grafted into chitin [67–70,73,76–78]. For the development of experimental procedures, it must be taken into account that chitin is not soluble in aqueous media and, therefore, the reaction must be carried out mostly under heterogeneous conditions. Hence, almost no-control over the macromolecular structure is attained, giving rise to a heterogeneous distribution of the grafting chains along the chitin backbone, and in some cases, only low degrees of grafting could be reached.

The *grafting from* copolymerization of acrylic monomers onto chitin using cerium (IV) as redox initiator has been the subject of some studies [67–69,78]. In the pioneering work by Kurita *et al* the influence of several conditions of the copolymerization reaction of acrylamide and acrylic acid onto chitin was investigated [67]. These authors reported a procedure that allows reaching percentages of grafts above 200%. The obtained copolymers showed enhanced solubility and hygroscopic behavior [67]. Methyl acrylate [68] and methyl methacrylate [69] are other acrylic monomers that have been grafted on chitin in the past under similar conditions.

The other free radical initiator that has been successfully used for the grafting of acrylic monomers onto chitin is potassium persulfate [70,73,76,77]. Hydrogels prepared with chitin-*g*-poly(acrylic acid) by the *grafting from* method have been proposed as a wound dressing material [70,76,77]. The highly water-absorbable film showed a good capacity of absorbing exudates from wounds, thus keeping a moist wound environment [70]. Subsequently, it was shown that the inclusion of glycidyltrimethylammonium chloride improves the wound healing properties of this hydrogel [76,77].

Acrylic acid was also grafted on chitin nanofibers by the *grafting from* method using potassium persulfate. This material showed a stable dispersion in aqueous media at alkaline pH due to the stabilizing effect of electrostatic repulsions between nanofibers [73].

Chitin-*g*-polystyrene copolymer has also been prepared by the *grafting from* method using ammonium persulfate. The effect of some experimental parameters was evaluated, and the resulted material was a copolymer grafted at the C-6 position of chitin backbone [74].

Recently, polypyrrole, an electrically conducting polymer, was grafted on chitin to enhance its mechanical properties. The copolymerization reaction was carried out by the *grafting from* method using ammonium persulfate. The crystallinity of the graft copolymers decreased as a function of the increment of grafting percentage [79]. Itaconic acid, indole, and ε-caprolactone are also other examples of monomers that have been grafted into chitin by the *grafting from* procedure [71,72,75].

3.2. Chitosan "grafting from" copolymers

Unlike chitin, the copolymerization reaction of chitosan could be accomplished by the *grafting from* procedure under homogeneous conditions in aqueous media. At some degree, it allows having more control over the macromolecular structure of the obtained copolymer as compared with chitin.

In this case, a greater variety of monomers have been grafted to chitosan via the *grafted from* procedure, for example: acrylic monomers [80–98], styrene [90], oligoethylene glycol methacrylate [99], N-vinyl-2-pyrrolidone [100,101], ε-caprolactone [15,16,101–103], lactide [104], urethane [105], indole [72], aniline [106], among others. The type of polymerization and initiator to be employed depend on the selected monomer.

One of the problems of the *grafting from* procedure is the difficulty to effectively control the chemoselectivity of the reaction. To overcome this drawback, the *protection-graft-deprotection* method has been employed [83,101–104]. With this purpose, chitosan amino groups are initially protected by *N*-phthaloylation [9]. Then, the copolymerization reaction is conducted with *N*-phthaloyl chitosan, and finally, amino groups are regenerated with hydrazine monohydrate. Thus, the side chains are anchored at the C-3 and C-6 hydroxyl groups of chitosan backbone, while amino groups remain free. The main disadvantage of this technique is that the copolymerization reaction should be carried out in organic solvents.

N-isopropyl acrylamide is one of the most frequently grafted acrylic monomers on chitosan backbone, perhaps due to its thermosensitive properties and its promising applications for the preparation of advanced materials, especially on the biomedical field including drug delivery systems and tissue engineering [81–87,91–93,98]. Ammonium and potassium persulfate are the preferred radical initiator [82,84,85,87,91–93], but also cerium ammonium nitrate [81,86] and azo compounds [98] have been utilized. In general, the *grafting from* synthesis of poly(NIPAm) copolymers are simple and could be accomplished in one step. A strategy proposed by Chen *et al.* involves the synthesis via atom-transfer radical polymerization from the bromo isobutyryl-terminated chitosan at the C-6 hydroxyl group [83].

It has been established that the thermosensitive properties of NIPA are governed by the variation of hydrophilic and hydrophobic interactions by increasing the temperature. At low temperatures, water molecules form regular ice-like structures around hydrophobic methyl groups. When the temperature increases, that hydrophobic hydration collapses. As a result, hydrophobic interactions are generated between the methyl groups of different segments of NIPA chains, giving rise to a polymer network. From a thermodynamic point of view, this phase transition should generate a loss of conformational entropy, due to the ordering of the polymer in the network, which must be compensated by the translational entropy gain of the ejected water molecules. Therefore, as a result of the phase transition, there is an increase in the total entropy, which is greater than the enthalpy gain (the transition is endothermic), all of which results in a decrease in Gibbs free energy [7]. That is, the phase transition depends on the size and closeness of the grafted NIPA chain segments that are involved in the transition. Therefore, an adequate control of the molecular

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architecture allows to effectively modulate the properties of the materials and their response to changes in temperature [7,81,107].

The rheological response of the solutions of this copolymer to changes in temperature is completely reversible. It has been postulated that the increase in the elastic response is due to the formation of hydrophobic crosslinked points at the expense of the amount of sol fraction, for that reason "the connectivity in the gel network is governed by the net number of formed enthalpic-hydrophobic driven-junctions" [81]. The fast thermoreversible response exhibited by these copolymers could be associated with this phenomenon.

Polyelectrolyte complex membranes formed between this copolymer and pectin exhibit temperature and pH dual-stimuli response. Figure 6 shows the release of a model substance as a function of pH and temperature [108], and it can be appreciated how this type of material can respond simultaneously to both parameters.

More information about the structure, properties and potential applications of chitosan-*g*-NIPA copolymers could be found in other specific reviews [7,109].

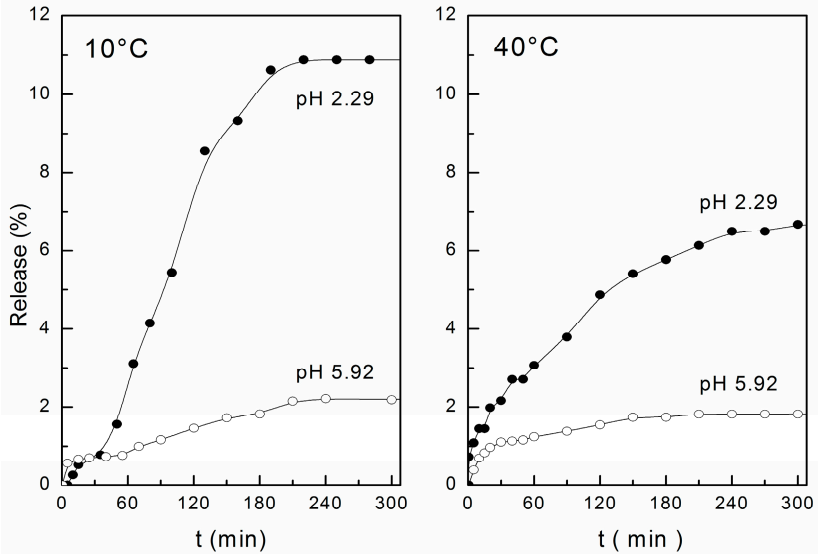

Figure 6. Release profile of Coomassie Blue dye from polyelectrolyte complex membranes formed between this chitosan-*g*-NIPAm and pectin as a function of pH and temperature. Reprinted from Ref. [108], Copyright 2011, with permission from Elsevier.

ε-caprolactone is the other monomer also often grafted onto chitosan. Poly(ε-caprolactone) is a hydrophobic, biodegradable and biocompatible polymer with excellent mechanical properties, so it is comprehensible to search new hybrid materials via grafting copolymerization. Because one of the properties of chitosan that is important to take advantage of is its hydrophilicity and solubility in acidic aqueous solutions, the *protect-graft-deprotect* strategy has been the preferred method [101–103]. Nevertheless, in this case, different synthetic approaches have been tested. The typical amino group protection by N-phthaloylation has been followed in most of the cases [101–103]. In these cases, tin octanoate was selected as a catalyst [101,102], but it has been also showed that N-phthaloyl chitosan is also by itself a catalyst for the ring-opening polymerization of caprolactone monomers and hydroxyl groups acting as initiators [103]. Moreover, there are other reports where methanesulfonic acid was used as a solvent for chitosan and at the same time served to protect the amino groups, and as a catalyst for the ring-opening reaction [15,16]. This copolymer could be used as an efficient stabilizer of gold nanoparticles [101] and could form amphiphilic copolymer micelles suitable for the drug delivery of hydrophobic anticancer molecules [16].

In conclusion, it can be highlighted that the *grafting from* method has the advantage that chitosan can be functionalized in a fairly easy manner, generally in a single reaction step. If it is required to control the chemoselectivity of the copolymerization and to direct the reaction towards the hydroxyl groups at C-6 and C-3 positions, it is necessary to follow the strategy of protecting

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amino groups before copolymerization. The main drawback of the *grafting from* method is that there is a poor control over the structure of the copolymer, both in terms of the dispersion of the grafted chain length, as well as their distribution throughout the chitosan backbone (Figure 5a).

3.3. Chitosan "grafting onto" copolymers

As it is discussed above, the *grafting onto* is the other technique of preparing graft copolymers. Its main advantage is that it is possible to obtain derivatives with a better control of the macromolecular architecture and, therefore, it should be possible to have a greater possibility of modulating the properties and applications of these materials. There are several types of homopolymers that have been grafted onto chitosan, including poly(ε-caprolactone) [110–112], poly(ethylene glycol) and Pluronic [11,36–39,113–126], poly(*N*-isopropyl acrylamide) [40,41,83,127–131] and poly(*N*-vinylcaprolactam) [132–139], among others.

The grafting of end-functionalized poly(ε-caprolactone) has been conducted by the *protect-graft-deprotect* procedure, using **EDC** condensing agent for carboxylic-terminated poly(caprolactone) (Figure 7) [111,112], or the reaction of isocyanate groups with chitosan hydroxyl groups [110]. It has been reported that the resultant material could be self-assembled into micelles and used as stabilizers to prepare silver nanoparticles with good antimicrobial activity [112].

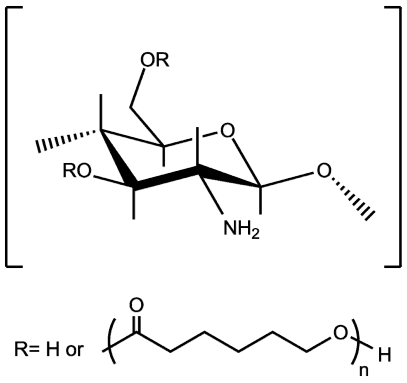

Figure 7. Chemical structure of chitosan-*g*-poly(ε-caprolactone)

Chitosan grafted with Pluronic, poly(ethylene oxide)-*b*-poly(propylene oxide)-*b*-poly(ethylene oxide), copolymer have also been synthesized by the *grafting onto* method. With this purpose, Pluronic is "activated" with succinic anhydride, and the resulted carboxylated Pluronic grafted onto chitosan in the presence of **EDC/NHS** system (Figure 8) [124–126]. This water-soluble thermosensitive copolymer has been evaluated as a potential injectable cell delivery carrier with the aim of using it as a scaffold for cartilage regeneration [125]. Its suitability in the preparation of nanocapsules for drug delivery was also verified [126].

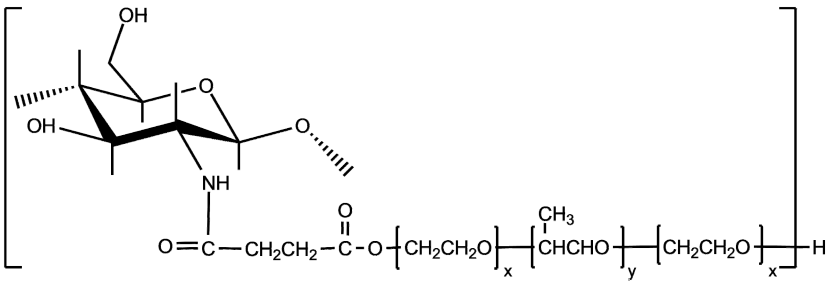

Figure 8. Chemical structure of chitosan-*g*-Pluronic

The grafting of poly(ethylene glycol) onto chitosan backbone has been accomplished via PEGylation of amino groups throughout conjugation with methoxy PEG-nitrophenyl carbonate

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[116], methoxy PEG-succinimidyl carbonate [118], amidation with carboxylated PEG [119] or reductive amination (Figure 9) [114,115,117,120,121]. The use of "click chemistry" tools has also been reported for the *N*- [36,37] or *O*-PEGylation of chitosan [38,39]. However, the grafting onto the -OH groups at C-6 of chitosan structure is an alternative option of chitosan modification, because it allows the total availability of free amino groups. In this sense, some studies related to *O*-substitution graft copolymers have been developed by etherification reaction [11,113,122,123]. For this purpose, the amino groups of chitosan were protected with phthalic anhydride by the above-mentioned procedure. The resultant material (degree of substitution about 15%) shows solubility in a wide range of pH [113]. PEGylated chitosan has been considered as a bioactive delivery carrier for insulin [123], DNA [116], heparin [118], albumin [120], among others. A detailed review of the methods of synthesis, characterization and pharmaceutical applications of PEGylated chitosan derivatives can be consulted [140].

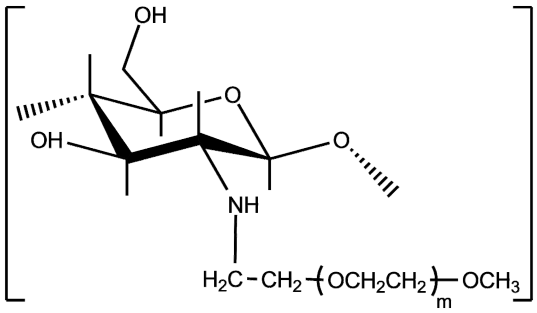


Figure 9. Chemical structure of chitosan-*g*-poly(ethylene glycol)

Cs-*g*-PNIPAm copolymer has also been synthesized by the *graft onto* method via the amidation between carboxylic-end NIPAm chains and chitosan amino groups using carbodiimide compounds like **DCC** [127], or **EDC** (Figure 10) [128–130]. Similarly, the same reaction, but between O-carboxymethyl chitosan and amino-end PNIPAm chains has also been proposed [131], having the advantage of leaving the amino groups free. Bao *et al.* have also made use of "click chemistry" reactions to anchor NIPAm chains onto chitosan backbone [40,41]. Due to its thermoresponsive behavior, this copolymer form hydrogels *in situ*, which favors some properties as enhancement of drug residential time, ocular absorption, pharmacokinetics and bioavailability of hydrophobic drugs [7,127,130].

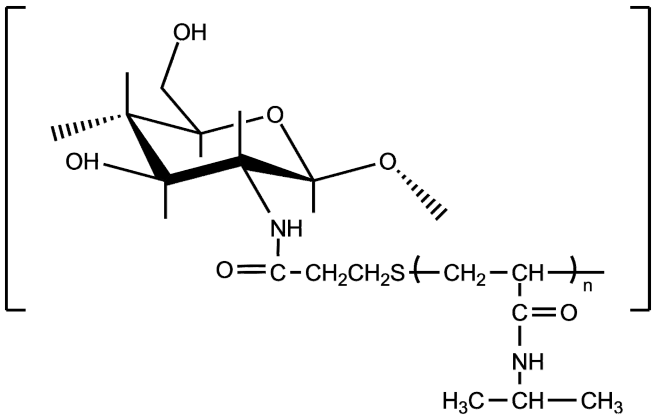
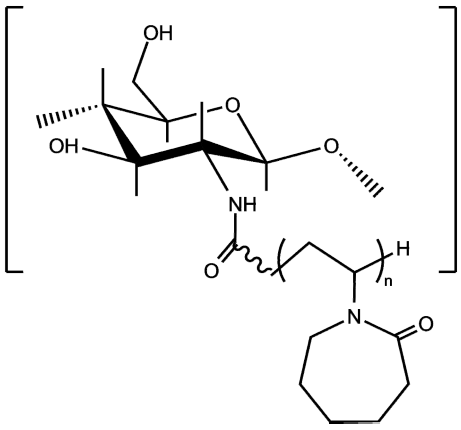


Figure 10. Chemical structure of chitosan-*g*-poly(*N*-isopropyl acrylamide)

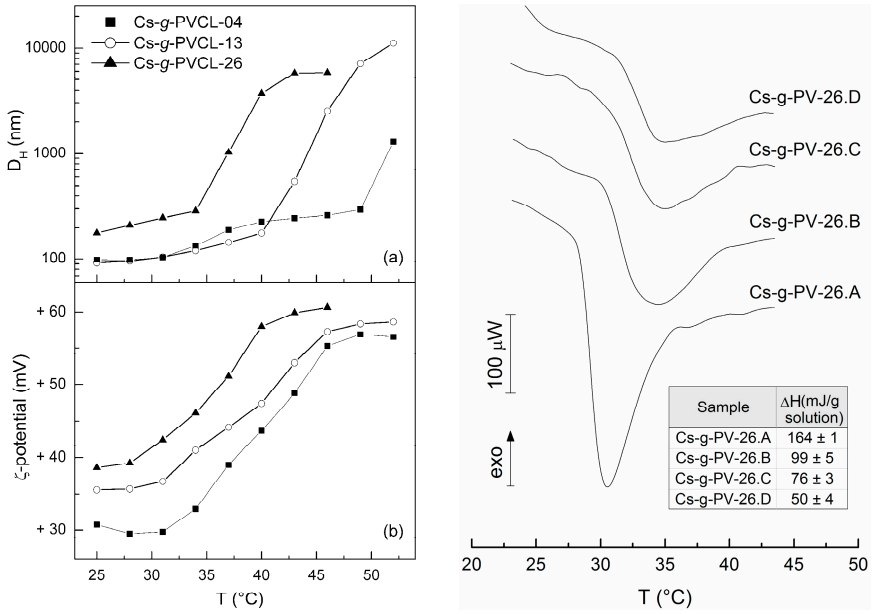
The grafting onto approach to synthesize chitosan-*graft*-PVCL has been conducted by the amidation between PVCL-COOH and chitosan amino groups using **EDC/NHS** system [132–135,137,138] or **DMTMM** (Figure 11) [136,139].



386

387 **Figure 11.** Chemical structure of chitosan-*g*-poly(*N*-vinyl caprolactam)

388 It has been established that the molecular architecture of this copolymer plays a prominent role
389 in their thermoresponsive properties (LCST within 34-45 °C) [136,139]. Figure 11 shows the
390 dependence of the phase transition on the length of the grafted chain or the closeness between them
391 along the chitosan backbone. The increment of the length of the grafted chains implies that longer
392 hydrophobic segments appear, which favors polymer-polymer long-range interactions and giving
393 lower phase transition temperature (Figure 12a). The spacing between PVCL chains along the
394 chitosan backbone also impacts on the transition: as they are closer, the lower the cloud point
395 temperature and the greater the enthalpic change (Figure 12b). As the spacing between grafted
396 chains is more reduced, the hydrophobic intercatenary interactions between PVCL segments are
397 favored, giving rise to the above-mentioned behavior [136]. Indulekha et al. reported the study of
398 CS-*g*-PVCL gel as a transdermal drug delivery system for pain management, which showed
399 biocompatibility and drug permeation through *in vitro* skin test [138]. Jayakumar et al. have studied
400 Cs-*g*-PVCL based nanoparticles as a promising candidate for cancer drug delivery [132–135,137].



401

402 **Figure 12. (a)** Dependence of the hydrodynamic diameter, D_H, on temperature, of Cs-*g*-PVCL
403 aqueous solutions (pH 6) for different number-average molecular weights of PVCL-grafted chains (4,
404 13 and 26 kDa). Reprinted by permission from Springer Nature: Ref. [139], Copyright 2015. **(b)**
405 Micro-DSC curve of 10 wt% aqueous solutions (pH 6) of Cs-*g*-PVCL, varying the spacing between
406 grafted side chains. Reprinted from Ref. [136], Copyright 2015, with permission from Elsevier.

Table 1 presents a compendium of the most representative monomers that have been grafted into chitosan, as well as the main applications proposed.

Table 1. Main monomers used for derivatization of chitin and chitosan by grafting copolymerization.

Monomers	Applications	References
Chitin "grafting from" copolymers		
Acrylamide	Water absorbents, chelating agents	[67]
Acrylic acid	Water absorbents, chelating agents. Wound dressing. Nanofibers	[67,70,73]
Methyl methacrylate	Gel-like mass for biomedical field	[69]
Itaconic acid	Waste-water treatment	[71]
Indole	Antimicrobial activity	[72]
ε-caprolactone	Biomedical field	[141]
Glycidytrimethylammonium chloride	Wound healing	[76]
Pyrrole	Electrically-conducting material	[79]
Chitosan "grafting from" copolymers		
Acrylic acid	Controlled release devices, ion-exchange bioseparation, antibacterial activity, removal of heavy metal ions	[80,88,89,96]
N-butyl acrylate	Biodegradable packaging materials, recovery of heavy metals from waste waters	[90,94]
Iodine	Cervical antibacterial biomembrane	[95]
acrylamide-co-acrylic acid	Drug release hydrogels	[97]
Styrene	Recovery of heavy metals from waste waters	[90]
Aniline	Antibacterial activity	[106]
NIPAm	Biomedical field: tissue engineering, drug delivery systems.	[81–87,91–93,108,130,142]
Lactide	Gene delivery, complex with DNA	[104]
ε-caprolactone	Nanoparticle stabilizer, drug delivery systems	[16,101–103]
N-vinyl-2-pyrrolidone	Antimicrobial activity, nanoparticle stabilizer	[100,101]
Carbamate (urethane)	Drug delivery systems	[105]
Indole	Antimicrobial activity	[72]
Chitosan "grafting onto" copolymers		
Pluronic	Injectable cell delivery carrier, gene expression, controlled release	[125,126]
ε-caprolactone	Drug carriers, antimicrobial activity	[110–112]
Ethylene glycol	Bioactive molecules delivery, polymeric surfactants, gene delivery, apoptosis-inducing activity.	[113,116,118,120,122,123]
NIPAm	Drug/gene delivery,	[40,41,83,127–131]
PVCL	Controlled drug delivery systems	[132–139]

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3.4. Chitosan network systems prepared by radiation

Ionizing radiation constitutes an environmentally friendly tool to prepare graft copolymers from chitin and chitosan. Fundamentally, UV- and γ-radiation have been used for the preparation of chitosan derivatives. UV-initiated polymerization has some benefits, such as lower reaction temperature, fewer amounts of initiator, higher reaction rate, and shorter polymerization times, among others. The principal disadvantage of this method of modification is the absence of specificity. Usually, the resultant radiation-based graft copolymers tend to exhibit a crosslinked network structure.

On the one hand, chitosan-based graft copolymers have received special attention for applications as flocculants due to their biodegradability, absorption and charge neutralization ability, among others. It could be mentioned those materials based on acrylic monomers [143–147], displaying important flocculation properties. There are also reports of radiation-induced chitosan grafted with poly(maleic acid) showing high sorption capacity of Co(II) [148,149]. On the other hand, Burillo *et al.* have developed thermosensitive graft copolymers based on chitosan derivatives by gamma radiation [150–153].

4. Chitosan-*grafted*-cyclodextrin derivatives

Supramolecular polymer chemistry has gained interest in macromolecular research. A number of molecular architectures have been introduced to develop new materials, in which cyclodextrins (**CD**s) have been extensively used. **CD**s are non-toxic cyclic oligosaccharides, formed by 6 to 9 α-D-glucose units linked by (1→4) glycosidic bonds (Figure 13). They own a truncated cone-shape geometry, with a hydrophilic external surface and a relatively more hydrophobic internal cavity [154]. This arrangement favors host-guest interactions through the inclusion of a wide variety of small organic molecules -mainly hydrophobic-, such as adamantane, eugenol, doxorubicin, etc. (Figure 14) [155–157]. This important property confers to **CD**s a special attention as an effective molecular carrier during the design of advanced drug delivery systems. According to Rekharsky and Inoue, the general tendencies of the dependence between thermodynamic quantities can be understood in terms of hydrophobicity, steric effects during the guest-host interaction, the involved guest-host hydrogen bonding and the flexibility of the guest molecule [158]. Thermodynamic studies about the stability of the inclusion complex demonstrated that the enthalpy gain due to the guest inclusion is compensated with the loss of entropy that results from the considerable conformational changes that take place in the **CD**s during the complexation, and the entropy gain due to the desolvation of both host and guest [158,159].

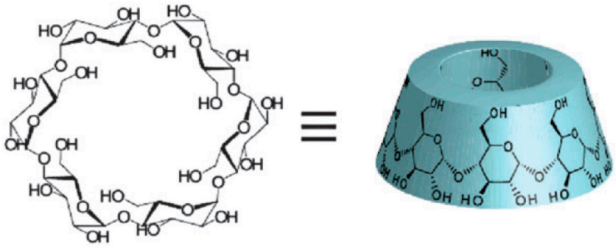

Figure 13. Structure of α-cyclodextrin (formed by six glucosidic units). The arrangement of the external hydrophilic surface and the relatively hydrophobic internal cavity is evident. Reproduced from Ref [160] with permission of The Royal Society of Chemistry.

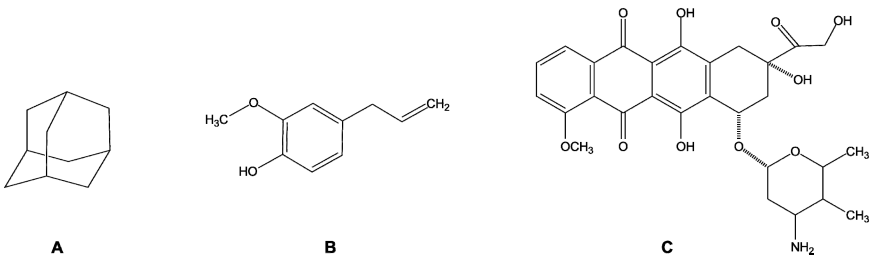

Figure 14. Chemical structure of (A) adamantane, (B) eugenol, (C) doxorubicin.

Many investigations have been carried out with the aim of proposing methods to prepare chitosan grafted **CD**s derivatives in order to take advantage of both: the mucoadhesive properties and reactive functional groups of chitosan and the ability of **CD**s to interact with hydrophobic guest substances [161–163]. In the presence of a guest molecule, chitosan-*g*-**CD**s solutions could form intramolecular and intermolecular complexes, which can lead to a large increase in the viscosity or to the formation of temporary and reversible supramolecular network systems. Consequently, an adequate control of the grafting reaction is of utmost importance in order to regulate the molecular architecture, and therefore the behavior and properties of the polymer materials. For this purpose, the arsenal of methods available for the chemical modification of chitosan can be applied at the time of grafting the cyclodextrin. So far, the following main methods have been proposed:

5. Reductive amination reaction. Usually, the **CD** is modified in order to attach an aldehyde group. The inclusion of the **CD** moieties into the chitosan backbone is carried out by the formation of a Schiff base, followed by the reduction with a proper agent. The reductive amination procedure is one of the most used because it is a simple, easy and little degradative method [156,164–166].
6. The second most important method is via amidation of **CD**s modified with a carboxylic group with the amino groups of chitosan. In this case, two strategies have been applied: *i*) the classic condensation reaction [167,168], and *ii*) by amidation using coupling activators of the carboxylic acid group, like **EDC**/**NHS** [162,169–173]. The former reaction requires high temperatures due to the high activation energies involved, while the use of condensation agents in the later, selectively promotes the formation of the amide bond in aqueous solution under mild and controllable conditions.
7. The nucleophilic substitution of halides or tosyl groups by chitosan amino groups is another recurrent way to attach **CD**s into the chitosan backbone [155,157,174–179].
8. A method so far little used, but in the future can provide derivatives with a high regioselectivity, is anchoring β-cyclodextrin onto chitosan by click chemistry. In this way, using the Huisgen cycloaddition reaction, β-CD chains have been grafted onto the chitosan backbone through the amino group (position 2) [43] or to the O-6 [42].
9. Other methods, among which *i*) the preparation of epoxy-activated chitosan and its reaction with hydroxyl groups of **CD** [180] or *ii*) the anchoring of **CD** into chitosan using 1,6-hexamethylene diisocyanate [181–183], among others, can be mentioned.

In this sense, Auzély-Velty and Rinaudo have reported a procedure, in which a monosubstituted β-**CD**, possessing a *D*-galacturonic acid group on the primary face of **CD**, was grafted onto the chitosan backbone by reductive amination reaction [156,165]. The characterization of the graft copolymer confirmed a successful inclusion of **CD** on the chitosan chain with almost no degradation of the polymer. These authors also observed a slight reduction in the solubility of the derivative (at grafting degrees 10-12%) as compared with that of the pristine chitosan [165]. At a given concentration, the viscosity of the copolymer solution is higher than that the original chitosan, confirming the presence of interchain interactions induced by the presence of grafted **CD** [156].

The host properties of **CD** and chitosan-*g*-**CD** were comparatively studied toward a low or high molecular weight guest. In the former case, 4-tert-butylbenzoic acid and (+)-catechin low molecular weight guests were chosen, and the inclusion complex was analyzed by means of NMR [165].

Experimental data corroborated that the complexation of 4-tert-butylbenzoic acid is a dynamic process, in the sense that the guest molecule is constantly switching between the free and bound states. Moreover, it was possible to conclude that chitosan-*g*-**CD** exhibits the same host-guest properties as the native **CD** toward the low molecular weight hydrophobic guest, suggesting that the grafting process have not significant influence over the binding capacity of **CD** [165]. In the second case, the interaction of chitosan-*g*-**CD** with two macromolecular guests (adamantane attached to chitosan or poly(ethylene glycol)) was evaluated [156]. On the one hand, NMR analyses demonstrated that the hydrophobic sites of the macromolecular guest interact with the grafted **CD** moieties in the same way as with the non-grafted one. On the other hand, rheological experiments showed that PEG end-capped with adamantane mixed with **CD**-chitosan solutions give a significant increase in the viscosity due to cross-linking of **CD**-chitosan chains through host-guest inclusion complexation with PEG-di-adamantane guest. Nevertheless, when the complexation takes place with the chitosan-di-adamantane derivative, a gel-like behavior was appreciated [156]. These characteristics of the inclusion complex with di-adamantane macromolecular derivatives open interesting possibilities to produce advanced materials with controlled sol-gel properties.

One of the drawbacks of chitosan-*g*-**CD**s as a drug delivery system is the poor solubility of chitosan at neutral pH values. In this context, Sajomsang *et al*. have proposed the quaternization of chitosan amino groups in order to obtain a water-soluble grafted [176,177]. Synthesis strategy involves the quaternization of previously prepared chitosan-*g*-**CD**s, carried out by the nucleophilic substitution of the remained free amino groups, yielding a water-soluble quaternized chitosan-*g*-**CD**. The degree of quaternization (DQ), reached values between 60 and 85%. The mucoadhesive properties of the grafted polymer were dependent on the DQ, being stronger as the DQ increases, while its cytotoxicity does not show any dependence with the DQ [177]. The formation of an inclusion complex between the quaternized chitosan-*g*-**CD**s and eugenol as model guest molecule has also been studied. In this case, it was confirmed that eugenol is included in the hydrophobic cavity of **CD**s, but a self-aggregated micelle-type structure was formed, within which, extra eugenol molecules were entrapped as illustrated in Figure 15. The greatest mucoadhesion was attained with the complex having 11% **CD** substitution, suggests that in this case, electrostatic interaction has a key role in governing the adhesion between mucin and the chitosan derivative [155]. Moreover, an enhanced mucoadhesion has been reported for this system when **CD**s were attached to the chitosan backbone throughout a citric acid molecule. This effect is possibly due to additional intermolecular hydrogen bonding between the carboxyl and hydroxyl groups from the citric acid spacer and mucus glycoprotein [168,184].

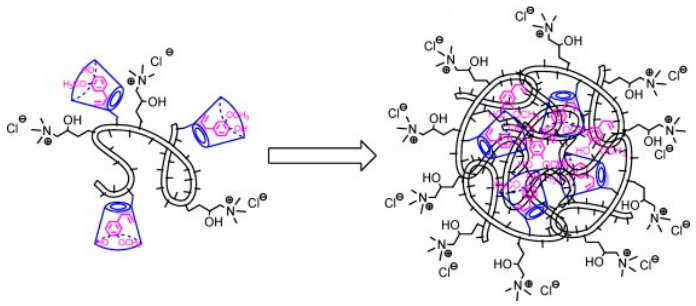

Figure 15. Schematic structure of inclusion complex between eugenol (pink) and quaternized chitosan (black) grafted with β-cyclodextrin (blue) forming self-aggregated micellar structures. Reprinted from reference [155], Copyright 2012, with permission from Elsevier.

Another extensive coupling method used to graft **CD** into chitosan chain is based on amidation reaction. This reaction occurs among a component containing a free amino group, like chitosan, with a substituted carboxylic acid-cyclodextrin to generate the amide bond. This reaction is mediated by diimide derivatives, among them, **EDC** is the most used due to its water solubility. Daimon *et al.* described the preparation of a chitosan-*g*-**CD**s by the condensation reaction of chitosan and β-**CD**-carboxylate [162,163]. The interaction between chitosan-*g*-**CD**s and insulin was evaluated.

Insulin was strongly bound to β-**CD** residues due to the specific host-guest inclusion complex with insulin. The electrostatic interactions between chitosan-*g*-**CD**s and insulin allowed a strong binding in a wide range of pH [162]. The conclusion of several studies is that chitosan-*g*-**CD**s have the remarkable potential to be applied in the delivery of peptides and proteins as an efficient delivery carrier [162,163,173].

Kono *et al.* described the preparation of a hydrogel based on carboxymethyl chitosan and carboxymethyl **CD**. A reductive amidation reaction was conducted employing **EDC-NHS** as the coupling agent. It allowed simultaneous grafting of **CD** into chitosan and crosslinking. Acetylsalicylic acid was chosen as a model drug to explore its properties as a carrier for drug delivery system. According to their results, the observed drug release profile could be attributed to the formation an inclusion complex of aspirin inside **CD** cavities [170].

Apart from the aforementioned applications for controlled release systems, other studies aimed at the use of chitosan/cyclodextrin materials for the removal of metals or organic micropollutants from wastewaters has been described as well [185,186]. For example, Zhao *et al.* prepared chitosan-β-cyclodextrin absorbent material, using EDTA as cross-linker. According to these authors, "chitosan chain is considered as the backbone, and the immobilized cyclodextrin cavities capture the organic compounds via host-guest inclusion complexation, while EDTA-groups complex metals" [186]. A β-cyclodextrin-chitosan-graphene oxide composite material has been also proposed. It is claimed that this material is appropriate for the removal of manganese ions [185].

Finally, it should be noted that there is an increasing number of publications in which chitosan and cyclodextrin are used as important components in the preparation of nano-vehicles or stimuli-sensitive carriers [157,172,178,187–190].

5. Dendronized chitosan

Dendrimers are commonly represented as highly symmetrical molecules, displayed in tiers with an algorithmic growth. They are characterized by a high end functional groups located on the surface of a spherical conformation, leading a molecule owing a large amount of functional sites easily accessible to the media, with an isolate core. This typical architecture influences the physical properties, like solution behavior, especially at high molecular weights. In dendrimer construction, two synthetic approaches have been employed: divergent and convergent. On the former, stepwise growing occurs from the center by means of a series of high selective reactions over a single molecule, whereas on the latter, the synthesis begins in the periphery and ends in the core. Despite the important biomedical applications of dendrimers as viral and pathogenic cell adhesion inhibitors, references about dendronized chitosan derivatives are still scarce [191]. Here is a general brief description about these novel chitosan derivatives.

Some of the first reports of the preparation and characterization of chitosan dendrimer hybrid molecules are those presented by Sashiwa *et al.* [192–195]. They reported the preparation of sialic acid bound dendronized chitosan using gallic acid as the focal point, and tri(ethylene glycol) as spacer arm. It was suggested to be a non-toxic alternative and inhibitors of hemagglutination of influenza viruses.

The preparation of a Pb^{2+} heavy metal bioabsorbent CDH, PAMAM-g-chitosan, was achieved by divergent approach synthesis. The addition of methylacrylate over amino groups of chitosan powder surface was driven by the Michel addition reaction followed by the amidation of terminal groups with EDTA, different generation of PAMAM were obtained by the subsequent propagation of PAMAM [196].

The preparation of a water soluble quaternized carboxymethyl chitosan/poly(amido amine) dendrimer with core-shell nanoparticles was also described [197,198]. The synthesis of this dendronized chitosan involves a two-step reaction: the activation of carboxylic groups in quaternized carboxymethyl chitosan and the subsequent condensation reaction. The obtained chitosan dendrimer hybrid could self-aggregate into core-shell nanoparticles due to the combination of hydrophobic and electrostatic interactions and hydrogen bonding. These dendrimer nanoparticles exhibited antibacterial activity against to Gramm negative bacteria as *E. coli*.

Similar nanostructures were also prepared with carboxymethyl chitosan-modified magnetic core composed of magnetite nanoparticles and dendritic branches with carboxymethyl chitosan terminal groups [199]. These dendrimers exhibit selective adsorption for anionic and cationic compounds at specific pH and their potential use to remove dyes was successfully proved.

6. Chitosan modification using ionic liquids

The ionic liquids (**IL**) have become a versatile media to perform chitin and chitosan derivatization that was not available few of decades ago. Ionic liquids are salts that remain liquid below 100°C; in a practical sense, are those salts that should be handled as liquids at room temperature. Most of them are formed by uneven ionic moieties, usually large cations paired with anions of relatively smaller size. The combination and modification of cations and anions make it possible to obtain ionic liquids with diverse chemical characteristics and functional properties. Thus, **IL** have been praised as customizable solvents; some of them with remarkable properties that have found its way to industrial scale applications. Many **IL** have been also classified as "green" solvents due to their reduced vapor pressure, conventional non-flammability, and exceptional solvation potential [200,201].

The **IL** capacity to dissolve polysaccharides was first reported in 1934. However, this does not receive considerable scientific attention, until recently. One of the main focus of interest has been the capacity of some **IL** to dissolve typically intractable polysaccharides as cellulose or chitin [202–205]. Imidazolium-based **IL**, particularly 1-ethyl-3-methylimidazolium (**Emim**) and 1-butyl-3-methylimidazolium (**Bmim**) in chloride or acetate form (Figure 16), are commonly used to prepare chitin and chitosan solutions that could reach relatively high concentration (over 10 w%). Other types of **IL** have been reported to dissolve chitosan to different extents, for example, pyridinium-based **IL** functionalized with sulfonic acid [206] or amino acid-based **IL** [207]. The chitosan-**IL** solutions provide alternative media to get homogeneous reaction conditions and also enable derivatizations that are not favored in aqueous environments. The availability of this type of chitin-chitosan solvent system began to gain relevance in scientific research and applications development.

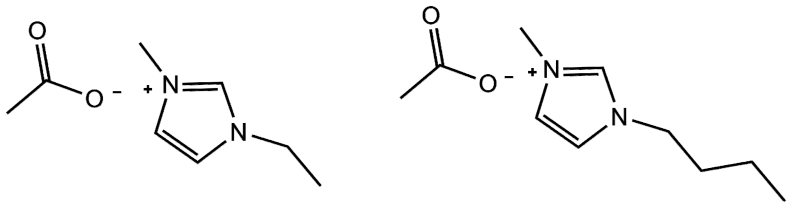

Figure 16. Chemical structure of the acetate salts of 1-ethyl-3-methylimidazolium, **Emim**, and 1-butyl-3-methylimidazolium, **Bmim**.

Actually, several types of chemical modifications of chitin-chitosan in **IL** have been reported. Some of them have been compiled in focused reviews [208,209]. Chitosan has several functional chemical groups susceptible to react, which allow the production of a range of derivatives and grafting. Below is a succinct summary of the most relevant chitosan derivation procedures in **IL** reported in the literature and some examples of the obtained products are included in Figure 17.

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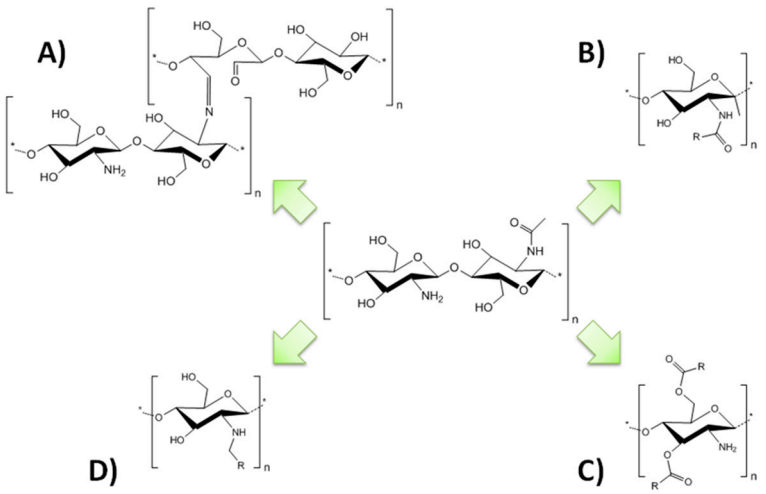

Figure 17. Some examples of chitosan derivatization made in **IL**. A) Chitosan-graft-oxicellulose, B) N-acylation, C) O-acylation, D) Alkylation.

6.1. Acylation

Acetylation was one of the first chemical modification procedures performed on chitin-chitosan dissolved in ionic liquids. Homogeneous acetylation of chitin and chitosan in halide imidazolium-based **IL** has been reported [210,211]. Based on the degrees of substitution and spectroscopic evidence reported both N-acetylation and O-acetylation was achieved indistinctly. With **IL** the acetylation of chitosan proceeds in mild and homogeneous conditions, making this methodology more straightforward compared to usual procedures [209]. Other acylation procedures have been reported. The **IL** 1-butyl-3-methylimidazolium acetate (**BmimAc**) was used as the reaction solvent to obtain N-linoleyl chitosan oligomers. Narrow-distribution low molecular chitosan was used as starting material that was acylated with linoleic acid using **EDC** and 4-(dimethylamino) pyridine (DMAP) as catalysts on mild reaction conditions. The nanomicelles of the obtained amphiphilic molecules are proposed as drug vector [212]. Similarly, the use of glycine chloride ([Gly]Cl) aqueous solution as media to synthesize N-acyl chitosan derivatives (i.e. N-maleyl, N-succinyl chitosan, and N-acetylated) was reported as a procedure to obtain fibers with improved mechanical properties [213]. Another acylation type modification was achieved reacting chitosan with monomethyl fumaric acid mediated by **EDC**. The reaction media was an aqueous solvent system including 4 w% of the **IL**, 1-sulfobutyl-3-methylimidazolium trifluoromethanesulfonate ($BSmimCF_3SO_3$). The product, monomethyl fumaric-chitosan amide, has improved water solubility and antioxidant activity [214]. Chitosan has been also reacted with a carboxyl group-bearing **IL** (1-carboxypropyl-3-methyl imidazolium chloride) to obtain an acyl conjugate. Spectroscopic techniques (NMR and FTIR) were used to elucidate the structure of the chitosan-ionic liquid conjugate. This compound shows good anion adsorption performance and was proposed for wastewater treatment [215].

6.2. Alkylation

Several alkylation type modifications of chitosan have been done using **IL** as media and catalyst. The nucleophilic substitution of 2,3-epoxypropyltrimethyl ammonium chloride (EPTAC) onto chitosan, using ionic liquid of 1-allyl-3-methylimidazole chloride (AmimCl) as a homogeneous reaction media, produced N-[(2-hydroxyl)-propyl-3-trimethyl ammonium] chitosan chloride (HTCC). In this system, the attack of the amino groups of chitosan to the C atom with less steric hindrance in EPTAC is thermodynamically favored according to quantum chemistry calculations [216]. Chitosan was reacted with four alkyl halides in a basic form of the **Bmim IL** to prepare a series of alkylated chitosans with different carbon chain substituents (i.e. ethyl-, butyl-, dodecyl-, and cetyl-chitosan). The analysis of FTIR spectra indicates the occurrence of O-alkylation; however, the

N-alkylation prevails at the reaction conditions used. The antibacterial activity of alkylated chitosans decreased with the growth of the DS or the growth of the carbon chain [217]. Another report of *N*-alkylation of chitosan in **IL** is the production of N-[(2-Hydroxyl)-propyl-3-trimethyl ammonium] chitosan chloride (HTCC) in AmimCl [218]. In contrast, there are few examples of O-alkylation of chitosan achieved in **IL**. Dodecanol was selectively linked to hydroxyl groups of chitosan using N,N'-carbonyldiimidazole as a bonding agent and **BmimCl** as homogeneous media. The authors attribute the selective alkylation of hydroxyl groups of CS, without protecting amino groups, to the particular properties of the ionic liquid solvent [219].

6.3. Grafting

The solvent capacity of several **IL** has been used to achieve grafting on chitin or chitosan. Chitin graft polystyrene was obtained by atom-transfer radical polymerization (ATRP) in AmimBr [220]. Methacryloyloxyethyl trimethylammonium brushes were formed on chitosan by single electron transfer living radical polymerization in **BmimCl** [221]. The synthesis of chitosan graft polyethylenimine copolymers was developed in **BmimAc** [222]. Two different research groups have reported the chitosan grafting with polycaprolactone using **IL** as a solvent. Wang and collaborators use **EmimCl** as solvent and stannous octoate as catalyst [223], whereas Yang and co-workers use a ring-opening graft polymerization route with N-protected chitosan dissolved in **BmimAc** [216]

Ionic liquids allow the homogeneous mixture of polysaccharides in solution. This has been used to produce several composite materials. Furthermore, these solvent systems have enabled the possibility to carry out inter-polysaccharide reactions that have been proved difficult to do in other media. Thus, it was possible to produce chitosan graft oxycellulose using a mixture of two **IL**, AmimCl as the solvent and 1-sulfobutyl-3-methylimidazolium hydrogen sulfate ($SmimHSO_4$) **IL** as the catalyst of the reaction [224]. Another example is the covalent linking of chitosan and xylan through the Maillard reaction in **BmimCl** [225].

6.4. Other derivatizations

The crosslinking of chitosan in **IL** has been explored. Chemical ionogels were obtained crosslinking chitosan with glutaraldehyde in **EmimAc** [226]. Recently was reported the design of a dicationic **IL** (1,10-(butane-1,4-diyl)bis(3-(4-bromobutyl)-1H-imidazole-3-ium)bromide) used as crosslinking agent for chitosan. The composite materials of chitosan crosslinked with **IL** were tested as catalysts of the cycloaddition reaction of CO_2 with various epoxides [227].

Other derivatization reactions of chitosan performed in ionic liquids solutions include the formation of a Schiff base conjugate using **BmimCl** as solvent [228], and the sulfonation of chitosan in an aqueous solvent system containing [Gly]Cl [229].

6.5. Degradation

A homogeneous reaction media like the obtained using **IL** represent an opportunity window to test diverse modifications in the chemical structure of chitin and chitosan. One of the basic modifications of these polysaccharides is the deacetylation. This has been achieved by hydrothermal treatment using aqueous **BmimAc** as reaction medium and catalyst [230]. However, there are more scientific reports on the hydrolysis of chitin and chitosan in **IL**.

A mixture of **BmimCl**, **BmimBr**, and hydrochloric acid was effectively used to depolymerize of chitin [231]. Improved reaction rates were reported when chitosan dissolved in AmimCl was treated with sulfonic acid-functionalized ionic liquids based in propylpyridinium and microwave irradiation [206]. An aqueous solution–ionic liquid biphasic catalytic system was proposed for the oxidative degradation of chitosan. Chitosan was dissolved in diluted HCl and the hydrophobic ionic liquid 1-N-butyl-3-methylimidazolium bis((trifluoromethyl)sulfonyl) imide ([bmim][Tf_2N]) containing with iron(II) phthalocyanine (FePc) complete the oxidative catalytic system [232]. Furthermore, a nitrogen-containing furan derivative has been obtained directly from chitin

dissolved in a range of imidazolium-based **IL**, containing HCl or HBr as additives, after a thermal treatment [233].

6.6. Biocatalyzed reactions

Ionic liquids have been also used as effective media for biocatalyzed reactions. It is considered that many enzymes, particularly those that tolerate conventional organic solvents, can achieve comparable activities in ionic liquids. Moreover, ionic liquids solvent systems could overcome some limitations that are observed in the biotransformation of highly polar substrates, such as polysaccharides [200]. Consequently, several research groups have studied enzymatic modifications of chitin-chitosan using **IL** as reaction media or additive. Bacterial and fungal chitinases dispersed in an aqueous solvent system containing **EmimAc** were applied to produce monomers and oligosaccharides from chitin. A notorious enzymatic activity reduction was observed when **IL** concentration is over 20 v% [234]. Chitosan oligomers were produced with amylose in a [Gly]BF_4 aqueous medium. Similarly, an enzymatic activity reduction was observed when the **IL** concentration goes over 8 v% [235]. On the other hand, commercial lipase was used for the synthesis of chitosan esters via transesterification with methyl palmitate. The reaction media contain a mixture of a hydrophilic **IL**, **EmimAc**, and a hydrophobic **IL**, **Bmim** tetrafluoroborate [236].

The ionic liquids have become a promising solvent platform for controlled chemical modification of chitosan. The "customization" of **IL** could provide tunable homogeneous phase media to circumvent the common drawbacks of the heterogeneous conditions (i.e. require harsh reaction settings, high variability, low product yields, extended reaction times, etc.) [208,209]. Most of the cited authors in this section remark the "green" solvent condition of **IL** refereed to their low vapor pressure, non-flammability, thermal and chemical stability. Furthermore, the reuse and recycling of **IL** have received particular attention. There are examples of controlled reactions, even regioselective, derivatization of chitosan using **IL** as media, additive or catalysts. However, the main concerns about the use of **IL** focus on their biocompatibility and their cost, as they are not readily available yet. The application of **IL** for polysaccharide processing is relatively recent subject, the possibilities enabled are numerous thus considerable research effort is ongoing worldwide.

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References

1. Kurita, K. Chitin and Chitosan: Functional Biopolymers from Marine Crustaceans. *Mar. Biotechnol.* **2006**, *8*, 203–226, doi:10.1007/s10126-005-0097-5.
2. Peniche, C.; Argüelles-Monal, W.; Goycoolea, F. M. Chitin and Chitosan: Major Sources, Properties and Applications. In *Monomers, Polymers and Composites from Renewable Resources*; Belgacem, M. N., Gandini, A., Eds.; Elsevier: Amsterdam, 2008; pp. 517–542 ISBN 978-0-08-045316-3.
3. Sabaa, M. W. Chitosan-g-Copolymers: Synthesis, Properties, and Applications. In *Polysaccharide Based Graft Copolymers*; Kalia, S., Sabaa, M. W., Eds.; Springer Berlin Heidelberg, 2013; pp. 111–147 ISBN 978-3-642-36565-2.
4. Amato, A.; Migneco, L. M.; Martinelli, A.; Pietrelli, L.; Piozzi, A.; Francolini, I. Antimicrobial activity of catechol functionalized-chitosan versus Staphylococcus epidermidis. *Carbohydr. Polym.* **2018**, *179*, 273–281, doi:10.1016/j.carbpol.2017.09.073.
5. Kurita, K. Controlled functionalization of the polysaccharide chitin. *Prog. Polym. Sci.* **2001**, *26*, 1921–1971, doi:10.1016/S0079-6700(01)00007-7.
6. Jenkins, D. W.; Hudson, S. M. Review of Vinyl Graft Copolymerization Featuring Recent Advances toward Controlled Radical-Based Reactions and Illustrated with

Chitin/Chitosan Trunk Polymers. *Chem. Rev.* **2001**, *101*, 3245–3274, doi:10.1021/cr000257f.

7. Argüelles-Monal, W.; Recillas-Mota, M.; Fernández-Quiroz, D. Chitosan-Based Thermosensitive Materials. In *Biological Activities and Application of Marine Polysaccharides*; Shalaby, E. A., Ed.; InTech, 2017; pp. 279–302 ISBN 978-953-51-2859-5.
8. Nishimura, S.; Kohgo, O.; Kurita, K.; Kuzuhara, H. Chemospecific manipulations of a rigid polysaccharide: syntheses of novel chitosan derivatives with excellent solubility in common organic solvents by regioselective chemical modifications. *Macromolecules* **1991**, *24*, 4745–4748, doi:10.1021/ma00017a003.
9. Kurita, K.; Ikeda, H.; Yoshida, Y.; Shimojoh, M.; Harata, M. Chemoselective Protection of the Amino Groups of Chitosan by Controlled Phthaloylation: Facile Preparation of a Precursor Useful for Chemical Modifications. *Biomacromolecules* **2002**, *3*, 1–4, doi:10.1021/bm0101163.
10. Kurita, K.; Ikeda, H.; Shimojoh, M.; Yang, J. *N*-Phthaloylated Chitosan as an Essential Precursor for Controlled Chemical Modifications of Chitosan: Synthesis and Evaluation. *Polym. J.* **2007**, *39*, 945, doi:10.1295/polymj.PJ2007032.
11. Makuška, R.; Gorochovceva, N. Regioselective grafting of poly(ethylene glycol) onto chitosan through C-6 position of glucosamine units. *Carbohydr. Polym.* **2006**, *64*, 319–327, doi:10.1016/j.carbpol.2005.12.006.
12. Montiel-Herrera, M.; Gandini, A.; Goycoolea, F. M.; Jacobsen, N. E.; Lizardi-Mendoza, J.; Recillas-Mota, M. T.; Argüelles-Monal, W. M. Furan–chitosan hydrogels based on click chemistry. *Iran. Polym. J.* **2015**, *24*, 349–357, doi:10.1007/s13726-015-0325-4.
13. Wang, X.; Ma, J.; Wang, Y.; He, B. Structural characterization of phosphorylated chitosan and their applications as effective additives of calcium phosphate cements. *Biomaterials* **2001**, *22*, 2247–2255, doi:10.1016/S0142-9612(00)00413-0.
14. Sashiwa, H.; Kawasaki, N.; Nakayama, A.; Muraki, E.; Yamamoto, N.; Aiba, S. Chemical Modification of Chitosan. 14: Synthesis of Water-Soluble Chitosan Derivatives by Simple Acetylation. *Biomacromolecules* **2002**, *3*, 1126–1128, doi:10.1021/bm0200480.
15. Duan, K.; Chen, H.; Huang, J.; Yu, J.; Liu, S.; Wang, D.; Li, Y. One-step synthesis of amino-reserved chitosan-graft-polycaprolactone as a promising substance of biomaterial. *Carbohydr. Polym.* **2010**, *80*, 498–503, doi:10.1016/j.carbpol.2009.12.013.
16. Gu, C.; Le, V.; Lang, M.; Liu, J. Preparation of polysaccharide derivates chitosan-graft-poly(ε-caprolactone) amphiphilic copolymer micelles for 5-fluorouracil drug delivery. *Colloids Surf. B Biointerfaces* **2014**, *116*, 745–750, doi:10.1016/j.colsurfb.2014.01.026.
17. Roberts, G. A. F. *Chitin Chemistry*; Macmillan: London, 1992; ISBN 978-0-333-52417-6.
18. *Material Science of Chitin and Chitosan*; Uragami, T., Tokura, S., Eds.; 2006 edition.; Springer: Tokyo : Berlin ; New York, 2006; ISBN 978-3-540-32813-1.

19. *Chitin and Chitosan Derivatives: Advances in Drug Discovery and Developments*; Kim, S.-K., Ed.; 1 edition.; CRC Press: Boca Raton, 2013; ISBN 978-1-4665-6628-6.
20. Carvalho, L. C. R.; Queda, F.; Santos, C. V. A.; Marques, M. M. B. Selective Modification of Chitin and Chitosan: En Route to Tailored Oligosaccharides. *Chem. – Asian J.* **2016**, *11*, 3468–3481, doi:10.1002/asia.201601041.
21. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Click Chemistry: Diverse Chemical Function from a Few Good Reactions. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021, doi:10.1002/1521-3773(20010601)40:11<2004::AID-ANIE2004>3.0.CO;2-5.
22. Kolb, H. C.; Sharpless, K. B. The growing impact of click chemistry on drug discovery. *Drug Discov. Today* **2003**, *8*, 1128–1137, doi:10.1016/S1359-6446(03)02933-7.
23. Huisgen, R. 1,3-Dipolar cycloaddition – Introduction, survey, mechanism. In *1,3-dipolar cycloaddition chemistry*; Padwa, A., Ed.; John Wiley and Sons: New York, 1984; Vol. 1, pp. 1–176 ISBN 978-0-471-08364-1.
24. Wang, Z. Diels-Alder Reaction. In *Comprehensive Organic Name Reactions and Reagents*; John Wiley & Sons, Inc., 2010 ISBN 978-0-470-63885-9.
25. Wang, Z. Retro-Diels-Alder Reaction. In *Comprehensive Organic Name Reactions and Reagents*; John Wiley & Sons, Inc., 2010 ISBN 978-0-470-63885-9.
26. Gandini, A. The furan/maleimide Diels–Alder reaction: A versatile click–unclick tool in macromolecular synthesis. *Prog. Polym. Sci.* **2013**, *38*, 1–29, doi:10.1016/j.progpolymsci.2012.04.002.
27. Elchinger, P.-H.; Faugeras, P.-A.; Boëns, B.; Brouillette, F.; Montplaisir, D.; Zerrouki, R.; Lucas, R. Polysaccharides: The "Click" Chemistry Impact. *Polymers* **2011**, *3*, 1607–1651, doi:10.3390/polym3041607.
28. Uliniuc, A.; Popa, M.; Hamaide, T.; Dobromir, M. New approaches in hydrogel synthesis - Click chemistry: A review. *Cellul. Chem. Technol.* **2012**, *46*, 1–11.
29. Barbosa, M.; Martins, C.; Gomes, P. "Click" chemistry as a tool to create novel biomaterials: a short review. *UPorto J. Eng.* **2015**, *1*, 22–34.
30. Meng, X.; Edgar, K. J. "Click" reactions in polysaccharide modification. *Prog. Polym. Sci.* **2016**, *53*, 52–85, doi:10.1016/j.progpolymsci.2015.07.006.
31. Kritchenkov, A. S.; Skorik, Y. A. Click reactions in chitosan chemistry. *Russ. Chem. Bull.* **2017**, *66*, 769–781, doi:10.1007/s11172-017-1809-5.
32. Bertoldo, M.; Nazzi, S.; Zampano, G.; Ciardelli, F. Synthesis and photochromic response of a new precisely functionalized chitosan with "clicked" spiropyran. *Carbohydr. Polym.* **2011**, *85*, 401–407, doi:10.1016/j.carbpol.2011.02.043.
33. Ifuku, S.; Wada, M.; Morimoto, M.; Saimoto, H. A short synthesis of highly soluble chemoselective chitosan derivatives via "click chemistry." *Carbohydr. Polym.* **2012**, *90*, 1182–1186, doi:10.1016/j.carbpol.2012.06.074.
34. Li, X.; Yuan, W.; Gu, S.; Ren, J. Synthesis and self-assembly of tunable thermosensitive chitosan amphiphilic copolymers by click chemistry. *Mater. Lett.* **2010**, *64*, 2663–2666, doi:10.1016/j.matlet.2010.08.077.

35. Zampano, G.; Bertoldo, M.; Ciardelli, F. Defined Chitosan-based networks by C-6-Azide–alkyne "click" reaction. *React. Funct. Polym.* **2010**, *70*, 272–281, doi:10.1016/j.reactfunctpolym.2010.01.004.
36. Kulbokaite, R.; Ciuta, G.; Netopilik, M.; Makuska, R. N-PEG'ylation of chitosan via "click chemistry" reactions. *React. Funct. Polym.* **2009**, *69*, 771–778, doi:10.1016/j.reactfunctpolym.2009.06.010.
37. Truong, V. X.; Ablett, M. P.; Gilbert, H. T. J.; Bowen, J.; Richardson, S. M.; Hoyland, J. A.; Dove, A. P. In situ-forming robust chitosan-poly(ethylene glycol) hydrogels prepared by copper-free azide–alkyne click reaction for tissue engineering. *Biomater. Sci.* **2013**, *2*, 167–175, doi:10.1039/C3BM60159E.
38. Oliveira, J. R.; Martins, M. C. L.; Mafra, L.; Gomes, P. Synthesis of an O-alkynyl-chitosan and its chemoselective conjugation with a PEG-like amino-azide through click chemistry. *Carbohydr. Polym.* **2012**, *87*, 240–249, doi:10.1016/j.carbpol.2011.07.043.
39. Tirino, P.; Laurino, R.; Maglio, G.; Malinconico, M.; d'Ayala, G. G.; Laurienzo, P. Synthesis of chitosan–PEO hydrogels via mesylation and regioselective Cu(I)-catalyzed cycloaddition. *Carbohydr. Polym.* **2014**, *112*, 736–745, doi:10.1016/j.carbpol.2014.06.026.
40. Bao, H.; Li, L.; Leong, W. C.; Gan, L. H. Thermo-Responsive Association of Chitosan-graft-Poly(N-isopropylacrylamide) in Aqueous Solutions. *J. Phys. Chem. B* **2010**, *114*, 10666–10673, doi:10.1021/jp105041z.
41. Bao, H.; Li, L.; Gan, L. H.; Ping, Y.; Li, J.; Ravi, P. Thermo- and pH-Responsive Association Behavior of Dual Hydrophilic Graft Chitosan Terpolymer Synthesized via ATRP and Click Chemistry. *Macromolecules* **2010**, *43*, 5679–5687, doi:10.1021/ma100894p.
42. Chen, Y.; Ye, Y.; Li, R.; Guo, Y.; Tan, H. Synthesis of chitosan 6-OH immobilized cyclodextrin derivates via click chemistry. *Fibers Polym.* **2013**, *14*, 1058–1065, doi:10.1007/s12221-013-1058-7.
43. Lu, L.; Shao, X.; Jiao, Y.; Zhou, C. Synthesis of chitosan-graft-β-cyclodextrin for improving the loading and release of doxorubicin in the nanopaticles. *J. Appl. Polym. Sci.* **2014**, *131*, 41034, doi:10.1002/app.41034.
44. Guerry, A.; Bernard, J.; Samain, E.; Fleury, E.; Cottaz, S.; Halila, S. Aniline-Catalyzed Reductive Amination as a Powerful Method for the Preparation of Reducing End-"Clickable" Chitooligosaccharides. *Bioconjug. Chem.* **2013**, *24*, 544–549, doi:10.1021/bc3003716.
45. Guerry, A.; Cottaz, S.; Fleury, E.; Bernard, J.; Halila, S. Redox-stimuli responsive micelles from DOX-encapsulating polycaprolactone-g-chitosan oligosaccharide. *Carbohydr. Polym.* **2014**, *112*, 746–752, doi:10.1016/j.carbpol.2014.06.052.
46. Yuan, W.; Li, X.; Gu, S.; Cao, A.; Ren, J. Amphiphilic chitosan graft copolymer via combination of ROP, ATRP and click chemistry: Synthesis, self-assembly, thermosensitivity, fluorescence, and controlled drug release. *Polymer* **2011**, *52*, 658–666, doi:10.1016/j.polymer.2010.12.052.

47. Zhang, K.; Zhuang, P.; Wang, Z.; Li, Y.; Jiang, Z.; Hu, Q.; Liu, M.; Zhao, Q. One-pot synthesis of chitosan-g-(PEO-PLLA-PEO) via "click" chemistry and "SET-NRC" reaction. *Carbohydr. Polym.* **2012**, *90*, 1515–1521, doi:10.1016/j.carbpol.2012.07.023.
48. Jung, S.; Yi, H. Fabrication of Chitosan-Poly(ethylene glycol) Hybrid Hydrogel Microparticles via Replica Molding and Its Application toward Facile Conjugation of Biomolecules. *Langmuir* **2012**, *28*, 17061–17070, doi:10.1021/la303567p.
49. Gao, Y.; Zhang, Z.; Chen, L.; Gu, W.; Li, Y. Synthesis of 6-N,N,N-Trimethyltriazole Chitosan via "Click Chemistry" and Evaluation for Gene Delivery. *Biomacromolecules* **2009**, *10*, 2175–2182, doi:10.1021/bm900341d.
50. Ifuku, S.; Wada, M.; Morimoto, M.; Saimoto, H. Preparation of highly regioselective chitosan derivatives via "click chemistry." *Carbohydr. Polym.* **2011**, *85*, 653–657, doi:10.1016/j.carbpol.2011.03.030.
51. Chen, Y.; Wang, F.; Yun, D.; Guo, Y.; Ye, Y.; Wang, Y.; Tan, H. Preparation of a C6 quaternary ammonium chitosan derivative through a chitosan schiff base with click chemistry. *J. Appl. Polym. Sci.* **2013**, *129*, 3185–3191, doi:10.1002/app.38431.
52. Zhao, Q.; Zhang, J.; Song, L.; Ji, Q.; Yao, Y.; Cui, Y.; Shen, J.; Wang, P. G.; Kong, D. Polysaccharide-based biomaterials with on-demand nitric oxide releasing property regulated by enzyme catalysis. *Biomaterials* **2013**, *34*, 8450–8458, doi:10.1016/j.biomaterials.2013.07.045.
53. Ifuku, S.; Matsumoto, C.; Wada, M.; Morimoto, M.; Saimoto, H. Preparation of highly regioselective amphiprotic chitosan derivative via "click chemistry." *Int. J. Biol. Macromol.* **2013**, *52*, 72–76, doi:10.1016/j.ijbiomac.2012.08.012.
54. Jirawutthiwongchai, J.; Krause, A.; Draeger, G.; Chirachanchai, S. Chitosan-Oxanorbornadiene: A Convenient Chitosan Derivative for Click Chemistry without Metal Catalyst Problem. *ACS Macro Lett.* **2013**, *2*, 177–180, doi:10.1021/mz400006j.
55. Jirawutthiwongchai, J.; Draeger, G.; Chirachanchai, S. Rapid Hybridization of Chitosan-Gold-Antibodies via Metal-free Click in Water-based Systems: A Model Approach for Naked-eye Detectable Antigen Sensors. *Macromol. Rapid Commun.* **2014**, *35*, 1204–1210, doi:10.1002/marc.201400092.
56. Hu, L.; Zhao, P.; Deng, H.; Xiao, L.; Qin, C.; Du, Y.; Shi, X. Electrical signal guided click coating of chitosan hydrogel on conductive surface. *RSC Adv.* **2014**, *4*, 13477–13480, doi:10.1039/C3RA47507G.
57. Li, Q.; Tan, W.; Zhang, C.; Gu, G.; Guo, Z. Novel triazolyl-functionalized chitosan derivatives with different chain lengths of aliphatic alcohol substituent: Design, synthesis, and antifungal activity. *Carbohydr. Res.* **2015**, *418*, 44–49, doi:10.1016/j.carres.2015.10.005.
58. Sarwar, A.; Katas, H.; Samsudin, S. N.; Zin, N. M. Regioselective Sequential Modification of Chitosan via Azide-Alkyne Click Reaction: Synthesis, Characterization, and Antimicrobial Activity of Chitosan Derivatives and Nanoparticles. *PLOS ONE* **2015**, *10*, e0123084, doi:10.1371/journal.pone.0123084.

59. Koshiji, K.; Nonaka, Y.; Iwamura, M.; Dai, F.; Matsuoka, R.; Hasegawa, T. C6-Modifications on chitosan to develop chitosan-based glycopolymers and their lectin-affinities with sigmoidal binding profiles. *Carbohydr. Polym.* **2016**, *137*, 277–286, doi:10.1016/j.carbpol.2015.10.073.
60. Peng, P.; Cao, X.; Peng, F.; Bian, J.; Xu, F.; Sun, R. Binding cellulose and chitosan via click chemistry: Synthesis, characterization, and formation of some hollow tubes. *J. Polym. Sci. Part Polym. Chem.* **2012**, *50*, 5201–5210, doi:10.1002/pola.26371.
61. Ryu, H. J.; Mahapatra, S. S.; Yadav, S. K.; Cho, J. W. Synthesis of click-coupled graphene sheet with chitosan: Effective exfoliation and enhanced properties of their nanocomposites. *Eur. Polym. J.* **2013**, *49*, 2627–2634, doi:10.1016/j.eurpolymj.2013.06.005.
62. Yadav, S. K.; Mahapatra, S. S.; Yadav, M. K.; Dutta, P. K. Mechanically robust biocomposite films of chitosan grafted carbon nanotubes via the [2 + 1] cycloaddition of nitrenes. *RSC Adv.* **2013**, *3*, 23631–23637, doi:10.1039/C3RA41990H.
63. Gandini, A. Polymers from Renewable Resources: A Challenge for the Future of Macromolecular Materials. *Macromolecules* **2008**, *41*, 9491–9504, doi:10.1021/ma801735u.
64. Montiel-Herrera, M.; Gandini, A.; Goycoolea, F. M.; Jacobsen, N. E.; Lizardi-Mendoza, J.; Recillas-Mota, M.; Argüelles-Monal, W. M. N -(furfural) chitosan hydrogels based on Diels–Alder cycloadditions and application as microspheres for controlled drug release. *Carbohydr. Polym.* **2015**, *128*, 220–227, doi:10.1016/j.carbpol.2015.03.052.
65. Odian, G. *Principles of Polymerization*; 4th ed.; John Wiley & Sons: Hoboken, New Jersey, 2004; ISBN 978-0-471-27400-1.
66. Mourya, V. K.; Inamdar, N. N. Chitosan-modifications and applications: Opportunities galore. *React. Funct. Polym.* **2008**, *68*, 1013–1051, doi:10.1016/j.reactfunctpolym.2008.03.002.
67. Kurita, K.; Kawata, M.; Koyama, Y.; Nishimura, S.-I. Graft copolymerization of vinyl monomers onto chitin with cerium (IV) ion. *J. Appl. Polym. Sci.* **1991**, *42*, 2885–2891, doi:10.1002/app.1991.070421104.
68. Lagos, A.; Yazdani-pedram, M.; Reyes, J.; Campos, N. Ceric Ion-Initiated Grafting of Poly(Methyl Acrylate) onto Chitin. *J. Macromol. Sci. Part A* **1992**, *29*, 1007–1015, doi:10.1080/10601329208054137.
69. Ren, L.; Miura, Y.; Nishi, N.; Tokura, S. Modification of chitin by ceric salt-initiated graft polymerisation — preparation of poly(methyl methacrylate)-grafted chitin derivatives that swell in organic solvents. *Carbohydr. Polym.* **1993**, *21*, 23–27, doi:10.1016/0144-8617(93)90113-I.
70. Tanodekaew, S.; Prasitsilp, M.; Swasdison, S.; Thavornyutikarn, B.; Pothsree, T.; Pateepasen, R. Preparation of acrylic grafted chitin for wound dressing application. *Biomaterials* **2004**, *25*, 1453–1460, doi:10.1016/j.biomaterials.2003.08.020.
71. Mostafa, T.; Naguib, H.; Sabaa, M.; Mokhtar, S. Graft copolymerization of itaconic acid onto chitin and its properties. *Polym. Int.* **2005**, *54*, 221–225, doi:10.1002/pi.1690.

72. Mokhtar, S. M.; Mostafa, T. B.; Hewedy, M. A. Chemical induced grafting of indole onto chitin & chitosan - and their antimicrobial activity. *Aust. J. Basic Appl. Sci.* **2010**, *4*, 3268–3279.
73. Ifuku, S.; Iwasaki, M.; Morimoto, M.; Saimoto, H. Graft polymerization of acrylic acid onto chitin nanofiber to improve dispersibility in basic water. *Carbohydr. Polym.* **2012**, *90*, 623–627, doi:10.1016/j.carbpol.2012.05.087.
74. Abu Naim, A.; Umar, A.; Sanagi, M. M.; Basaruddin, N. Chemical modification of chitin by grafting with polystyrene using ammonium persulfate initiator. *Carbohydr. Polym.* **2013**, *98*, 1618–1623, doi:10.1016/j.carbpol.2013.07.054.
75. Jayakumar, R.; Tamura, H. Synthesis, characterization and thermal properties of chitin-g-poly(ε-caprolactone) copolymers by using chitin gel. *Int. J. Biol. Macromol.* **2008**, *43*, 32–36, doi:10.1016/j.ijbiomac.2007.09.003.
76. Pilakasiri, K.; Molee, P.; Sringernyuang, D.; Sangjun, N.; Channasanon, S.; Tanodekaew, S. Efficacy of chitin-PAA-GTMAC gel in promoting wound healing: animal study. *J. Mater. Sci. Mater. Med.* **2011**, *22*, 2497–2504, doi:10.1007/s10856-011-4420-6.
77. Uppanan, P.; Channasanon, S.; Veeranondh, S.; Tanodekaew, S. Synthesis of GTMAC modified chitin–PAA gel and evaluation of its biological properties. *J. Biomed. Mater. Res. A* **2011**, *98A*, 185–191, doi:10.1002/jbm.a.33104.
78. Huang, C.-M.; Chen, L.-C.; Yang, H.-C.; Li, M.-H.; Pan, T.-C. Preparation of acrylic acid-modified chitin improved by an experimental design and its application in absorbing toxic organic compounds. *J. Hazard. Mater.* **2012**, *241–242*, 190–196, doi:10.1016/j.jhazmat.2012.09.032.
79. Rao, V.; Praveen, P.; Latha, D. A novel method for synthesis of polypyrrole grafted chitin. *J. Polym. Res.* **2016**, *9*, 1–6, doi:10.1007/s10965-016-1075-5.
80. Peniche, C.; Argüelles-Monal, W.; Davidenko, N.; Sastre, R.; Gallardo, A.; San Román, J. Self-curing membranes of chitosan/PAA IPNs obtained by radical polymerization: preparation, characterization and interpolymer complexation. *Biomaterials* **1999**, *20*, 1869–1878.
81. Recillas, M.; Silva, L. L.; Peniche, C.; Goycoolea, F. M.; Rinaudo, M.; Argüelles-Monal, W. M. Thermoresponsive behavior of chitosan-g-N-isopropylacrylamide copolymer solutions. *Biomacromolecules* **2009**, *10*, 1633–41, doi:10.1021/bm9002317.
82. Lavrič, P. K.; Warmoeskerken, M. M. C. G.; Jocic, D. Functionalization of cotton with poly-NiPAAm/chitosan microgel. Part I. Stimuli-responsive moisture management properties. *Cellulose* **2012**, *19*, 257–271, doi:10.1007/s10570-011-9632-x.
83. Chen, C.; Liu, M.; Gao, C.; Lü, S.; Chen, J.; Yu, X.; Ding, E.; Yu, C.; Guo, J.; Cui, G. A convenient way to synthesize comb-shaped chitosan-graft-poly(N-isopropylacrylamide) copolymer. *Carbohydr. Polym.* **2013**, *92*, 621–628, doi:10.1016/j.carbpol.2012.09.014.
84. Spizzirri, U. G.; Iemma, F.; Cirillo, G.; Altimari, I.; Puoci, F.; Picci, N. Temperature-sensitive hydrogels by graft polymerization of chitosan and

N-isopropylacrylamide for drug release. *Pharm. Dev. Technol.* **2013**, *18*, 1026–1034, doi:10.3109/10837450.2011.644298.

85. Huang, C.-H.; Wang, C.-F.; Don, T.-M.; Chiu, W.-Y. Preparation of pH- and thermo-sensitive chitosan-PNIPAAm core–shell nanoparticles and evaluation as drug carriers. *Cellulose* **2013**, *20*, 1791–1805, doi:10.1007/s10570-013-9951-1.
86. Raskin, M. M.; Schlachet, I.; Sosnik, A. Mucoadhesive nanogels by ionotropic crosslinking of chitosan-g-oligo(NiPAam) polymeric micelles as novel drug nanocarriers. *Nanomed.* **2016**, *11*, 217–233, doi:10.2217/nnm.15.191.
87. Liu, S.; Zhang, J.; Cui, X.; Guo, Y.; Zhang, X.; Hongyan, W. Synthesis of chitosan-based nanohydrogels for loading and release of 5-fluorouracil. *Colloids Surf. Physicochem. Eng. Asp.* **2016**, *490*, 91–97, doi:10.1016/j.colsurfa.2015.11.029.
88. Cao, L.; Wang, X.; Wang, G.; Wang, J. A pH-sensitive porous chitosan membrane prepared via surface grafting copolymerization in supercritical carbon dioxide. *Polym. Int.* **2015**, *64*, 383–388, doi:10.1002/pi.4798.
89. Metzler, M.; Chylińska, M.; Kaczmarek, H. Preparation and characteristics of nanosilver composite based on chitosan-*graft*-acrylic acid copolymer. *J. Polym. Res.* **2015**, *22*, 146, doi:10.1007/s10965-015-0781-8.
90. García-Valdez, O.; Champagne-Hartley, R.; Saldívar-Guerra, E.; Champagne, P.; Cunningham, M. F. Modification of chitosan with polystyrene and poly(N-butyl acrylate) via nitroxide-mediated polymerization and grafting from approach in homogeneous media. *Polym. Chem.* **2015**, *6*, 2827–2836, doi:10.1039/C5PY00028A.
91. Khan, A.; Othman, M. B. H.; Chang, B. P.; Akil, H. M. Preparation, physicochemical and stability studies of chitosan-PNIPAM based responsive microgels under various pH and temperature conditions. *Iran. Polym. J.* **2015**, *24*, 317–328, doi:10.1007/s13726-015-0324-5.
92. Echeverria, C.; Soares, P.; Robalo, A.; Pereira, L.; Novo, C. M. M.; Ferreira, I.; Borges, J. P. One-pot synthesis of dual-stimuli responsive hybrid PNIPAAm-chitosan microgels. *Mater. Des.* **2015**, *86*, 745–751, doi:10.1016/j.matdes.2015.07.170.
93. Fernández-Gutiérrez, M.; Fusco, S.; Mayol, L.; Román, J. S.; Borzacchiello, A.; Ambrosio, L. Stimuli-responsive chitosan/poly(N-isopropylacrylamide) semi-interpenetrating polymer networks: effect of pH and temperature on their rheological and swelling properties. *J. Mater. Sci. Mater. Med.* **2016**, *27*, 109, doi:10.1007/s10856-016-5719-0.
94. Anbinder, P.; Macchi, C.; Amalvy, J.; Somoza, A. Chitosan-graft-poly(N-butyl acrylate) copolymer: Synthesis and characterization of a natural/synthetic hybrid material. *Carbohydr. Polym.* **2016**, *145*, 86–94, doi:10.1016/j.carbpol.2016.02.072.
95. Chen, Y.; Yang, Y.; Liao, Q.; Yang, W.; Ma, W.; Zhao, J.; Zheng, X.; Yang, Y.; Chen, R. Preparation, property of the complex of carboxymethyl chitosan grafted copolymer with iodine and application of it in cervical antibacterial biomembrane. *Mater. Sci. Eng. C* **2016**, *67*, 247–258, doi:10.1016/j.msec.2016.05.027.
96. Lin, Y.; Hong, Y.; Song, Q.; Zhang, Z.; Gao, J.; Tao, T. Highly efficient removal of copper ions from water using poly(acrylic acid)-grafted chitosan adsorbent. *Colloid Polym. Sci.* **2017**, *295*, 627–635, doi:10.1007/s00396-017-4042-8.

97. Bashir, S.; Teo, Y. Y.; Ramesh, S.; Ramesh, K. Physico-chemical characterization of pH-sensitive N-Succinyl chitosan-g-poly(acrylamide-co-acrylic acid) hydrogels and in vitro drug release studies. *Polym. Degrad. Stab.* **2017**, *139*, 38–54, doi:10.1016/j.polymdegradstab.2017.03.014.

98. Khalaj Moazen, M.; Ahmad Panahi, H. Magnetic iron oxide nanoparticles grafted N-isopropylacrylamide/chitosan copolymer for the extraction and determination of letrozole in human biological samples. *J. Sep. Sci.* **2017**, *40*, 1125–1132, doi:10.1002/jssc.201601081.

99. Munro, N. H.; Hanton, L. R.; Moratti, S. C.; Robinson, B. H. Synthesis and characterisation of chitosan-graft-poly(OEGMA) copolymers prepared by ATRP. *Carbohydr. Polym.* **2009**, *77*, 496–505, doi:10.1016/j.carbpol.2009.01.026.

100. Aziz, M. S. A.; Naguib, H. F.; Saad, G. R. Nanocomposites Based on Chitosan-Graft-Poly(N-Vinyl-2-Pyrrolidone): Synthesis, Characterization, and Biological Activity. *Int. J. Polym. Mater. Polym. Biomater.* **2015**, *64*, 578–586, doi:10.1080/00914037.2014.996707.

101. Leiva, A.; Bonardd, S.; Pino, M.; Saldías, C.; Kortaberria, G.; Radić, D. Improving the performance of chitosan in the synthesis and stabilization of gold nanoparticles. *Eur. Polym. J.* **2015**, *68*, 419–431, doi:10.1016/j.eurpolymj.2015.04.032.

102. Liu, L.; Wang, Y.; Shen, X.; Fang, Y. Preparation of chitosan-g-polycaprolactone copolymers through ring-opening polymerization of ϵ-caprolactone onto phthaloyl-protected chitosan. *Biopolymers* **2005**, *78*, 163–170, doi:10.1002/bip.20261.

103. Liu, L.; Chen, L.; Fang, Y. Self-Catalysis of Phthaloylchitosan for Graft Copolymerization of ε-Caprolactone with Chitosan. *Macromol. Rapid Commun.* **2006**, *27*, 1988–1994, doi:10.1002/marc.200600508.

104. Liu, L.; Shi, A.; Guo, S.; Fang, Y.; Chen, S.; Li, J. Preparation of chitosan-g-polylactide graft copolymers via self-catalysis of phthaloylchitosan and their complexation with DNA. *React. Funct. Polym.* **2010**, *70*, 301–305, doi:10.1016/j.reactfunctpolym.2010.02.003.

105. Mirabbasi, F.; Dorkoosh, F. A.; Moghimi, A.; Shahsavari, S.; Babanejad, N.; Seifirad, S. Preparation of Mesalamine Nanoparticles Using a Novel Polyurethane-Chitosan Graft Copolymer. *Pharm. Nanotechnol.* **2017**, *5*, 230–239, doi:10.2174/2211738505666171103120026.

106. Cabuk, M.; Yavuz, M.; Unal, H. I. Electrokinetic properties of biodegradable conducting polyaniline-graft-chitosan copolymer in aqueous and non-aqueous media. *Colloids Surf. Physicochem. Eng. Asp.* **2014**, *460*, 494–501, doi:10.1016/j.colsurfa.2014.02.053.

107. Feil, H.; Bae, Y. H.; Feijen, J.; Kim, S. W. Effect of comonomer hydrophilicity and ionization on the lower critical solution temperature of N-isopropylacrylamide copolymers. *Macromolecules* **1993**, *26*, 2496–2500, doi:10.1021/ma00062a016.

108. Recillas, M.; Silva, L. L.; Peniche, C.; Goycoolea, F. M.; Rinaudo, M.; Román, J. S.; Argüelles-Monal, W. M. Thermo- and pH-responsive polyelectrolyte complex

membranes from chitosan-g-N-isopropylacrylamide and pectin. *Carbohydr. Polym.* **2011**, *86*, 1336–1343, doi:10.1016/j.carbpol.2011.06.047.

109. Marques, N. do N.; Maia, A. M. da S.; Balaban, R. de C. Development of dual-sensitive smart polymers by grafting chitosan with poly (N-isopropylacrylamide): an overview. *Polímeros* **2015**, *25*, 237–246, doi:10.1590/0104-1428.1744.
110. Liu, L.; Li, Y.; Liu, H.; Fang, Y. Synthesis and characterization of chitosan-graft-polycaprolactone copolymers. *Eur. Polym. J.* **2004**, *40*, 2739–2744, doi:10.1016/j.eurpolymj.2004.07.016.
111. Liu, L.; Xu, X.; Guo, S.; Han, W. Synthesis and self-assembly of chitosan-based copolymer with a pair of hydrophobic/hydrophilic grafts of polycaprolactone and poly(ethylene glycol). *Carbohydr. Polym.* **2009**, *75*, 401–407, doi:10.1016/j.carbpol.2008.07.038.
112. Gu, C.; Zhang, H.; Lang, M. Preparation of mono-dispersed silver nanoparticles assisted by chitosan-g-poly(ε-caprolactone) micelles and their antimicrobial application. *Appl. Surf. Sci.* **2014**, *301*, 273–279, doi:10.1016/j.apsusc.2014.02.059.
113. Gorochovceva, N.; Makuška, R. Synthesis and study of water-soluble chitosan-O-poly(ethylene glycol) graft copolymers. *Eur. Polym. J.* **2004**, *40*, 685–691, doi:10.1016/j.eurpolymj.2003.12.005.
114. Bhattarai, N.; Matsen, F. A.; Zhang, M. PEG-Grafted Chitosan as an Injectable Thermoreversible Hydrogel. *Macromol. Biosci.* **2005**, *5*, 107–111, doi:10.1002/mabi.200400140.
115. Bhattarai, N.; Ramay, H. R.; Gunn, J.; Matsen, F. A.; Zhang, M. PEG-grafted chitosan as an injectable thermosensitive hydrogel for sustained protein release. *J. Controlled Release* **2005**, *103*, 609–624, doi:10.1016/j.jconrel.2004.12.019.
116. Jiang, X.; Dai, H.; Leong, K. W.; Goh, S.-H.; Mao, H.-Q.; Yang, Y.-Y. Chitosan‐g‐PEG/DNA complexes deliver gene to the rat liver via intrabiliary and intraportal infusions. *J. Gene Med.* **2006**, *8*, 477–487, doi:10.1002/jgm.868.
117. Du, J.; Hsieh, Y.-L. PEGylation of chitosan for improved solubility and fiber formation via electrospinning. *Cellulose* **2007**, *14*, 543–552, doi:10.1007/s10570-007-9122-3.
118. Bae, K. H.; Moon, C. W.; Lee, Y.; Park, T. G. Intracellular Delivery of Heparin Complexed with Chitosan-g-Poly(Ethylene Glycol) for Inducing Apoptosis. *Pharm. Res.* **2009**, *26*, 93–100, doi:10.1007/s11095-008-9713-1.
119. Liang, Y.; Deng, L.; Chen, C.; Zhang, J.; Zhou, R.; Li, X.; Hu, R.; Dong, A. Preparation and properties of thermoreversible hydrogels based on methoxy poly(ethylene glycol)-grafted chitosan nanoparticles for drug delivery systems. *Carbohydr. Polym.* **2011**, *83*, 1828–1833, doi:10.1016/j.carbpol.2010.10.048.
120. Papadimitriou, S. A.; Achilias, D. S.; Bikiaris, D. N. Chitosan-g-PEG nanoparticles ionically crosslinked with poly(glutamic acid) and tripolyphosphate as protein delivery systems. *Int. J. Pharm.* **2012**, *430*, 318–327, doi:10.1016/j.ijpharm.2012.04.004.

121. Jiang, G.; Sun, J.; Ding, F. PEG-g-chitosan thermosensitive hydrogel for implant drug delivery: cytotoxicity, in vivo degradation and drug release. *J. Biomater. Sci. Polym. Ed.* **2014**, *25*, 241–256, doi:10.1080/09205063.2013.851542.
122. Vasquez, D.; Milusheva, R.; Baumann, P.; Constantin, D.; Chami, M.; Palivan, C. G. The Amine Content of PEGylated Chitosan Bombyx mori Nanoparticles Acts as a Trigger for Protein Delivery. *Langmuir* **2014**, *30*, 965–975, doi:10.1021/la404558g.
123. Ho, T. H.; Le, T. N. T.; Nguyen, T. A.; Dang, M. C. Poly(ethylene glycol) grafted chitosan as new copolymer material for oral delivery of insulin. *Adv. Nat. Sci. Nanosci. Nanotechnol.* **2015**, *6*, 035004, doi:10.1088/2043-6262/6/3/035004.
124. Chung, H. J.; Go, D. H.; Bae, J. W.; Jung, I. K.; Lee, J. W.; Park, K. D. Synthesis and characterization of Pluronic® grafted chitosan copolymer as a novel injectable biomaterial. *Curr. Appl. Phys.* **2005**, *5*, 485–488, doi:10.1016/j.cap.2005.01.015.
125. Park, K. M.; Lee, S. Y.; Joung, Y. K.; Na, J. S.; Lee, M. C.; Park, K. D. Thermosensitive chitosan–Pluronic hydrogel as an injectable cell delivery carrier for cartilage regeneration. *Acta Biomater.* **2009**, *5*, 1956–1965, doi:10.1016/j.actbio.2009.01.040.
126. Zhang, W.; Gilstrap, K.; Wu, L.; K. C., R. B.; Moss, M. A.; Wang, Q.; Lu, X.; He, X. Synthesis and Characterization of Thermally Responsive Pluronic F127−Chitosan Nanocapsules for Controlled Release and Intracellular Delivery of Small Molecules. *ACS Nano* **2010**, *4*, 6747–6759, doi:10.1021/nn101617n.
127. Cao, Y.; Zhang, C.; Shen, W.; Cheng, Z.; Yu, L. (Lucy); Ping, Q. Poly(N-isopropylacrylamide)–chitosan as thermosensitive in situ gel-forming system for ocular drug delivery. *J. Controlled Release* **2007**, *120*, 186–194, doi:10.1016/j.jconrel.2007.05.009.
128. Mao, Z.; Ma, L.; Yan, J.; Yan, M.; Gao, C.; Shen, J. The gene transfection efficiency of thermoresponsive N,N,N-trimethyl chitosan chloride-g-poly(N-isopropylacrylamide) copolymer. *Biomaterials* **2007**, *28*, 4488–4500, doi:10.1016/j.biomaterials.2007.06.033.
129. Lee, E. J.; Kim, Y. H. Synthesis and thermo-responsive properties of chitosan-g-poly (N-isopropylacrylamide) and HTCC-g-poly(N-isopropylacrylamide) copolymers. *Fibers Polym.* **2010**, *11*, 164–169, doi:10.1007/s12221-010-0164-z.
130. Sanoj Rejinold, N.; Sreerekha, P. R.; Chennazhi, K. P.; Nair, S. V.; Jayakumar, R. Biocompatible, biodegradable and thermo-sensitive chitosan-g-poly (N-isopropylacrylamide) nanocarrier for curcumin drug delivery. *Int. J. Biol. Macromol.* **2011**, *49*, 161–172, doi:10.1016/j.ijbiomac.2011.04.008.
131. Antoniraj, M. G.; Kumar, C. S.; Kandasamy, R. Synthesis and characterization of poly (N-isopropylacrylamide)-g-carboxymethyl chitosan copolymer-based doxorubicin-loaded polymeric nanoparticles for thermoresponsive drug release. *Colloid Polym. Sci.* **2016**, *294*, 527–535, doi:10.1007/s00396-015-3804-4.
132. Rejinold, N. S.; Chennazhi, K. P.; Nair, S. V.; Tamura, H.; Jayakumar, R. Biodegradable and thermo-sensitive chitosan-g-poly(N-vinylcaprolactam) nanoparticles as a 5-fluorouracil carrier. *Carbohydr. Polym.* **2011**, *83*, 776–786, doi:10.1016/j.carbpol.2010.08.052.

133. Sanoj Rejinold, N.; Muthunarayanan, M.; Divyarani, V. V.; Sreerekha, P. R.; Chennazhi, K. P.; Nair, S. V.; Tamura, H.; Jayakumar, R. Curcumin-loaded biocompatible thermoresponsive polymeric nanoparticles for cancer drug delivery. *J. Colloid Interface Sci.* **2011**, *360*, 39–51, doi:10.1016/j.jcis.2011.04.006.
134. Rejinold, N. S.; Thomas, R. G.; Muthiah, M.; Chennazhi, K. P.; Park, I.-K.; Jeong, Y. Y.; Manzoor, K.; Jayakumar, R. Radio frequency triggered curcumin delivery from thermo and pH responsive nanoparticles containing gold nanoparticles and its in vivo localization studies in an orthotopic breast tumor model. *RSC Adv.* **2014**, *4*, 39408–39427, doi:10.1039/C4RA05727A.
135. Sanoj Rejinold, N.; Thomas, R. G.; Muthiah, M.; Chennazhi, K. P.; Manzoor, K.; Park, I.-K.; Jeong, Y. Y.; Jayakumar, R. Anti-cancer, pharmacokinetics and tumor localization studies of pH-, RF- and thermo-responsive nanoparticles. *Int. J. Biol. Macromol.* **2015**, *74*, 249–262, doi:10.1016/j.ijbiomac.2014.11.044.
136. Fernández-Quiroz, D.; González-Gómez, Á.; Lizardi-Mendoza, J.; Vázquez-Lasa, B.; Goycoolea, F. M.; San Román, J.; Argüelles-Monal, W. M. Effect of the molecular architecture on the thermosensitive properties of chitosan-g-poly(N-vinylcaprolactam). *Carbohydr. Polym.* **2015**, *134*, 92–101, doi:10.1016/j.carbpol.2015.07.069.
137. Rejinold, N. S.; Thomas, R. G.; Muthiah, M.; Lee, H. J.; Jeong, Y. Y.; Park, I.-K.; Jayakumar, R. Breast Tumor Targetable Fe3O4 Embedded Thermo-Responsive Nanoparticles for Radiofrequency Assisted Drug Delivery. *J. Biomed. Nanotechnol.* **2016**, *12*, 43–55, doi:10.1166/jbn.2016.2135.
138. Indulekha, S.; Arunkumar, P.; Bahadur, D.; Srivastava, R. Thermoresponsive polymeric gel as an on-demand transdermal drug delivery system for pain management. *Mater. Sci. Eng. C* **2016**, *62*, 113–122, doi:10.1016/j.msec.2016.01.021.
139. Fernández-Quiroz, D.; González-Gómez, Á.; Lizardi-Mendoza, J.; Vázquez-Lasa, B.; Goycoolea, F. M.; Román, J. S.; Argüelles-Monal, W. M. Conformational study on the thermal transition of chitosan-g-poly(N-vinylcaprolactam) in aqueous solution. *Colloid Polym. Sci.* **2016**, *294*, 555–563, doi:10.1007/s00396-015-3816-0.
140. Casettari, L.; Vllasaliu, D.; Castagnino, E.; Stolnik, S.; Howdle, S.; Illum, L. PEGylated chitosan derivatives: Synthesis, characterizations and pharmaceutical applications. *Prog. Polym. Sci.* **2012**, *37*, 659–685, doi:10.1016/j.progpolymsci.2011.10.001.
141. Jayakumar, R.; Tamura, H. Synthesis, characterization and thermal properties of chitin-g-poly(ε-caprolactone) copolymers by using chitin gel. *Int. J. Biol. Macromol.* **2008**, *43*, 32–36, doi:10.1016/j.ijbiomac.2007.09.003.
142. Khalaj Moazen, M.; Ahmad Panahi, H. Magnetic iron oxide nanoparticles grafted N-isopropylacrylamide/chitosan copolymer for the extraction and determination of letrozole in human biological samples. *J. Sep. Sci.* **2017**, *40*, 1125–1132, doi:10.1002/jssc.201601081.
143. Wang, J.-P.; Chen, Y.-Z.; Ge, X.-W.; Yu, H.-Q. Gamma radiation-induced grafting of a cationic monomer onto chitosan as a flocculant. *Chemosphere* **2007**, *66*, 1752–1757, doi:10.1016/j.chemosphere.2006.06.072.

144. Wang, J.-P.; Chen, Y.-Z.; Zhang, S.-J.; Yu, H.-Q. A chitosan-based flocculant prepared with gamma-irradiation-induced grafting. *Bioresour. Technol.* **2008**, *99*, 3397–3402, doi:10.1016/j.biortech.2007.08.014.
145. Zheng, H.; Sun, Y.; Zhu, C.; Guo, J.; Zhao, C.; Liao, Y.; Guan, Q. UV-initiated polymerization of hydrophobically associating cationic flocculants: Synthesis, characterization, and dewatering properties. *Chem. Eng. J.* **2013**, *234*, 318–326, doi:10.1016/j.cej.2013.08.098.
146. Sun, Y.; Ren, M.; Zhu, C.; Xu, Y.; Zheng, H.; Xiao, X.; Wu, H.; Xia, T.; You, Z. UV-Initiated Graft Copolymerization of Cationic Chitosan-Based Flocculants for Treatment of Zinc Phosphate-Contaminated Wastewater. *Ind. Eng. Chem. Res.* **2016**, *55*, 10025–10035, doi:10.1021/acs.iecr.6b02855.
147. Sun, Y.; Zhu, C.; Sun, W.; Xu, Y.; Xiao, X.; Zheng, H.; Wu, H.; Liu, C. Plasma-initiated polymerization of chitosan-based CS-g-P(AM-DMDAAC) flocculant for the enhanced flocculation of low-algal-turbidity water. *Carbohydr. Polym.* **2017**, *164*, 222–232, doi:10.1016/j.carbpol.2017.02.010.
148. Zhuang, S.; Yi, Y.; Wang, J. Removal of Cobalt Ions from Aqueous Solution Using Chitosan Grafted with Maleic Acid by Gamma Radiation. *Nucl. Eng. Technol.* **2018**, doi:10.1016/j.net.2017.11.007.
149. Saleh, A. S.; Ibrahim, A. G.; Elsharma, E. M.; Metwally, E.; Siyam, T. Radiation grafting of acrylamide and maleic acid on chitosan and effective application for removal of Co(II) from aqueous solutions. *Radiat. Phys. Chem.* **2018**, *144*, 116–124, doi:10.1016/j.radphyschem.2017.11.018.
150. Sosnik, A.; Imperiale, J. C.; Vázquez-González, B.; Raskin, M. M.; Muñoz-Muñoz, F.; Burillo, G.; Cedillo, G.; Bucio, E. Mucoadhesive thermo-responsive chitosan-g-poly(N-isopropylacrylamide) polymeric micelles via a one-pot gamma-radiation-assisted pathway. *Colloids Surf. B Biointerfaces* **2015**, *136*, 900–907, doi:10.1016/j.colsurfb.2015.10.036.
151. Cruz, A.; García-Uriostegui, L.; Ortega, A.; Isoshima, T.; Burillo, G. Radiation grafting of N-vinylcaprolactam onto nano and macrogels of chitosan: Synthesis and characterization. *Carbohydr. Polym.* **2017**, *155*, 303–312, doi:10.1016/j.carbpol.2016.08.083.
152. Montes, J. Á.; Ortega, A.; Burillo, G. Dual-stimuli responsive copolymers based on N-vinylcaprolactam/chitosan. *J. Radioanal. Nucl. Chem.* **2014**, *303*, 2143–2150, doi:10.1007/s10967-014-3805-7.
153. Pérez-Calixto, M. P.; Ortega, A.; Garcia-Uriostegui, L.; Burillo, G. Synthesis and characterization of N-vinylcaprolactam/N,N-dimethylacrylamide grafted onto chitosan networks by gamma radiation. *Radiat. Phys. Chem.* **2016**, *119*, 228–235, doi:10.1016/j.radphyschem.2015.10.030.
154. Harada, A.; Hashidzume, A.; Takashima, Y. Cyclodextrin-Based Supramolecular Polymers. In *Supramolecular Polymers Polymeric Betains Oligomers*; Advances in Polymer Science; Springer: Berlin, Heidelberg, 2001; Vol. 201.
155. Sajomsang, W.; Nuchuchua, O.; Gonil, P.; Saesoo, S.; Sramala, I.; Soottitantawat, A.; Puttipipatkhachorn, S.; Ruktanonchai, U. R. Water-soluble β-cyclodextrin grafted

with chitosan and its inclusion complex as a mucoadhesive eugenol carrier. *Carbohydr. Polym.* **2012**, *89*, 623–631, doi:10.1016/j.carbpol.2012.03.060.

156. Auzély-Velty, R.; Rinaudo, M. New Supramolecular Assemblies of a Cyclodextrin-Grafted Chitosan through Specific Complexation. *Macromolecules* **2002**, *35*, 7955–7962, doi:10.1021/ma020664o.
157. Yu, N.; Li, G.; Gao, Y.; Liu, X.; Ma, S. Stimuli-sensitive hollow spheres from chitosan-graft-β-cyclodextrin for controlled drug release. *Int. J. Biol. Macromol.* **2016**, *93*, 971–977, doi:10.1016/j.ijbiomac.2016.09.068.
158. Rekharsky, M. V.; Inoue, Y. Complexation Thermodynamics of Cyclodextrins. *Chem. Rev.* **1998**, *98*, 1875–1918, doi:10.1021/cr970015o.
159. Liu, Y.; Han, B.-H.; Li, B.; Zhang, Y.-M.; Zhao, P.; Chen, Y.-T.; Wada, T.; Inoue, Y. Molecular Recognition Study on Supramolecular System. 14.1 Synthesis of Modified Cyclodextrins and Their Inclusion Complexation Thermodynamics with l-Tryptophan and Some Naphthalene Derivatives. *J. Org. Chem.* **1998**, *63*, 1444–1454, doi:10.1021/jo971466b.
160. Harada, A.; Takashima, Y.; Yamaguchi, H. Cyclodextrin-based supramolecular polymers. *Chem. Soc. Rev.* **2009**, *38*, 875–882, doi:10.1039/B705458K.
161. Auzély, R.; Rinaudo, M. Controlled Chemical Modifications of Chitosan. Characterization and Investigation of Original Properties. *Macromol. Biosci.* **2003**, *3*, 562–565, doi:10.1002/mabi.200300018.
162. Daimon, Y.; Izawa, H.; Kawakami, K.; Żywicki, P.; Sakai, H.; Abe, M.; Hill, J. P.; Ariga, K. Media-dependent morphology of supramolecular aggregates of β-cyclodextrin-grafted chitosan and insulin through multivalent interactions. *J. Mater. Chem. B* **2014**, *2*, 1802–1812, doi:10.1039/C3TB21528H.
163. Daimon, Y.; Kamei, N.; Kawakami, K.; Takeda-Morishita, M.; Izawa, H.; Takechi-Haraya, Y.; Saito, H.; Sakai, H.; Abe, M.; Ariga, K. Dependence of Intestinal Absorption Profile of Insulin on Carrier Morphology Composed of β-Cyclodextrin-Grafted Chitosan. *Mol. Pharm.* **2016**, *13*, 4034–4042, doi:10.1021/acs.molpharmaceut.6b00561.
164. Tojima, T.; Katsura, H.; Han, S.-M.; Tanida, F.; Nishi, N.; Tokura, S.; Sakairi, N. Preparation of an α-cyclodextrin–linked chitosan derivative via reductive amination strategy. *J. Polym. Sci. Part Polym. Chem.* **1998**, *36*, 1965–1968, doi:10.1002/(SICI)1099-0518(199808)36:11<1965::AID-POLA33>3.0.CO;2-A.
165. Auzély-Velty, R.; Rinaudo, M. Chitosan Derivatives Bearing Pendant Cyclodextrin Cavities: Synthesis and Inclusion Performance. *Macromolecules* **2001**, *34*, 3574–3580, doi:10.1021/ma001873g.
166. Venter, J. P.; Kotzé, A. F.; Auzély-Velty, R.; Rinaudo, M. Synthesis and evaluation of the mucoadhesivity of a CD-chitosan derivative. *Int. J. Pharm.* **2006**, *313*, 36–42, doi:10.1016/j.ijpharm.2006.01.016.
167. El-Tahlawy, K.; Gaffar, M. A.; El-Rafie, S. Novel method for preparation of β-cyclodextrin/grafted chitosan and it's application. *Carbohydr. Polym.* **2006**, *63*, 385–392, doi:10.1016/j.carbpol.2005.08.057.

168. Chaleawlert-umpon, S.; Nuchuchua, O.; Saesoo, S.; Gonil, P.; Ruktanonchai, U. R.; Sajomsang, W.; Pimpha, N. Effect of citrate spacer on mucoadhesive properties of a novel water-soluble cationic β-cyclodextrin-conjugated chitosan. *Carbohydr. Polym.* **2011**, *84*, 186–194, doi:10.1016/j.carbpol.2010.11.017.

169. Furusaki, E.; Ueno, Y.; Sakairi, N.; Nishi, N.; Tokura, S. Facile preparation and inclusion ability of a chitosan derivative bearing carboxymethyl-β-cyclodextrin. *Carbohydr. Polym.* **1996**, *29*, 29–34, doi:10.1016/0144-8617(95)00133-6.

170. Kono, H.; Teshirogi, T. Cyclodextrin-grafted chitosan hydrogels for controlled drug delivery. *Int. J. Biol. Macromol.* **2015**, *72*, 299–308, doi:10.1016/j.ijbiomac.2014.08.030.

171. Takechi-Haraya, Y.; Tanaka, K.; Tsuji, K.; Asami, Y.; Izawa, H.; Shigenaga, A.; Otaka, A.; Saito, H.; Kawakami, K. Molecular Complex Composed of β-Cyclodextrin-Grafted Chitosan and pH-Sensitive Amphipathic Peptide for Enhancing Cellular Cholesterol Efflux under Acidic pH. *Bioconjug. Chem.* **2015**, *26*, 572–581, doi:10.1021/acs.bioconjchem.5b00037.

172. Song, M.; Li, L.; Zhang, Y.; Chen, K.; Wang, H.; Gong, R. Carboxymethyl-β-cyclodextrin grafted chitosan nanoparticles as oral delivery carrier of protein drugs. *React. Funct. Polym.* **2017**, *117*, 10–15, doi:10.1016/j.reactfunctpolym.2017.05.008.

173. Zhang, X.; Wu, Z.; Gao, X.; Shu, S.; Zhang, H.; Wang, Z.; Li, C. Chitosan bearing pendant cyclodextrin as a carrier for controlled protein release. *Carbohydr. Polym.* **2009**, *77*, 394–401, doi:10.1016/j.carbpol.2009.01.018.

174. Chen, S.; Wang, Y. Study on β-cyclodextrin grafting with chitosan and slow release of its inclusion complex with radioactive iodine. *J. Appl. Polym. Sci.* **2001**, *82*, 2414–2421, doi:10.1002/app.2092.

175. Martel, B.; Devassine, M.; Crini, G.; Weltrowski, M.; Bourdonneau, M.; Morcellet, M. Preparation and sorption properties of a β-cyclodextrin-linked chitosan derivative. *J. Polym. Sci. Part Polym. Chem.* **2001**, *39*, 169–176, doi:10.1002/1099-0518(20010101)39:1<169::AID-POLA190>3.0.CO;2-G.

176. Gonil, P.; Sajomsang, W.; Ruktanonchai, U. R.; Pimpha, N.; Sramala, I.; Nuchuchua, O.; Saesoo, S.; Chaleawlert-umpon, S.; Puttipipatkhachorn, S. Novel quaternized chitosan containing β-cyclodextrin moiety: Synthesis, characterization and antimicrobial activity. *Carbohydr. Polym.* **2011**, *83*, 905–913, doi:10.1016/j.carbpol.2010.08.080.

177. Sajomsang, W.; Gonil, P.; Ruktanonchai, U. R.; Pimpha, N.; Sramala, I.; Nuchuchua, O.; Saesoo, S.; Chaleawlert-umpon, S.; Puttipipatkhachorn, S. Self-aggregates formation and mucoadhesive property of water-soluble β-cyclodextrin grafted with chitosan. *Int. J. Biol. Macromol.* **2011**, *48*, 589–595, doi:10.1016/j.ijbiomac.2011.01.028.

178. Yuan, Z.; Ye, Y.; Gao, F.; Yuan, H.; Lan, M.; Lou, K.; Wang, W. Chitosan-graft-β-cyclodextrin nanoparticles as a carrier for controlled drug release. *Int. J. Pharm.* **2013**, *446*, 191–198, doi:10.1016/j.ijpharm.2013.02.024.

179. Phunpee, S.; Suktham, K.; Surassmo, S.; Jarussophon, S.; Rungnim, C.; Soottitantawat, A.; Puttipipatkhachorn, S.; Ruktanonchai, U. R. Controllable encapsulation of α-mangostin with quaternized β-cyclodextrin grafted chitosan using high shear mixing. *Int. J. Pharm.* **2018**, *538*, 21–29, doi:10.1016/j.ijpharm.2017.12.016.
180. Zhang, X.; Wang, Y.; Yi, Y. Synthesis and characterization of grafting β-cyclodextrin with chitosan. *J. Appl. Polym. Sci.* **2004**, *94*, 860–864, doi:10.1002/app.20759.
181. Chiu, S.-H.; Chung, T.-W.; Giridhar, R.; Wu, W.-T. Immobilization of β-cyclodextrin in chitosan beads for separation of cholesterol from egg yolk. *Food Res. Int.* **2004**, *37*, 217–223, doi:10.1016/j.foodres.2003.12.001.
182. Zha, F.; Li, S.; Chang, Y. Preparation and adsorption property of chitosan beads bearing β-cyclodextrin cross-linked by 1,6-hexamethylene diisocyanate. *Carbohydr. Polym.* **2008**, *72*, 456–461, doi:10.1016/j.carbpol.2007.09.013.
183. Sreenivasan, K. Synthesis and preliminary studies on a β-cyclodextrin-coupled chitosan as a novel adsorbent matrix. *J. Appl. Polym. Sci.* **1998**, *69*, 1051–1055, doi:10.1002/(SICI)1097-4628(19980808)69:6<1051::AID-APP1>3.0.CO;2-F.
184. Sajomsang, W.; Nuchuchua, O.; Saesoo, S.; Gonil, P.; Chaleawlert-umpon, S.; Pimpha, N.; Sramala, I.; Soottitantawat, A.; Puttipipatkhachorn, S.; Ruktanonchai, U. R. A comparison of spacer on water-soluble cyclodextrin grafted chitosan inclusion complex as carrier of eugenol to mucosae. *Carbohydr. Polym.* **2013**, *92*, 321–327, doi:10.1016/j.carbpol.2012.08.106.
185. Yan, J.; Li, X.; Qiu, F.; Zhao, H.; Yang, D.; Wang, J.; Wen, W. Synthesis of β-cyclodextrin–chitosan–graphene oxide composite and its application for adsorption of manganese ion (II). *Mater. Technol.* **2016**, *31*, 406–415, doi:10.1179/1753555715Y.0000000071.
186. Zhao, F.; Repo, E.; Yin, D.; Chen, L.; Kalliola, S.; Tang, J.; Iakovleva, E.; Tam, K. C.; Sillanpää, M. One-pot synthesis of trifunctional chitosan-EDTA-β-cyclodextrin polymer for simultaneous removal of metals and organic micropollutants. *Sci. Rep.* **2017**, *7*, 15811, doi:10.1038/s41598-017-16222-7.
187. Krauland, A.; Alonso, M. Chitosan/cyclodextrin nanoparticles as macromolecular drug delivery system. *Int. J. Pharm.* **2007**, *340*, 134–142, doi:10.1016/j.ijpharm.2007.03.005.
188. Thanh Nguyen, H.; Goycoolea, F. M. Chitosan/Cyclodextrin/TPP Nanoparticles Loaded with Quercetin as Novel Bacterial Quorum Sensing Inhibitors. *Molecules* **2017**, *22*, 1975, doi:10.3390/molecules22111975.
189. Zhou, H. Y.; Wang, Z. Y.; Duan, X. Y.; Jiang, L. J.; Cao, P. P.; Li, J. X.; Li, J. B. Design and evaluation of chitosan-β-cyclodextrin based thermosensitive hydrogel. *Biochem. Eng. J.* **2016**, *111*, 100–107, doi:10.1016/j.bej.2016.03.011.
190. Anirudhan, T. S.; Divya, P. L.; Nima, J. Synthesis and characterization of novel drug delivery system using modified chitosan based hydrogel grafted with cyclodextrin. *Chem. Eng. J.* **2016**, *284*, 1259–1269, doi:10.1016/j.cej.2015.09.057.

191. Sashiwa, H. Chemical Aspects of Chitin and Chitosan Derivatives. In *Chitin and Chitosan Derivatives: Advances in Drug Discovery and Developments*; Kim, S.-K., Ed.; CRC Press: Boca Raton, 2013; pp. 93–111 ISBN 978-1-4665-6628-6.
192. Sashiwa, H.; Shigemasa, Y.; Roy, R. Chemical Modification of Chitosan. 3. Hyperbranched Chitosan−Sialic Acid Dendrimer Hybrid with Tetraethylene Glycol Spacer. *Macromolecules* **2000**, *33*, 6913–6915, doi:10.1021/ma0005769.
193. Sashiwa, H.; Shigemasa, Y.; Roy, R. Chemical Modification of Chitosan. 10. Synthesis of Dendronized Chitosan−Sialic Acid Hybrid Using Convergent Grafting of Preassembled Dendrons Built on Gallic Acid and Tri(ethylene glycol) Backbone. *Macromolecules* **2001**, *34*, 3905–3909, doi:10.1021/ma001832k.
194. Sashiwa, H.; Shigemasa, Y.; Roy, R. Chemical Modification of Chitosan 11: Chitosan–Dendrimer Hybrid as a Tree Like Molecule. *Carbohydr. Polym.* **2002**, *49*, 195–205, doi:10.1016/S0144-8617(01)00322-8.
195. Sashiwa, H.; Yajima, H.; Aiba, S. Synthesis of a Chitosan−Dendrimer Hybrid and Its Biodegradation. *Biomacromolecules* **2003**, *4*, 1244–1249, doi:10.1021/bm030021w.
196. Zarghami, Z.; Akbari, A.; Latifi, A. M.; Amani, M. A. Design of a new integrated chitosan-PAMAM dendrimer biosorbent for heavy metals removing and study of its adsorption kinetics and thermodynamics. *Bioresour. Technol.* **2016**, *205*, 230–238, doi:10.1016/j.biortech.2016.01.052.
197. Wen, Y.; Tan, Z.; Sun, F.; Sheng, L.; Zhang, X.; Yao, F. Synthesis and characterization of quaternized carboxymethyl chitosan/poly(amidoamine) dendrimer core–shell nanoparticles. *Mater. Sci. Eng. C* **2012**, *32*, 2026–2036, doi:10.1016/j.msec.2012.05.019.
198. Wen, Y.; Yao, F.; Sun, F.; Tan, Z.; Tian, L.; Xie, L.; Song, Q. Antibacterial action mode of quaternized carboxymethyl chitosan/poly(amidoamine) dendrimer core–shell nanoparticles against Escherichia coli correlated with molecular chain conformation. *Mater. Sci. Eng. C* **2015**, *48*, 220–227, doi:10.1016/j.msec.2014.11.066.
199. Kim, H.-R.; Jang, J.-W.; Park, J.-W. Carboxymethyl chitosan-modified magnetic-cored dendrimer as an amphoteric adsorbent. *J. Hazard. Mater.* **2016**, *317*, 608–616, doi:10.1016/j.jhazmat.2016.06.025.
200. van Rantwijk, F.; Madeira Lau, R.; Sheldon, R. A. Biocatalytic transformations in ionic liquids. *Trends Biotechnol.* **2003**, *21*, 131–138, doi:10.1016/S0167-7799(03)00008-8.
201. Petkovic, M.; Seddon, K. R.; Rebelo, L. P. N.; Silva Pereira, C. Ionic liquids: a pathway to environmental acceptability. *Chem. Soc. Rev.* **2011**, *40*, 1383–403, doi:10.1039/c004968a.
202. Xie, H.; Zhang, S.; Li, S. Chitin and chitosan dissolved in ionic liquids as reversible sorbents of CO2. *Green Chem.* **2006**, *8*, 630–633, doi:10.1039/B517297G.
203. Liebert, T.; Heinze, T. Interaction of Ionic Liquids with Polysaccharides 5. Solvents and Reaction Media for the Modification of Cellulose. *Bioresources* **2008**, *3*, 576–601.
204. Zakrzewska, M. E.; Bogel-Łukasik, E.; Bogel-Łukasik, R. Solubility of Carbohydrates in Ionic Liquids. *Energy Fuels* **2010**, *24*, 737–745, doi:10.1021/ef901215m.

205. Isik, M.; Sardon, H.; Mecerreyes, D. Ionic Liquids and Cellulose: Dissolution, Chemical Modification and Preparation of New Cellulosic Materials. *Int. J. Mol. Sci.* **2014**, *15*, 11922–11940, doi:10.3390/ijms150711922.
206. Chen, Q.; Xiao, W.; Zhou, L.; Wu, T.; Wu, Y. Hydrolysis of chitosan under microwave irradiation in ionic liquids promoted by sulfonic acid-functionalized ionic liquids. *Polym. Degrad. Stab.* **2012**, *97*, 49–53, doi:10.1016/j.polymdegradstab.2011.10.014.
207. Tian, T.-C.; Xie, C.-X.; Li, L.; Wei, Q.-L.; Yu, S.-T.; Zhang, T. Research on the structure of amino acid ILs and its solubility for chitosan with chemical software. *Polym. Degrad. Stab.* **2016**, *126*, 17–21, doi:10.1016/j.polymdegradstab.2016.01.010.
208. Yang, X.; Qiao, C.; Li, Y.; Li, T. Dissolution and resourcfulization of biopolymers in ionic liquids. *React. Funct. Polym.* **2016**, *100*, 181–190, doi:10.1016/j.reactfunctpolym.2016.01.017.
209. Silva, S. S.; Mano, J. F.; Reis, R. L. Ionic liquids in the processing and chemical modification of chitin and chitosan for biomedical applications. *Green Chem.* **2017**, *19*, 1208–1220, doi:10.1039/C6GC02827F.
210. Mine, S.; Izawa, H.; Kaneko, Y.; Kadokawa, J. Acetylation of α-chitin in ionic liquids. *Carbohydr. Res.* **2009**, *344*, 2263–2265, doi:10.1016/j.carres.2009.08.004.
211. Liu, L.; Zhou, S.; Wang, B.; Xu, F.; Sun, R. Homogeneous acetylation of chitosan in ionic liquids. *J. Appl. Polym. Sci.* **2013**, *129*, 28–35, doi:10.1002/app.38701.
212. Liu, Y.; Huang, Y.; Boamah, P.-O.; Cao, L.; Zhang, Q.; Lu, Z.; Li, H. Homogeneous synthesis of linoleic acid-grafted chitosan oligosaccharide in ionic liquid and its self-assembly performance in aqueous solution. *J. Appl. Polym. Sci.* **2015**, *132*, 41727, doi:10.1002/app.41727.
213. Li, L.; Yuan, B.; Liu, S.; Yu, S.; Xie, C.; Liu, F.; Zhang, C. N-acyl chitosan and its fiber with excellent moisture absorbability and retentivity: Preparation in a novel [Gly]Cl/water homogeneous system. *J. Appl. Polym. Sci.* **2013**, *129*, 3282–3289, doi:10.1002/app.39039.
214. Wang, Z.; Zheng, L.; Li, C.; Zhang, D.; Xiao, Y.; Guan, G.; Zhu, W. Modification of chitosan with monomethyl fumaric acid in an ionic liquid solution. *Carbohydr. Polym.* **2015**, *117*, 973–979, doi:10.1016/j.carbpol.2014.10.021.
215. Wei, Y.; Huang, W.; Zhou, Y.; Zhang, S.; Hua, D.; Zhu, X. Modification of chitosan with carboxyl-functionalized ionic liquid for anion adsorption. *Int. J. Biol. Macromol.* **2013**, *62*, 365–369, doi:10.1016/j.ijbiomac.2013.09.020.
216. Yang, L.; Zhang, J.; He, J.; Zhang, J.; Gan, Z. Homogeneous synthesis of amino-reserved chitosan-graft-polycaprolactone in an ionic liquid and the application in cell cultivation. *Polym. Int.* **2015**, *64*, 1045–1052, doi:10.1002/pi.4912.
217. Pei, L.; Cai, Z.; Shang, S.; Song, Z. Synthesis and antibacterial activity of alkylated chitosan under basic ionic liquid conditions. *J. Appl. Polym. Sci.* **2014**, *131*, 40052, doi:10.1002/app.40052.
218. Yang, X.; Zhang, C.; Qiao, C.; Mu, X.; Li, T.; Xu, J.; Shi, L.; Zhang, D. A simple and convenient method to synthesize N-[(2-hydroxyl)-propyl-3-trimethylammonium]

chitosan chloride in an ionic liquid. *Carbohydr. Polym.* **2015**, *130*, 325–332, doi:10.1016/j.carbpol.2015.05.014.

219. Chen, H.; Cui, S.; Zhao, Y.; Zhang, S.; Chen, H.; Peng, X.; Wang, B. O-Alkylation of Chitosan for Gene Delivery by Using Ionic Liquid in an in-situ Reactor. *Engineering* **2012**, *04*, 114, doi:10.4236/eng.2012.410B029.
220. Yamamoto, K.; Yoshida, S.; Mine, S.; Kadokawa, J. Synthesis of chitin-graft-polystyrene via atom transfer radical polymerization initiated from a chitin macroinitiator. *Polym. Chem.* **2013**, *4*, 3384–3389, doi:10.1039/C3PY00152K.
221. Lin, C.; Liu, D.; Luo, W.; Liu, Y.; Zhu, M.; Li, X.; Liu, M. Functionalization of chitosan via single electron transfer living radical polymerization in an ionic liquid and its antimicrobial activity. *J. Appl. Polym. Sci.* **2015**, *132*, 42754, doi:10.1002/app.42754.
222. Chen, H.; Cui, S.; Zhao, Y.; Zhang, C.; Zhang, S.; Peng, X. Grafting Chitosan with Polyethylenimine in an Ionic Liquid for Efficient Gene Delivery. *PLOS ONE* **2015**, *10*, e0121817, doi:10.1371/journal.pone.0121817.
223. Wang, Z.; Zheng, L.; Li, C.; Zhang, D.; Xiao, Y.; Guan, G.; Zhu, W. A novel and simple procedure to synthesize chitosan-graft-polycaprolactone in an ionic liquid. *Carbohydr. Polym.* **2013**, *94*, 505–510, doi:10.1016/j.carbpol.2013.01.090.
224. Zhou, Y.; Fan, M.; Luo, X.; Huang, L.; Chen, L. Acidic ionic liquid catalyzed crosslinking of oxycellulose with chitosan for advanced biocomposites. *Carbohydr. Polym.* **2014**, *113*, 108–114, doi:10.1016/j.carbpol.2014.06.081.
225. Luo, Y.; Ling, Y.; Wang, X.; Han, Y.; Zeng, X.; Sun, R. Maillard reaction products from chitosan–xylan ionic liquid solution. *Carbohydr. Polym.* **2013**, *98*, 835–841, doi:10.1016/j.carbpol.2013.06.023.
226. Guyomard-Lack, A.; Buchtová, N.; Humbert, B.; Bideau, J. L. Ion segregation in an ionic liquid confined within chitosan based chemical ionogels. *Phys. Chem. Chem. Phys.* **2015**, *17*, 23947–23951, doi:10.1039/C5CP04198H.
227. Taheri, M.; Ghiaci, M.; Shchukarev, A. Cross-linked chitosan with a dicationic ionic liquid as a recyclable biopolymer-supported catalyst for cycloaddition of carbon dioxide with epoxides into cyclic carbonates. *New J. Chem.* **2018**, *42*, 587–597, doi:10.1039/C7NJ03665E.
228. Hua, D.; Jiang, J.; Kuang, L.; Jiang, J.; Zheng, W.; Liang, H. Smart Chitosan-Based Stimuli-Responsive Nanocarriers for the Controlled Delivery of Hydrophobic Pharmaceuticals. *Macromolecules* **2011**, *44*, 1298–1302, doi:10.1021/ma102568p.
229. Wang, Z.; Zheng, L.; Li, C.; Wu, S.; Xiao, Y. Preparation and antimicrobial activity of sulfopropyl chitosan in an ionic liquid aqueous solution. *J. Appl. Polym. Sci.* **2017**, *134*, 44989, doi:10.1002/app.44989.
230. Ishii, D.; Ohashi, C.; Hayashi, H. Facile enhancement of the deacetylation degree of chitosan by hydrothermal treatment in an imidazolium-based ionic liquid. *Green Chem.* **2014**, *16*, 1764–1767, doi:10.1039/C3GC41852A.
231. Zhang, Z.; Li, C.; Wang, Q.; Zhao, Z. K. Efficient hydrolysis of chitosan in ionic liquids. *Carbohydr. Polym.* **2009**, *78*, 685–689, doi:10.1016/j.carbpol.2009.06.002.

232. Zhao, X.; Kong, A.; Hou, Y.; Shan, C.; Ding, H.; Shan, Y. An innovative method for oxidative degradation of chitosan with molecular oxygen catalyzed by metal phthalocyanine in neutral ionic liquid. *Carbohydr. Res.* **2009**, *344*, 2010–2013, doi:10.1016/j.carres.2009.06.019.

233. Chen, X.; Liu, Y.; Kerton, F. M.; Yan, N. Conversion of chitin and N-acetyl-D-glucosamine into a N-containing furan derivative in ionic liquids. *RSC Adv.* **2015**, *5*, 20073–20080, doi:10.1039/C5RA00382B.

234. Husson, E.; Hadad, C.; Huet, G.; Laclef, S.; Lesur, D.; Lambertyn, V.; Jamali, A.; Gottis, S.; Sarazin, C.; Nhien, A. N. V. The effect of room temperature ionic liquids on the selective biocatalytic hydrolysis of chitin via sequential or simultaneous strategies. *Green Chem.* **2017**, *19*, 4122–4131, doi:10.1039/C7GC01471F.

235. Yuan, B.; Li, L.; Xie, C.; Liu, K.; Yu, S. Preparation of oligochitosan via In situ enzymatic hydrolysis of chitosan by amylase in [Gly]BF4 ionic liquid/water homogeneous system. *J. Appl. Polym. Sci.* **2014**, *131*, 41152, doi:10.1002/app.41152.

236. Zhao, G.; Lang, X.; Wang, F.; Li, J.; Li, X. A one-pot method for lipase-catalyzed synthesis of chitosan palmitate in mixed ionic liquids and its characterization. *Biochem. Eng. J.* **2017**, *126*, 24–29, doi:10.1016/j.bej.2017.05.026.