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# Chitin and chitosan in selected biomedical applications

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ABSTRACT

Chitin (CT), the well-known natural biopolymer and chitosan (CS) (bio-based or "artificial polymer") are non-toxic, biodegradable and biocompatible in nature. The advantages of these biomaterials are such that, they can be easily processed into different forms such as membranes, sponges, gels, scaffolds, microparticles, nanoparticles and nanofibers for a variety of biomedical applications such as drug delivery, gene therapy, tissue engineering and wound healing. Present review focuses on the diverse applications of CT and CS membranes and scaffolds for drug delivery, tissue engineering and targeted regenerative medicine. The chitinous scaffolds of marine sponges' origin are discussed here for the first time. These CT based scaffolds obtained from Porifera possess remarkable and unique properties such as hydration, interconnected channels and diverse structural architecture. This review will provide a brief overview of CT and CS membranes and scaffolds toward different kinds of delivery applications such as anticancer drug delivery, osteogenic drug delivery, and growth factor delivery, because of their inimitable release behavior, degradation profile, mucoadhesive nature, etc. The review also provides an overview of the key

*Abbreviations:* ADM, acellular dermal matrix; ALP, alkaline phosphatase; ASGR, asialoglycoprotein receptors; ASOs, Smad3 antisense oligonucleotides; *B. subtilis*, *Bacillus subtilis*; BDNF, brain-derived neurotrophic factor; bFGF, basic fibroblast growth factor; BGC, bioactive glass ceramic or bioglass; BMP-7, bone morphogenetic protein-7; CCM, chitosan collagen matrix; CM, carboxymethyl; CNT, carbon nanotube; CS, chitosan; CS-*g*-$\beta$-CD, chitosan-grafted-$\beta$-cyclodextrin; CT, chitin; Dex, dexamethasone; *E. coli*, *Escherichia coli*; ECH, epichlorohydrin; ECM, extracellular matrix; EDC, 1-(3-dimethylaminopropyl)-3-ethyl-carbodimide hydrochloride; EtO, ethylene oxide gas; GA, glutaraldehyde; GAGs, glycosaminoglycans; GC, galactosylated chitosan; GFP, green fluorescence protein; GHA, galactosylated hyaluronic acid; GTMAC, glycidyltrimethylammonium chloride; HA, hyaluronic acid; HAp, hydroxyapatite; HCA, hydroxycarbonate apatite; HDF, human dermal fibroblasts; HDI, hexamethylene diisocyanate; hm CS, hydrophobically modified chitosan; HUVECs, human umbilical vein endothelial cells; ICC, inverted colloidal crystals; iPS, induced pluripotent stem cells; MeGC, methacrylated glycol chitosan; MPEG, methoxy poly(ethylene glycol); MSC, mesenchymal stem cells; $M_w$, molecular weight; nAg, nanosilver; nBGC, nano bioglass; NGF, nerve growth factor; NOCC, *N*,*O*-(carboxymethyl) chitosan; NS, neurosphere; *P. aeruginosa*, *Pseudomonas aeruginosa*; PAA, poly(acrylic acid); PBS, poly(butylene succinate); PCL, poly(caprolactone); PCLDLLA, poly($\varepsilon$-caprolactone-co-D,L-lactide); PDGF, platelet derived growth factor; PDGF-BB, platelet derived growth factor; pDNA, plasmid deoxyribonucleic acid; PEC, polyelectrolyte complex; PEEK, poly(ether-ether ketone); PEG, poly(ethylene glycol); PEO, poly(ethylene oxide); PGA, poly(glycolic acid); PLGA/PLAGA, poly(lactic-co-glycolic) acid; PLLA/PLA, poly(L-lactic acid); PMN, polymorphonuclear cells; PNIPAAm, poly(*N*-isopropylacrylamide); PTAH, phosphotungstic acid-hematoxylin; PTX, pentoxifylline; PVA, poly(vinyl alcohol); PVLA, poly(*N*-p-vinylbenzyl-4-o-$\beta$-D-galactopyranosyl-D-gluconamide); RGD, arginine–glycine–aspartic acid; rhBMP-2, recombinant human bone morphogenetic protein-2; S-B, rhBMP2 (without microspheres) encapsulated chitosan/collagen composite scaffold; S-MB, rhBMP2-PLGA microspheres loaded chitosan/collagen composite scaffold; *S. aureus*, *Staphylococcus aureus*; SBF, simulated body fluid; SCs, Schwann cells; $SiO_2$, silica; TCH, tetracycline hydrochloride; TGF-β, transforming growth factor-β; TMC, *N*,*N*,*N*-trimethyl chitosan chloride; VEGF, vascular endothelial growth factor; $\alpha$-CT, alpha chitin; $\beta$-CT, beta chitin; $\gamma$-CT, gamma chitin.

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features of CT and CS membranes and scaffolds such as their biodegradability, cytocompatibility and mechanical properties toward applications in tissue engineering and wound healing.



**Contents**



## 1. Introduction

Polysaccharides, as a class of natural macromolecules, have the tendency to be extremely bioactive, and are generally derived using different biotechnological approaches from agricultural feedstock or crustacean shell wastes. In terms of availability, CT is next to cellulose, available to the extent of over 10 Gigatons annually [1]. The application potential of CS, a deacetylated derivative of CT, is multidimensional, such as in food and nutrition, material science, biotechnology, pharmaceuticals, agriculture and environmental protection [2–7]. The net cationicity and the presence of multiple functionalities in the molecule make CS a sought-after biomolecule. The latter offers scope for manipulation for preparing a broad spectrum of derivatives for specific end use applications in diversified areas. The biomedical and therapeutic significance of CT/CS derivatives is a subject of significant concern all over the world.

CT and CS are linear polysaccharides, comprised of two monomeric units namely *N*-acetyl-2-amino-2-deoxy-D-glucose (*N*-acetylated groups) and 2-amino-2-deoxy-D-glucose residues (*N*-deacetylated groups, amino groups). CT samples contain low amount of 2-amino-2-deoxy-D-glucose and hence it is less soluble in acidic solvents, whereas CS samples contain lesser number of *N*-acetyl-2-amino-2-deoxy-D-glucose and hence it is soluble in acidic solvents [8]. Majority of the authors consider CT and CS as the polymer with the number of 2-amino-2-deoxy-D-glucose units, lower and higher than 60% [8]. The $\beta$-1,4-linkage provides a rigid and unbranched structure to CT and CS. The abundant hydroxyl groups (one primary hydroxyl at C-6 and one secondary hydroxyl at C-3), amino groups (at C-2) or its *N*-acetyl counterpart with a tendency for intra and intermolecular hydrogen bonds result in the formation of linear aggregates with extensive crystallinity. The latter contributes to the strength shown by chitinous structures, and also to the virtual insolubility of CT in common solvents, particularly in water at neutral pH. The molecular weight ($M_w$) of CT can be as high as $10^6$ Da and the structure of CT and CS is represented in Fig. 1.

CT exists in nature in three different polymorphic forms, with varying properties [4,9–11] and the different polymorphic forms are $\alpha$, $\beta$ and $\gamma$. The sources of $\alpha$-CT are crabs and shrimps; $\beta$-CT is squids and $\gamma$-CT is loligo. The three polymorphic forms differ in their arrangement of polymeric chain. In $\alpha$-CT, the polymeric chains are arranged antiparallel to each other, in $\beta$-CT, the polymeric chains are arranged parallel to each other and in $\gamma$-CT, the polymeric chains are arranged randomly in which two parallel chains and one antiparallel chain forms the polymeric structure [3]. Schematic illustration of the three polymorphic configurations of CT are shown in Fig. 2.

CS, a de-*N*-acetylated analog of CT, is a heteropolysaccharide consisting of linear $\beta$-1,4-linked units. Both the content and sequence of these units will determine the physico-chemical and biological properties of the polymer. Heterogeneous conditions during deacetylation provide a block-wise distribution, whereas under homogeneous conditions, random distribution of acetyl groups appears in CS [4]. CT and CS have versatile applications in tissue engineering [12–20], wound healing [21–28], as excipients for drug delivery [29–33] and gene delivery [34]. They offer the advantage of being easily processed into gels [35], membranes [36,37], nanofibers [38], nanofibrils [39], beads

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