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Minireview

Polysaccharide-based nanocomposites and their applications

Yingying Zheng [a,*], Jonathan Monty [b], Robert J. Linhardt [b,*]

[a] Department of Physics and Key Laboratory of ATMMT Ministry of Education, Zhejiang Sci-Tech University, Hangzhou 310018, People's Republic of China
[b] Department of Chemistry and Chemical Biology, Rensselaer Polytechnic Institute, Troy, NY 12180-3590, USA

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ABSTRACT

Polysaccharide nanocomposites have become increasingly important materials over the past decade. Polysaccharides offer a green alternative to synthetic polymers in the preparation of soft nanomaterials. They have also been used in composites with hard nanomaterials, such as metal nanoparticles and carbon-based nanomaterials. This mini review describes methods for polysaccharide nanocomposite preparation and reviews the various types and diverse applications for these novel materials.

1. Introduction

This mini review focuses on methods to prepare polysaccharide nanocomposites, the various types of polysaccharide nanocomposites, and their applications. Recent applications of polysaccharides used in preparing nanocomposites for biomedicine, for energy production and storage, for electrical devices, in separation science, and in industrial and materials applications, are reviewed. There are a number of older reviews published on polysaccharide nanocomposites, to which the authors would like to direct the attention of the reader.[1–8]

1.1. Polysaccharides

There are three major families of biopolymers, nucleic acids, proteins, and polysaccharides.[9] Polysaccharides are comprised of multiple saccharide units joined to one another through glycosidic linkages and have a number of unique features that differentiate them from the other families of biopolymers. Most polysaccharides are easily and inexpensively recovered natural products produced as energy storage or structural biopolymers by microbes, plants, and animals.[10] Polysaccharides offer a number of advantages over nucleic acids and proteins for applications in materials science. Polysaccharides are generally more stable than nucleic acids and proteins and are usually not irreversibly denatured on heating.[10] There are a diverse variety of polysaccharides with properties including: low, intermediate, and high molecular weights with differing polydispersities; linear or branched structures; monofunctional, having only hydroxyl groups, or polyfunctional, having hydroxyl, carboxyl, and/or amino groups; a high level of chirality; water soluble or insoluble properties; low toxicity, environmentally safe, and non-immunogenic.[10] The diverse structures and properties of carbohydrates offer molecular and biological advantages for their use in the preparation of nanomaterials and nanocomposites.

1.2. What is nanotechnology?

Nanotechnology is a branch of materials science that focuses on the preparation of nanoscale materials of dimensions ranging from 1 to 100 nm.[11] Nanoscale materials often have unique properties due to their small size.[11] Early nanomaterials were generally constructed of 'hard' materials such as metals and carbon-only nanostructures, such as carbon nanotubes (CNTs) or buckyballs.[12] More recently, 'soft' nanomaterials made of synthetic polymers and biopolymers have gained increased interest as part of an effort to avoid nanotoxicity and to ameliorate environmental issues.[13]

1.3. Overview of nanocomposites

Nanocomposites are generally comprised of multiple nanoscale materials or a nanoscale material incorporated into a bulk material. Such nanocomposites can correspond to combinations of a 'hard' and a 'soft' nanomaterial, two 'soft' nanomaterials, or

* Corresponding authors. Tel.: +86 571 86843468 (Y.Z.), +1 518 276 3404 (R.J.L.).
E-mail addresses: zhengyy1718@zstu.edu.cn (Y. Zheng), linhar@rpi.edu (R.J. Linhardt).

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two 'hard' nanomaterials.[13] Nanocomposites take on the properties of the materials present as well as their size scale. Challenges in preparing nanocomposites include: controlling their fabrication/synthesis; ensuring the compatibility of their different material components; and obtaining desirable/unique properties. Since polysaccharides form a 'soft' nanomaterial, this mini review will focus on combinations of 'hard' and 'soft' nanomaterials and combinations of 'soft' nanomaterials.

2. Composite formation

There are a number of ways to prepare or synthesize nanocomposites. These include electrospinning, film casting, dip coating, physically mixing, layer-by-layer assembly, ionotropic gelation, colloidal assembly, co-precipitation, in situ preparation, and covalent coupling. A schematic illustration of the ways in which nanocomposites are made is presented in Figure 1. These methods take advantage of hydrogen-bonding, Coulombic interactions, hydrophobic effects, and electrostatic, and ionic interactions. Examples of polysaccharide nanocomposites, prepared or synthesized by these different methods, are presented in Table 1.

2.1. Electrospinning

Electrospinning is a physical method of nanocomposite formulation that involves the extrusion of a solution of polymer in the presence or absence of dispersed nanomaterial through a syringe needle (spinneret) onto a collection plate in the presence of a high voltage field (Fig. 1A). Wet–dry electrospinning utilizes a volatile solvent that evaporates as the nanocomposite is spun, while wet–wet electrospinning can utilize a non-volatile solvent, such as a room temperature ionic liquid, which is spun into a second solvent in a collection dish located between the spinneret and collection plate.[14] Co-axial electrospinning is a newly introduced technology, which can fabricate fibers from two different components simultaneously. The resulting fibers have a core–sheath structure.

Water-soluble polysaccharides, such as starch, are generally wet–dry electrospun. However, few solvents can dissolve crystalline polysaccharides, such as cellulose and chitin, which significantly limits their use in electrospinning. Room temperature ionic liquids (RTILs) are tunable solvents that can be custom designed to dissolve intractable polymers, such as cellulose.[14] RTILs are non-volatile, liquid salt-based, organic solvents with high thermal stability and a large electrochemical window. They are recyclable and, hence, are considered 'green' solvents. Cellulose solutions in RTILs can be electrospun into an ethanol or water coagulation bath to obtain nanofibers (NFs) using simple wet–wet spinning.[15] Once spun, cellulose NFs can be used as a supporting matrix for covalently coupling small molecules[16] or large molecules, such as proteins,[17] to modify the fiber properties.

Co-spinning a polysaccharide with a second polysaccharide or a synthetic polymer is also possible. Cellulose can be co-dissolved with other polysaccharides, such as the anticoagulant heparin, in RTILs and electrospun together as composite fibers.[15] Chitosan has been wet–dry electrospun with collagen from hexafluoroisopropanol (HFIP)/trifluoroacetic acid (TFA) to obtain fibers that can mimic the properties of the extracellular matrix. Increasing the chitosan content decreased the average NF diameter, while reduced chitosan content fibers exhibit better mechanical properties and crosslinking with glutaraldehyde vapor can increase fiber stability.[18] Gelatin, a collagen derivative, can be wet–wet electrospun with the acidic polysaccharide hyaluronan from a dimethylformamide (DMF)/water solution.[19] The synthetic biodegradable poly(L-lactide-co-ε-caprolactone) has been electrospun with the anticoagulant polysaccharide heparin (tributyl ammonium salt) to obtain NFs with heparin as a dispersed phase in the NF matrix.[20] Co-electrospun cellulose acetate and biodegradable poly(*N*-vinylcaprolactam) (PVCL) afford tunable thermal responsive composites.[21]

Nanomaterials have also been incorporated into electrospun cellulose NFs to prepare core-sheath fibers. Conductive cable fibers with an insulating surface were prepared by coaxial electrospinning of multi-walled carbon nanotubes (MWCNTs) and cellulose.[22] Both the nanotubes and the cellulose were dissolved in ionic liquid, and then wet–wet electrospun into a water/ethanol coagulation bath. The nanotube core improved fiber thermal stability and tensile strength and showed electrical conductivity.[23]

2.2. Film casting, dip coating, and physical mixing

Film casting and dip coating methods are commonly used to prepare polysaccharide-based nanocomposites (Fig. 1B). Flexible energy storage devices based on nanocomposite cellulosic paper have been prepared from vertically aligned thin-walled MWCNTs grown on silicon substrates by thermal chemical vapor-deposition. Cellulose, dissolved in RTIL and infiltrated into the MWCNT forms a uniform cellulose-MWCNT cast film with excellent electrical properties.[24] Homogeneous dispersions of acid treated single-walled carbon nanotubes (SWCNTs) in a cellulose film can be prepared by film casting from *N*-methylmorpholine-*N*-oxide.[25] Cast films of the pullulan composited with nanofibrillated cellulose show improved thermal and mechanical properties and their malleability and mechanical properties could be further improved by adding glycerol.[26] Transparent nanocomposite films of chitosan and bacterial cellulose can also be film casted from aqueous acetic acid.[27] Film casting cellulose nanofiber/epoxy resin provides excellent thermally conductive, transparent nanocomposites.[28] Powders of pectin, a poly(α-1,4-galacturonic acid), milled with additives, can be cast from water to obtain antimicrobial nanocomposite films.[29]

Heparin–*N*-methylpyrollidone biocompatible surface dip-coatings with embedded biocidal Ag nanoparticles (NPs) have been explored for use in central venous catheters.[30] Ag-NP-lactose-modified chitosan coatings were tested on the surface of activated thermosets as bactericidal films.[31] Cotton fabrics have been coated with zinc oxide–soluble starch nanocomposites for antibacterial applications.[32]

A novel thermal processing method, involving cycling between 20 °C and −20 °C under controlled tension, can produce nanocomposites of poly(vinyl alcohol) and cellulose.[33] Chitosan, heparin, and hyaluronan can be dissolved in acetate buffer to form polyelectrolyte solutions for the preparation of polysaccharide-based polyelectrolyte complex NPs.[34] Sequential mixing of chitosan and heparin on Au-coated iron oxide nanoseeds affords polysaccharide iron oxide NPs for magnetic resonance imaging of tumors.[35] Microfibrillated cellulose was mixed into a starch solution to prepare biofoams of varying porosity and water content by freezing/freeze-drying.[36]

2.3. Layer by layer assembly

Inhibition of bacterial growth has also utilized a layer-by-layer, electrostatically structured polysaccharide film of alginate and chitosan-coated cellulose nanofibrous electrospun mats through the addition of layered silicate[37] (Fig. 1C). Layer-by-layer coating hyaluronic acid dispersed CNTs, followed by an enzyme layer and a final Nafion layer affords electrodes for mediatorless NADH biosensing.[38] After electrospinning chitosan/poly(ethylene oxide) blends, the resulting fibers can be immersed in a hyaluronic acid solution to electrostatically coat the fibers with a layer of hyaluronan.[39] This simple method is effective in forming polyanion/polycation complexes.

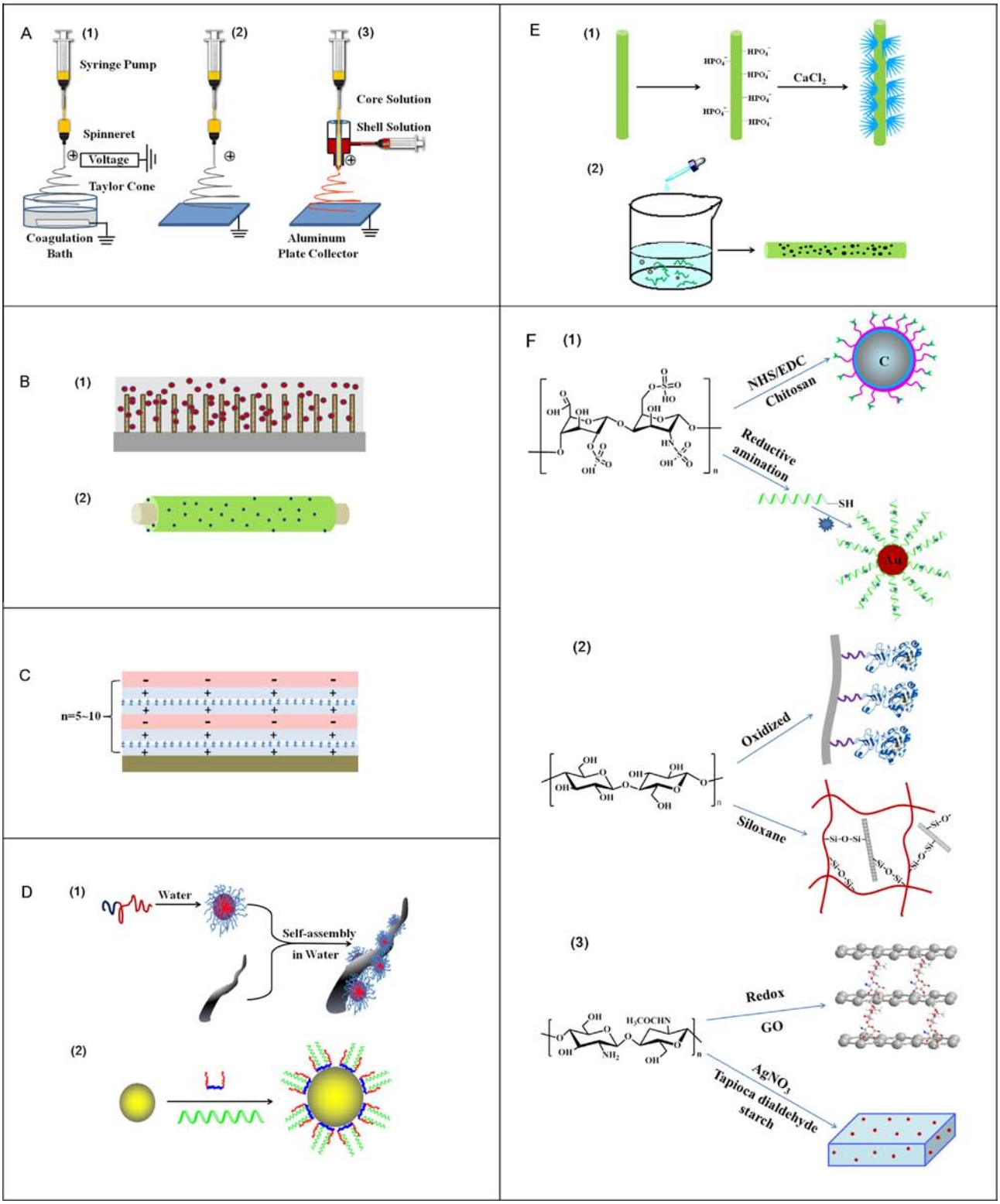

Figure 1. Schematic illustration of composite formation. (A) Electrospinning using (1) wet–wet; (2) wet–dry; and (3) co-axial methods. (B) Film coating of (1) cellulose cast from RTIL (spheres) onto MWCNTs (cylinders) grown on silicon wafer; (2) dip-coating in lactose-modified chitosan with embedded Ag NPs (spheres) on a thermoset core. (C) Layer-by-layer film of alginate (−), organic rectorite (+), and chitosan (*) on cellulose nanofiber mat. (D) Colloidal assembly (1) block polymer added to water forms a cationic micellar core-shell structure that self assembles on an anionic polysaccharide fiber; (2) poly(lactide-co-glycolide) (sphere) assembles a surface of pluronic block polymer (squiggle) and heparin (helix) in water. (E) In situ NP preparation (1) cellulose fiber (cylinder) is phosphorylated and hydroxyapatite nanocrystals are grown on the surface; (2) $AgNO_3$ added dropwise to a $NaBH_4$ solution containing cellulose NFs results in fiber (cylinder) containing Ag NPs (spheres). (F) Covalent coupling of (1) heparin NHS/EDC-linked to chitosan and coated on activated, poly(methyl methacrylate)-coated carbon (C) or reductively aminated with thioheparin (helix), labeled with fluorescent (star), and then coupled to Au NP (sphere); (2) cellulose oxidized and coupled to lysostaphin or siloxane treated and cross-linked to silica NF (cylinder); and (3) chitosan redox grafted to graphene oxide (GO) sheets or treated with tapioca-starch-dialdehyde for in situ synthesis of Ag NPs.

Table 1
The composite methods and applications of polysaccharide nanocomposites

Polysaccharide	Additive	Composite method	Applications	Refs.
Heparin	Ag	Reduction of Ag onto DAPHP	Antibacterial	71,72
	Au	Reduction of Au onto DAPHP	Antibacterial	71,72
		Reduction of Au by $NaBH_4$ onto Heparin-DOPA	Liver-specific CT imaging	59
		Au-thiol linkage	Imaging and induced cancer cell apoptosis	63
	CNTs	Coupling of activated heparin to nanotubes	Blood compatibility nanodevices	64
	Fe_3O_4	Co-precipitation	Targeted drug delivery	46
	Fibrin	Dehydrative coupling by EDC/NHS	Drug delivery: BMP-2	58
	Poly(glycolide-co-lactide) and pluronic	Solvent-diffusion method	Drug delivery: VEGF	42
	Poly(L-lactide-co-ε-caprolactone)	Co-electrospinning	Vascular tissue engineering	20
	Poly(lactide-co-glycolide), pluronic	Precipitation/solvent diffusion	Tumor imaging and therapy	69
	Gelatin, Ca–P/PHBV	Coating Ca–P/PHB with Gelatin, dehydrative coupling of gelatin and heparin by EDC/NHS	Bone tissue regeneration	60
Chitosan	Ag	Ascorbic acid reduction on lactose-modified chitosan	Antibacterial	31
	Ag, PVP	Dip-coating and thermal reduction	Antibacterial	74
	[Fe(pz){M(CN)4}] (M = Ni, Pd, Pt)	In situ preparation in the presence of chitosan	Spin-crossover properties	83
	Poly(lactide-co-glycolide), Pluronic	Precipitation/solvent diffusion	Tumor imaging and therapy	69
	Collagen	Electrospinning	Tissue engineering	86,18
	Heparin	Solution mixing	Tissue engineering	93
	Bacterial cellulose	Solution mixing, film casting	Food packaging and electronic displays	27
	Alginate	Electrospinning	Tissue engineering	94
	Monoclonal antibody	Ionotropic gelation	MAb delivery	43
Cellulose	Ag	Chemical or UV reduction of Ag on cellulose	Antibacterial	48
	CNTs	Mixing	Energy storage devices	24
		Coaxial electrospinning	Electronic devices; Energy storage	22
	Graphene	Solution Mixing	Electronic devices	84
	$CaCO_3$	In situ $CaCO_3$ preparation on cellulosic fibers	Reinforcing fillers in industrial polyethylene matrixes	49
	CdS	In situ CdS preparation on regenerated cellulose	Energy production: photocatalytic H_2 production	51
	TiO_2	In situ TiO_2 preparation in the presence of cellulosic fibers	Industrial papermaking	52
	ZnO	In situ ZnO preparation in cellulosic fibers	Multisource energy conversion	80
	Lysostaphin	Electrospinning	Wound healing	17
	Cibacron Blue F3GA	Covalent coupling of dye to electrospun cellulose	Bovine serum albumin affinity purification	16
	Poly(*N*-vinylcaprolactam)	Electrospinning	Protein affinity purification	21
	Epoxy resin	Film casting, dip-coating	Thermal conductivity	28
	Xylan-rich hemicelluloses	Solution mixing and film casting	Tensile strength and thermal stability	90
	Organic rectorite, chitosan, sodium alginate	Layer-by-layer techniques	Antibacterial	37
	Quaternized poly(1,2-butadiene)-block-poly(dimethylaminoethyl methacrylate)	Ionic assembly	Biomimetic nanocomposites	40
	Hydroxyapatite	Biomimetic technique	Bone tissue engineering	47
	Polyvinyl alcohol	Solution mixing, thermal processing (cycling)	Tissue engineering	33
	Pullulan	Film casting	Food packaging, electronic devices	26
Hyaluronan	Ag	Ag reduced with hyaluronan	Antibacterial	72
	Au	Ag reduced with hyaluronan	Antibacterial	71
	CNT	Solution mixing and coating	NADH biosensing	38
	Gelatin	Electrospinning	Tissue engineering	19
Starch	ZnO	In situ preparation in soluble starch	Antibacterial and UV protection cotton fabrics	32
	Polyaniline	In situ chemical oxidative polymerization of aniline	Removal of reactive dyes from synthetic effluent	62
	Cellulose	Solution mixing and freeze-drying	Packaging materials and biomedical materials	36
Alginate	Fe(pz){M(CN)4}] (M = Ni, Pd, Pt)	In situ preparation in alginate	Spin-crossover properties	83
	ZnO	In situ preparation in alginate	Antibacterial	50
	Cellulose nanocrystals, chitin whiskers, platelet-like starch nanocrystals, $CaCl_2$	Mixing and adsorption	Drug release	91
Pectin	Fe_3O_4	Co-precipitation and direct encapsulation	Cu^{2+} removal	45
Guar	Au	Au reduction by guar gum	Aq. ammonia sensor	75
	Montmorillonite	Solution intercalation	Drug delivery	82
Starch/chitosan	Ag	Reduction cross-linked tapioca dialdehyde starch–chitosan	Functional hydrogels	70

Table 1 (*continued*)

Polysaccharide	Additive	Composite method	Applications	Refs.
Chitosan/heparin	Activated carbon beads	EDC/NHS coupling of chitosan and heparin and carbon beads coating	Removal of chemotherapeutic, doxorubicin	55
	Fe_3O_4	In situ preparation of Fe_3O_4, EDC/NHS coupling of chitosan and heparin	Low-density lipoprotein removal	56
	Fe_3O_4, Au, Tween 80	Coating by ionic interaction	Magnetic resonance imaging with a tumor-targeting characteristic	35
	Bovine jugular veins	Self-assembly with NHS/EDC chemistry	Tissue engineering	57
Chitosan/hyaluronan	Heparin	Ionotropic gelation	Drug delivery	44
Hyaluronan/heparin	Steel	Covalently bonded	Drug eluting stents	95
Cellulose and chitin whiskers, platelet-like starch	Cyclodextrin/polymer inclusion	Solution mixing	Drug release	41

2.4. Colloidal assembly, ionotropic gelation, and co-precipitation

Colloidal assembly (Fig. 1D), between anionic cellulose nanofibrils and cationic synthetic poly(1,2-butadiene)-β-poly(2-dimethylaminoethyl methacrylate) block copolymer micelles, affords ionically stabilized biomimetic nanocomposites.[40] Supramolecular hydrogels, prepared containing cyclodextrin, polymer, and polysaccharide nanocrystals, can show accelerated gelation times, with enhanced mechanical strength and have been developed for the sustained release of drugs.[41] Spontaneous emulsion solvent diffusion of poly(lactide-co-glycolide), heparin, and pluronic affords heparin-functionalized NPs for controlled growth factor release.[42]

Ionotropic gelation of trimethyl chitosan NPs has been explored for the delivery of monoclonal antibodies.[43] Ionotropic gelation of chitosan–hyaluronic acid NPs loaded with heparin has been explored for the treatment of asthma.[44] Co-precipitation can be used to prepare an encapsulated, pectin-coated, iron oxide magnetic nanocomposite for Cu^{2+} removal.[45] Co-precipitation can afford heparin-coated iron oxide NPs loaded with anti-cancer drugs for targeted drug delivery.[46]

2.5. In situ NP preparation

Biomimetic techniques for induced apatite formation have been used to prepare hydroxyapatite/bacterial cellulose nanocomposite scaffolds[47] (Fig. 1E). Solution mixing of cellulose and Ag salts, with chemically- or UV-based reduction, affords antibacterial cellulose/Ag nanocomposites.[48] The in situ synthesis of $CaCO_3$ nanoparticles, in the presence of cellulose fibers, takes place from the drop-wise addition of solutions of NaOH to $CaCl_2$ and dimethylcarbonate.[49] The addition releases CO_2 and $CaCO_3$, with NPs forming on the cellulose surface. The in situ growth of ZnO NPs in alginate forms antibacterial nanocomposites.[50] Film casting regenerated cellulose from LiOH/urea solution, immersed into $CdCl_2$ and then into Na_2S solutions, affords a CdS NP-containing photocatalytic nanocomposite for H_2 production under visible light irradiation.[51] Titanium dioxide/cellulose was prepared by in situ synthesis of titanium dioxide from titanyl sulfate in film-cast nanocomposite paper sheets.[52] Sequential mixing of sodium sulfide, $ZnNO_3$, and sodium carboxymethyl cellulose, resulted in the in situ synthesis of Zn NPs, which were then film cast.[53]

2.6. Covalent coupling

Covalent coupling of bioactive ligands or modifiers to nanomaterials or nano-featured supports can be used to prepare polysaccharide-based nanocomposites (Fig. 1F). Activation chemistry includes the use of carbodiimides or other dehydrative coupling reagents, through ligand activation with reactive moieties including isothiocyanates, cyanogen bromide, epoxides, Schiff base chemistry, silanization, and grafting, or by co-synthesis.

2.6.1. Carbodiimide and dehydrative coupling

Coupling reagents, such as 1-ethyl-3-(3-dimethyl aminopropyl) carbodiimide (EDC) and *N*-hydroxysuccinimide (NHS), promote dehydrative coupling between amino, hydroxyl, or sulfhydryl groups and carboxylic acids.[54] Activated carbon beads coated with poly(methyl methacrylate) and with a second layer of chitosan to which heparin was covalently immobilized using EDC/NHS chemistry afford a nanocomposite matrix for the construction of a blood-compatible drug-removal filter.[55] Chitosan-coated iron oxide NPs can be functionalized with heparin, by EDC coupling, to prepare nanocomposites for selective low-density lipoprotein removal from plasma.[56] Heparin/chitosan NPs, prepared by physical self-assembly were immobilized onto the NFs of decellularized bovine jugular vein scaffold using EDC/NHS. These NP-immobilized scaffolds were conjugated to vascular endothelial growth factor (VEGF), and the controlled release of VEGF was explored for the enhanced regeneration of decellularized tissue-engineered scaffolds.[57] Heparin can be covalently bound to plasminogen-free fibrinogen, using NHS/EDC chemistry to form a heparin-conjugated fibrin (HCF) gel when mixed with thrombin. HCF provides an injectable system for sustained delivery of the growth factor, bone morphogenetic protein-2 (BMP-2) in bone tissue engineering studies.[58] Heparin, conjugated with the mussel-inspired adhesive amino acid, 3,4-dihydroxyphenylalanine, relies on NHS/EDC chemistry. This conjugate was added to citrate-reduced Au NPs to prepare a liver-specific computed tomography (CT) imaging reagent.[59] The amino groups present in gelatin can be used to conjugate heparin using carbodiimide chemistry.[60]

Dyes, covalently linked to nanocomposite chitosan, can be bound to nanocomposite carboxymethyl cellulose by carbodiimide coupling.[61] These dye conjugates can then be immobilized, via a sol-gel method, to a polysaccharide–compatible silicate matrix. Starch/polyaniline nanocomposites have been prepared through the chemical oxidative polymerization of aniline.[62]

2.6.2. Activation with reactive functionality

End-group, thiol-modified heparin, prepared by reductive amination, can be conjugated with fluorophores through carbodiimide chemistry. The fluorophore-labeled heparin is next immobilized onto the surface of Au NPs through a salt aging process to prepare NPs for the targeted detection of metastatic cancer cells. Poly(ethylene glycol)—RGD peptide has been tethered to these heparin–Au NPs.[63] Blood compatible carbon nanotubes have been made through the activation of the tetrabutylammonium salt of heparin with CNBr and coupling of activated heparin to poly

(ethyleneimine)-coated MWCNTs. The remaining amino groups were then conveniently labeled with fluorescein isothiocyanate (FITC).[64] Electrospun cellulose–chitosan NFs can be chemically treated to generate aldehyde groups for the covalent immobilization of the antimicrobial protein lysostaphin to prepare antibacterial fabrics in wound healing applications.[17] The surfaces of cellulose nanocrystals, decorated with epoxy functional groups introduced using epichlorohydrin, can be ring-opened with ammonium hydroxide for reaction with the FITC to prepare fluorescently labeled cellulose nanocrystals for bioimaging applications.[65] Nanocomposite hydrogels based on siloxane-derived hydroxypropyl methylcellulose interlinked with mesoporous silica NFs through a continuous network of Si—O—Si bonds have been explored as nanocomposite hydrogels for cartilage tissue engineering.[66] Cellulose-based ionogels can be produced using a chemically cross-linked polysaccharide, silanized hydroxypropyl methylcellulose. Silica NFs, covalently bound to the polysaccharide, increase ionic conductivity. These nanocomposite ionogels contain 98% water.[67] Cellulose nanocrystals have been labeled with FITC for fluorescence bioassays and bioimaging applications.[65] Cellulose NFs have been electrospun from RTILs and modified with affinity reagent for the purpose of protein affinity purification.[16] Chitosan grafting onto graphene oxide can be achieved by a redox grafting reaction.[68] A pluronic, activated using *para*-nitrophenyl chloroformate, has been coupled to chitosan or heparin in dimethylsulfoxide. Poly(lactide-co-glycolide) NPs with modified pluronic can be prepared by the nanoprecipitation/solvent diffusion method.[69] Covalently cross-linked tapioca dialdehyde starch–chitosan hydrogels have been used to form Ag NP-containing hybrid hydrogels. The aldehyde groups in tapioca dialdehyde starch make it possible to prepare a cross-linked hydrogel with amino-containing chitosan by the Schiff base reaction. The aldehyde groups reduce and stabilize the Ag NPs.[70]

2.6.3. Co-synthesis

Stabilized Au and Ag NPs can be prepared using 2,6-diaminopyridinyl heparin (or hyaluronan) synthesized through reductive amination. The aldehyde on the reducing end of underivatized polysaccharide is used to reduce $AuCl_4$ or $AgNO_3$, while the 2,6-diaminopyridinyl group provides a strong interaction with the Au or Ag NPs.[71–73] Poly(ethylene terephthalate) sheets can be dip coated in $AgNO_3$, poly(vinylpyrrolidone), and chitosan. After the films are dried, thermal reduction affords Ag NPs coordinated to the chitosan amino groups, providing antibacterial films.[74] Au NPs have been synthesized using guar gum as a reducing and capping agent.[75] Nanocomposites containing Ag can be prepared by microwave-assisted synthesis by using microcrystalline cellulose as reducing, stabilizing, and supporting agent.[76] Galactomannan polysaccharides can be used in the controlled formation of Au NPs.[77]

3. Types of polysaccharide nanocomposites and their applications

A wide variety of polysaccharide nanocomposites have been explored. These include polysaccharide nanocomposites containing metals, metal oxides and inorganic compounds, structured carbons, biomolecules, functional polymers, and multiple polysaccharides (Table 1).

There are many potential applications for such polysaccharide nanocomposites. These potential applications can be divided into many different overlapping groups. The major categories include: drug delivery, tissue engineering and wound healing, blood and biocompatibility, antibacterial properties, applications in biomedicine, energy production and storage, industrial applications, electronic devices, affinity materials, and mechanical and thermal properties (Table 1). Four different applications of polysaccharide-based nanocomposites are illustrated in Figure 2.

3.1. Metal-polysaccharide nanocomposites

Au NPs have been known for centuries and are generally prepared through the reduction of $HAuCl_4$. Heparin-coated Au NPs have also been used in liver-specific CT imaging[59] and in the targeted detection and apoptotic death of metastatic cancer cells[63] (Fig. 2A). Fluorescently labeled heparin immobilized onto Au NPs can specifically detect metastatic cancer cells due to their overexpression of heparanase. Heparin–Au NPs have also been conjugated with RGD peptides to selectively target metastatic cancer cells and induce apoptosis through heparin internalization. Heparin-immobilized NPs may have a future in cancer imaging and induced apoptosis of cancerous cells. Guar gum has been used as a reductant, capping, and stabilizing agent, in the 'green synthesis' of Au NPs.[75] These composites detect ammonia by surface plasmon resonance, representing a low-cost, highly sensitive, aqueous ammonia detector for clinical and medical applications. Galactomannan polysaccharides can also afford stabilized Au NPs.[77]

Ag NPs have been widely investigated because of their ease of synthesis, through reduction of $AgNO_3$, and their antibacterial properties. Green methods utilized to reduce Ag NPs can introduce both hyaluronan and heparin onto their surfaces.[71] In vitro and in vivo studies on these NPs showed anti-inflammatory, anticoagulant activity, and excellent antimicrobial properties against *Staphylococcus aureus* and *Escherichia coli*.[72] Moreover, the nanocomposites did not aggregate over several months when stored at room temperature. Central venous catheters have been coated with a copolymer (*N*-vinylpyrrolidinone and *n*-butyl methacrylate), Ag NPs, and heparin to produce anticoagulant and antibacterial surfaces.[30]

Ag NPs prepared in water under microwave heating using microcrystalline cellulose as a reducing, stabilizing, and supporting agent, afford NPs with sustainable biocidal activity.[76] Cellulose fiber-Ag NP composites have been prepared by several methods and tested for Ag release and antibacterial activity against *Bacillus subtilis*, *S. aureus*, and *Klebsiella pneumoniae*.[48] These nanocomposites might find interesting applications in clinical wound healing. Sodium carboxylmethyl cellulose-Ag nanocomposite films have been produced and loaded with curcumin.[78] These films show synergistic antimicrobial activity against *E. coli* suggesting promise as wound and burn dressings.

Ag–chitosan nanocomposite antimicrobial coatings for methacrylic thermosets can address the growing issue of bacterial adhesion to the surface of orthopedic and dental implants.[31] Coated thermosets showed in vitro antimicrobial protection for three weeks, after which the superficial release of Ag NPs compromised antibacterial activity. Thermal reduction produced Ag NP doped chitosan–poly(vinylpyrrolidone) films showed bactericidal activity against *S. aureus* and *E. coli* within 5 min, and retained stability for 35 days.[74] Large and uniform Ag NP-containing hybrid hydrogels have been prepared by in situ reduction of Ag^+ in cross-linked tapioca dialdehyde starch–chitosan hydrogels. By controlling the reduction conditions, such as polysaccharide concentration, aqueous $AgNO_3$ concentration, reaction time, and aqueous ammonium concentration, Ag NPs of different sizes and morphologies could be obtained.[70] These hydrogels showed good swelling behavior in water, and demonstrated high biocompatibility. A variety of metal NPs, including Ag, Au, Pt, and Pd were formed by reduction of corresponding metal salts with $NaBH_4$ in the presence of chitosan. Chitosan adsorbs to the surface of newly formed metal NPs acting as a stabilizer.[79]

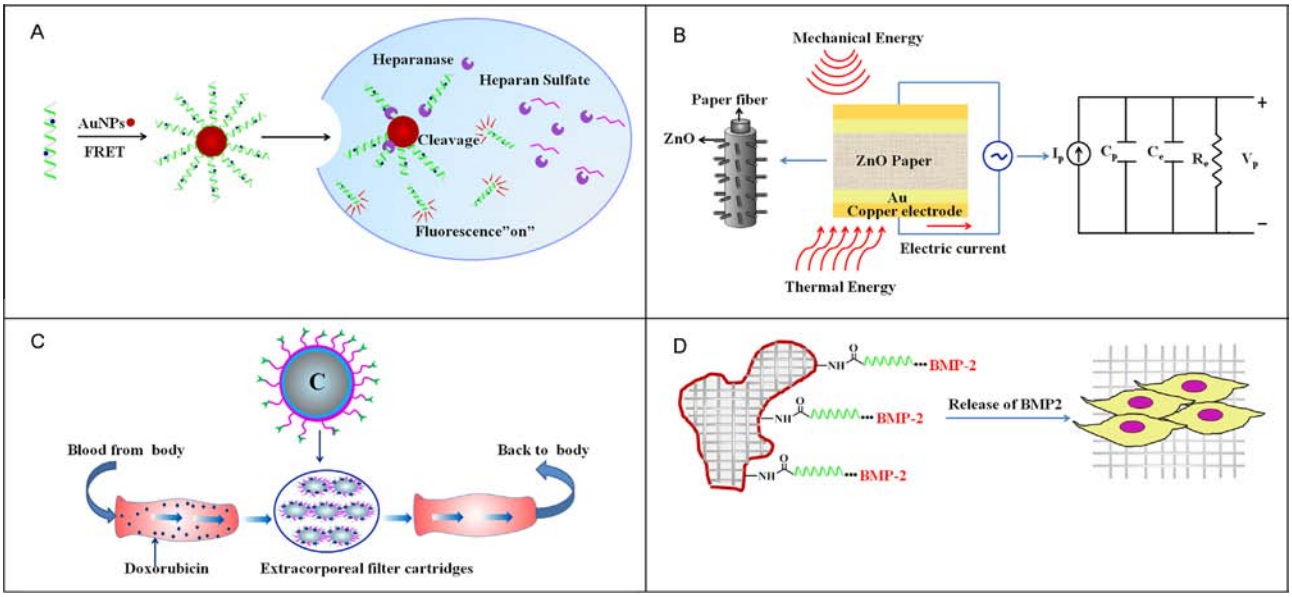

Figure 2. Applications of polysaccharide nanocomposites. A. Fluorescently labeled heparin (helix with star) is quenched when bound to Au NPs (sphere) and when released by heparanase (packman) quenching is reduced allowing the detection of heparinase-producing cancer cells. B. ZnO NPs grown on cellulose fibers transduce mechanical and thermal energy to electrical energy. C. Blood, containing doxorubicin drug, circulating through vessels is passed through an extracorporeal cartridge containing activated carbon beads (C) coated with a nanoporous poly(methyl methacrylate)/chitosan/heparin film to remove anticancer drug (dots) (see Fig. 1F(1)). D. Heparin (helix), coupled to gelatin lining a biodegradable $CaPO_4$-containing matrix (mesh), is used to release BMP-2 to promote cell differentiation.

3.2. Metal oxides and inorganic compound nanocomposites with polysaccharides

Using co-precipitation, heparin-coated superparamagnetic iron oxide NPs, were tested as potential image-guided anticancer drug delivery vehicles.[46] Doxorubicin and paclitaxel drug release profiles and cytotoxicity against ovarian cancer cell lines were measured. Heparin coating promoted a sustained release, and these NPs were effectively targeted. Iron oxide NPs were immobilized with chitosan and heparin by means of an Au coating.[35] An in vivo study on tumor targeting, showed fluorescence within the tumor after 1 h of the injection of the heparin-coated NPs. The study also showed that the nanocomposites could be used as an MRI agent. These composite NPs demonstrated low cytotoxicity. Chitosan and heparin conjugated to iron oxide NPs produce a means of removing low-density lipoprotein from blood plasma.[56] Heparin increases the biocompatibility of these NPs, which showed selectivity in removing low-density lipoproteins and could be removed magnetically and recycled. A pectin–iron oxide magnetic nanocomposite adsorbent demonstrates highly effective Cu^{2+} removal from wastewater. The adsorption mechanism is based on ion-exchange.[45]

ZnO exhibits both semiconductor and piezoelectric properties and can be used to produce electrical energy from ambient mechanical and thermal energy (Fig. 2B).[80] ZnO NPs, grown on the surface of cellulose fibers, can form a nanocomposite paper for thermal energy and mechanical energy harvesting, opening up a new approach for developing low-cost energy-scavenging systems. Nanocomposites consisting of ZnO and alginate showed antibacterial activity against *S. aureus* and *E. coli*.[50] These nanocomposites have potential as a biocompatible and renewable antimicrobial agent. Nano ZnO–soluble starch nanocomposites were synthesized using water as a solvent and soluble starch as a stabilizer and impregnated into cotton fabrics to impart antibacterial and UV-protection functions.[32]

TiO_2 grown in the presence of cellulosic fibers by hydrolysis of $TiSO_4$ in acidic medium affords composite handsheets with much higher opacity than conventional papers.[52] These results may benefit the industrial papermaking process where papers with higher opacity are needed.

CdS NPs with small particle sizes and large surface areas can be immobilized in the cellulose film to obtain CdS/cellulose nanocomposite.[51] These nanocomposite films can be used for the production of H_2 water photosplitting with visible light and excellent photostability for 'green' processes. In situ synthesis of ZnS NPs in carboxymethyl cellulose produced a solution that was casted into a homogeneous film.[53] The films show high optical transmission and offer a new approach for the production of security paper with optical signatures and organic based electronic devices.

$CaCO_3$/cellulose nanocomposite materials have been prepared by the controlled reaction of $CaCl_2$ with dimethylcarbonate in alkaline medium in the presence of cellulose fibers.[49] The resulting nanocomposites showed good mechanical performance and could be used in a poly(ethylene) matrix as reinforcing filler for traditional industrial applications.

Biomimetic techniques can be used to produce hydroxyapatite-cellulose nanocomposite scaffolds.[47] Stromal cells adhered and proliferated at a fast rate on these scaffolds, expressing high levels of osteopontin, osteocalcin, bone sialoprotein, and alkaline phosphatase mRNA, suggesting potential in bone tissue engineering.

Montmorillonite (MMT) and cellulose NPs were added to alginate to prepare organic- and inorganic-reinforced nanofiller bionanocomposites with different physico-mechanical and thermal properties.[81] Cellulose increases surface hydrophobicity and MMT increases film hydrophilicity. Cellulose also increases film tensile strength and tensile modulus, suggesting applications in food packaging. Guar gum-MMT nanocomposites can be prepared by a solution intercalation method.[82] X-ray diffraction patterns indicate intercalation resulting from treatment of montmorillonite by guar gum, and transmission electron microscopy shows intercalation and the presence of a partial exfoliation.

A family of Hofmann-like clathrate NPs of the $[Fe(pz)\{M(CN)_4\}]$ type (where M = Ni^{2+}, Pd^{2+}, Pt^{2+}) can be synthesized by successive coordination of the Fe^{2+}, pyrazine, and tetracyanometallates to functional amino and carboxylate groups inside the polysaccharide matrix pores. The Hofmann-like clathrate NPs, located in the

chitosan pores, are covalently linked to the amino groups of the chitosan and could also be involved in the hydrogen-bonding network via the remaining solvent molecules.[83]

3.3. Structured carbon-polysaccharide nanocomposites

Blood-compatible nano-based neo-proteoglycans have been prepared, which are comprised of a coating of MWCNTs with poly(ethyleneimine) and covalently conjugated heparin. Heparin retains its expected plasma-based anticoagulant activity when immobilized, resulting in blood-compatible MWCNTs.[64] Core-sheath MWCNT-cellulose fibers have been prepared by coaxial electrospinning.[22] The MWCNT-cellulose fibers formed a cable structure with a conductive core and insulating sheath and fiber mats demonstrated excellent conductivity because of a conductive pathway of bundled MWCNTs. These NFs could be used as a double-layer supercapacitor device because of the thin insulating cellulose sheath. Very high capacitance was obtained due to the inverse relationship between capacitance and distance between CNT electrodes. The fibers could also be used as a thin and flexible separator for an actuator. These electrode-spacer-electrolyte integrated nanocomposites were film casted to build a variety of thin flexible energy-storage devices.[24] The nanocomposite paper contains MWCNTs as the working electrode, the cellulose surrounding individual MWCNTs as the spacer, and the RTIL in cellulose as the self-sustaining electrolyte. The nanocomposite paper can be rolled up, twisted, or bent to any curvature and is completely recoverable. MWCNT-cellulose composite fibers were prepared using wet–wet solution spinning from RTIL.[23] Cellulose fibers show very high alignment of MWCNTs in the fiber axis direction. Moderate improvement in the tensile strength of MWCNT/cellulose composite fibers was observed up to a 0.05 mass fraction addition of MWCNTs.

A biocompatible nanocomposite consisting of SWCNTs dispersed in hyaluronan was investigated as a sensing platform for a mediatorless electrochemical detection of NADH.[38] SWCNT–hyaluronan bionanocomposite showed reversible electrochemistry, high short-term stability in NADH sensing, and high selectivity in NADH detection. The nanocomposite layer shows a strong SWCNT–hyaluronan interaction necessary for preparing biocompatible dispersions. SWCNTs/cellulose nanocomposites prepared using *N*-methylmorpholine-*N*-oxide monohydrate afford toughened, electro-conducting, transparent SWNT/cellulose films.[25] These transparent films may be used in applications such as transparent electrodes.

Activated carbon beads were coated with nanoporous poly (methyl methacrylate)–chitosan–heparin to be used in the removal of a chemotherapeutic agent, doxorubicin[55] (Fig. 2C). The intention of this study was to develop a feasible filtration agent as well as improve the biocompatibility and blood compatibility of carbon filters already in use in medical fields.

Amine-modified nanofibrillated cellulose was combined with reduced graphene oxide sheets to produce graphene–cellulose nanocomposite paper with enhanced mechanical and electrical properties.[84] The electrical properties are greater than any cellulose paper seen before, and the mechanical properties were not significantly diminished due to addition of graphene oxide. Moreover, the excellent physical properties are most likely due to the good dispersion resulting in strong hydrogen and chemical bonding between the reduced graphene and the nanofibrillated cellulose. Eco-friendly synthesis of carboxymethylcellulose–graphene oxide nanocomposite films relied on a simple solution mixing-evaporation method.[85] Graphene oxide was grafted with chitosan using a redox reaction to improve dispersion and biocompatibility.[68] Because of graphene's high Young's modulus, high thermal conductivity, and used as a zero-bandgap semiconductor, the successful grafting of chitosan on the graphene oxide surface affords nanocomposites with possible use in biosensors and other biomedical materials.

3.4. Biomolecule-polysaccharide nanocomposites

Electrospun collagen–chitosan NFs were stabilized by glutaraldehyde vapor via crosslinking, which afforded a biomimetic extracellular matrix for cell growth.[18] Neither collagen nor chitosan crystallized in electrospinning and crosslinking afforded an amorphous NF structure. Both endothelial cells and smooth muscle cells proliferate well on or within the NF, supporting the use of these scaffolds in tissue engineering. Collagen–chitosan–thermoplastic poly(urethane) blends were electrospun for biocompatible tissue-engineered scaffolds.[86] Porcine arterial endothelial cells and Schwann cells were seeded onto the scaffolds and showed enhanced proliferation on both randomly oriented and aligned NF scaffolds, suggesting that these scaffolds potentially allow for faster blood vessel repair and nerve regeneration.

Gelatin can be physically entrapped onto the surface of $Ca(PO_4)$-poly(hydroxybutyrate-co-hydroxyvalerate) nanocomposite scaffolds, after which heparin was immobilized onto the gelatin using standard carbodiimide chemistry[60] (Fig. 2D). This nanocomposite shows sustained release of BMP-2 for bone tissue engineering. Electrospinning hyaluronan and gelatin blends afford fibrous membranes with protein characteristics.[19] Decellularized bovine jugular vein scaffolds, containing heparin–chitosan NPs, loaded with VEGF, were used to increase the endothelialization and vascularization in the repair of cardiovascular damage.[57]

A heparin-conjugated fibrin has been used as an injectable system for sustained delivery of BMP-2.[58] BMP-2 released from the heparin–fibrin gel was bioactive suggesting its use in bone regeneration. Four techniques, (1) covalent crosslinking, (2) ionic crosslinking, (3) polyelectrolyte complex, and (4) self-assembly, for the preparation of hydrophobically modified polysaccharides, were reviewed for polysaccharide-based NP drug delivery systems.[5]

Antibodies targeting heparan sulfate proteoglycans were loaded into *N,N,N*-trimethyl chitosan NPs for selective delivery to hepatocellular carcinoma cells.[43] The study indicates that these nanocomplexes, while absorbed by both normal and cancerous cells, were retained longer in the hepatocellular carcinoma cells and demonstrated lower toxicity in healthy cells.

Lysostaphin, a bactericidal enzyme, was immobilized onto biocompatible fibers generated by electrospinning homogeneous solutions of cellulose, cellulose–chitosan, and cellulose–poly (methyl methacrylate).[17] These fibers were chemically treated to generate aldehyde groups for the covalent immobilization of lysostaphin, and the resulting fibers were used in bandage preparations showing activity against *S. aureus* with low toxicity toward keratinocytes.

3.5. Functional polymer–polysaccharide nanocomposites

A pluronic surface layer on poly(lactide-co-glycolide) NPs was functionally modified with heparin or chitosan to improve tumor targeting and imaging efficacy.[69] Heparin shows high-affinity binding and internalization by the rapidly dividing vascular endothelial cells in tumors. Chitosan facilitates tumor cell adsorption and tissue retention. The cytotoxicity of both the heparin-pluronic and the chitosan-pluronic is minimal, and the cellular uptake was enhanced for the coated NPs both in vitro and in vivo. Heparin-functionalized poly(lactide-co-glycolide) NPs were developed for the controlled release of growth factors. Pluronic was used as a hydrophilic surface layer and heparin as the functional moiety [42]. These NPs were loaded with lysozyme and VEGF showed 2-week to 1-month linear release profiles in vitro. Poly(ethylene glycol), functionalized with low molecular weight heparin, was

electrospun into NFs with either poly(ethylene oxide) or poly(lactide-co-glycolide) carrier.[87] NF fabrics of poly(L-lactide-co-ε-caprolactone) co-electrospun with collagen or heparin have been investigated for cell adhesion and proliferation and anticoagulant activity.[20] These fabrics have potential use in vascular tissue engineering.

A facile ionic assembly was prepared by ionic complexation of carboxymethylated nanofibrillated cellulose and micelles of quaternized poly(1,2-butadiene)-block-poly(dimethylaminoethyl methacrylate).[40] The amphiphilic block copolymer consists of a hydrophobic core segment with a stabilizing corona of hydrophilic chains. The cationic portion of block copolymer serves as a binder to the nanofibrillated cellulose, whereas the hydrophobic rubbery micellar cores facilitate energy dissipation and nanoscale lubrication between the nanocomposite domains under deformation, preventing macroscopic phase separation and giving rise to an alternating hard/soft architecture. Polysaccharide nanocrystals of cellulose and chitin, and platelet-like starch nanocrystals, were incorporated into supramolecular hydrogels based on cyclodextrin–polymer inclusion.[41] The polysaccharide nanocrystals increased the stability of the hydrogel framework and inhibited protein diffusion with no apparent cytotoxicity. Polysaccharide nanocrystals exhibit a polar surface covered with numerous hydroxyl groups, which are responsible for reinforcing nanocomposites.

Anisotropic poly(vinyl alcohol)–cellulose nanocomposite was used to prepare NFs.[33] The stress–strain tensile properties of porcine aorta were closely matched in both the circumferential and the axial directions by one type of this anisotropic nanocomposite. Tunable, thermo-responsive poly(*N*-vinylcaprolactam) was combined with cellulose acetate and electrospun.[21] The cellulose acetate was then converted to cellulose through alkaline hydrolysis and the composite fibers might be useful in the isolation and purification of proteins, and immobilization of enzymes.

Hyaluronan–poly(ethylene oxide) NF scaffolds mimic the architecture of the natural extracellular matrix.[88] Fibroblasts attached to these scaffolds spread, suggesting their use in tissue regeneration.

Starch/polyaniline nanocomposite was synthesized by chemical oxidative polymerization of aniline and was subsequently analyzed for dye removal from aqueous solution.[62] The inter-molecular hydrogen bonds broken in the composite became freely accessible for interactions with dye molecules.

Ionogels have been produced as a sustainable alternative to petrochemical-based polymer electrolytes.[67] These cellulose based ionogels displayed flexibility, thermal stability, and high ionic conductivity of a liquid.

3.6. Polysaccharide–polysaccharide nanocomposites

Electrospun cellulose–heparin micron- and nanometer-sized fibers show anticoagulant activity and good blood compatibility.[15] A facile approach was used to generate cellulose–chitosan hybrid NFs by electrospinning their ester derivatives and subsequently hydrolyzing these under alkaline conditions.[89] Aqueous solutions of cellulose and chitosan, casted to produce transparent films, display improved mechanical and thermal properties for biodegradable packaging and organic electronic displays.[27] Nanocomposite films with incorporation of cellulose NFs into xylan-rich hemicelluloses afford enhanced mechanical properties.[90] Nanocomposite films casted with pullulan and nanofibrillated cellulose are homogenous and transparent with excellent thermal and mechanical properties for use in sustainable food packaging and organic electronics.[26]

Organic rectorite and chitosan were used to produce an intercalated composite, which was then deposited upon cellulose NFs along with sodium alginate. These bilayers did not affect the fiber shape or 3D structure, and additional organic rectorite increased *E. coli* inhibition.[37] 3D layer-by-layer structured materials using this approach have potential use in tissue engineering and wound dressings.

Starch-reinforced cellulose NF foams can be prepared by freezing and freeze-drying.[36] Starch content could be used to control cell size and these nanostructured biofoams, show negligible shrinkage even at high cellulose NF contents. Cellulose nanocrystals, chitin whiskers, and platelet-like starch nanocrystals, were incorporated into alginate-based nanocomposite microspheres for drug delivery applications.[91] Bacterial cellulose–chitosan NFs, cross-linked with heparin, produce scaffolds suitable for vascular tissue engineering.[92] These scaffolds show good morphology, viability, and proliferation of MC3T3-E1 cells.

Heparin-containing NPs of a polyelectrolyte-complex of chitosan–heparin loaded with fibroblast growth factor were then adsorbed to the fiber surfaces for use as a growth factor delivery system.[93] The formation of polyelectrolyte-complex NPs was investigated at different charge mixing ratios for the chitosan–heparin and chitosan–hyaluronan polycation–polyanion pairs.[34] Electrospun chitosan and alginate polyionic, complexed, nanofibrous, cross-linked scaffolds exhibit increased cell adhesion and proliferation as tissue engineering scaffolds.[94] Chitosan dissolved in an aqueous ammonia/TFA solvent was electrospun to produce a network of fibers. Ionotropic gelation method was used to produce chitosan–hyaluronan NPs loaded with heparin.[44] Chitosan prolongs residence time of NPs at absorption sites, and hyaluronan acts as a mucoadhesive polymer. These NPs were internalized by mast cells, and the heparin in the NPs prevented histamine release suggesting their use in treating asthma. Aminotrimethoxysilane was anchored to the surface of stainless steel of a cardiovascular stent and hyaluronan was covalently immobilized as nanostructured coating onto this surface.[95] Heparin was then covalently bonded to the hyaluronan-immobilized stainless steel substrate and drug was loaded on these multiple coating layers for controlled drug-delivery and anticoagulant activity.

4. Summary and conclusions

Many different polysaccharide-based nanocomposites have been reviewed for a variety of potential applications. Polysaccharides are abundantly available and offer important properties in synthesis, fabrication, and structure. Applications range from biomaterials to electronics and other industrial uses. Polysaccharides also offer a ‘green’ alternative to oil-based synthetic polymers.

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