Carbohydrate-Based Nanofibers: Applications and Potentials

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Contents

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Abstract

Carbohydrate polymers have recently attracted great interest from academia and industry as one of the most abundant polymers in the world. Homopolymers or copolymers of monosaccharides, known as polysaccharides, are important part of carbohydrates and polymer materials with different sources from plants, microbes, and animals. Various structures and sources provide different chemical and mechanical properties and in result different applications. Carbohydrates are inexpensive materials, easily available, and renewable resources which present important characteristics including hydrophilicity and biocompatibility into polymeric systems. In this chapter potentials and applications of carbohydrate materials such as chitosan, chitin, cellulose, and alginate or their combinations in nanofiber form will be reviewed.

Keywords

Carbohydrate · Nanofibers · Applications

Introduction

Application of different natural and synthetic materials has attracted great interests in both research and industry fields. During these years, carbohydrates formed an advanced material group with excellent properties for different applications in engineering and biomedicine. Carbohydrate materials offer advantages including availability, cost efficiency, biocompatibility, and biodegradability in comparison with their counterparts in other material groups [1]. On the other hand, advent of nanotechnology introduced nanostructures with different scales and size ranges, alongside with advanced synthesis and characterizing methods. Nanotechnology

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showed that remanufacturing of materials with nanoscale sizes produced products with same materials but advanced properties. Among them, nanofibers as one-dimensional nanoparticle with two nanoscales showed promising potential applications. Development of high efficient synthesis methods provided opportunities for practical application of nanofibers. In addition fabrication of carbohydrate products from their nanofiber forms has been extensively investigated. In this chapter important carbohydrate materials and their potentials, synthesis methods, and applications will be reviewed.

Carbohydrate Nanofibers

In this section most important carbohydrates and their structure, advantages, and nanofiber preparation methods are reviewed. In recent years, applications of carbohydrate nanofibers have been focused on three interesting carbohydrates, alginate, chitosan, and cellulose. Alginate is a brown seaweed-derived carbohydrate containing mannuronic acid and guluronic acid [2]. Different alginate forms are used for various applications. This extensive attraction for alginate using is due to its excellent properties especially non-immunogenicity in addition with good biocompatibility and cost [3]. Lack of chain entanglements limits the electrospinning of aqueous solution of alginate and in result synthesis of uniform nanofibers [3]. Addition of cosolvent like glycerol or water-soluble synthetic polymers like poly(vinyl alcohol) (PVA) has been reported for successful alginate electrospinning [4, 5]. In addition, it has been reported that addition of poly (ethylene oxide) (PEO) with different concentrations could be useful to obtain uniform nanofibers. Another interesting member of carbohydrate-based material is chitosan, obtained from N-acetyl-β-D-glucosamine unites. Chitosan materials are used extensively in different applications especially biomedical fields, mainly due to antibacterial properties, cellular binding capability, biocompatibility, and biodegradability [3]. In electrospinning of chitosan, high electrical force is necessary to encounter surface tension of chitosan solution that comes from its polycationic nature. In addition other parameters like concentration, molecular weight, and degree of deacetylation are important in chitosan electrospinning [6]. Since the swell tendency of chitosan in aqueous solution, another polymer is added to electrospinning solution like PEO [7], polylactic acid (PLA) [8], and collagen [8]. Cellulose is another important carbohydrate consisting of β-D-glucose. Biodegradability and biocompatibility of cellulose allow extensive biological applications particularly in pharmaceutical research. However, cellulose is insoluble in common solvents and needs 320 °C temperature and 25 MPa pressure for formation of amorphous form in water, which limits its applications [3]. Different solvents are used in dissolving cellulose for electrospinning process. Furthermore, cellulose derivatives are used for solubility enhancement of cellulose and in result facilitate its electrospinning. In this regard acetate (CA) [9] and ethyl and methyl cellulose [10, 11] are extensively used. Different applications of carbohydrate nanofibers with different physicochemical properties are summarized in Table 1.

Table 1 Carbohydrate's nanofibers, properties, and applications

Main application	Carbohydrate nanofiber	Structural properties	Highlights	References
Tissue engineering	Starch/cellulose nanofibers	Diameter range of 40–90 nm	Enhanced water uptake ratio	[12]
		Interconnected porous morphology	Improved cell attachment and proliferation	
		Adequate mechanical properties	Cartilage tissue engineering applications	
	Cellulose acetate nanofibers containing carbon nanotube	3D[a] fibrous structures	Promoted fibroblast cell attachment, spreading, and proliferation	[15]
		Improved mechanical		
		Properties by nanotubes	Good protein adsorption capacity and hemocompatibility	
	Konjac glucomannan_ chitosan membranes	Average fiber diameter of 180–350 nm controlled with chitosan content	Enhanced bone mesenchymal stem cell adhesion	[16]
			Improved biocompatibility	
	Chitosan and cellulose acetate nanofibers	Diameter range of 200–500 nm	Faster and induced stem cell neuronal differentiation	[17]
	Chitosan and alginate-coated cellulose nanofibrous mats	Fibrous structure	Good biocompatibility for Beas-2B cells	[18]
		Successful deposition of chitosan and alginate		
	Chitosan/silica hybrid nanofibers	Average diameter of 182 nm	Cytocompatible scaffold with bone-forming 7F2 cells	[13]
		Self-assembled core-shell structure	Promoted cell attachment and proliferation	
	Chitosan/PVA nanofiber	3D, network, and porous structure	Pus and blood moisture absorption	[19]
			Wound dressings experiments in rats	
	Hyaluronic acid and polycaprolactone nanofibers	Average fiber diameters of 150 nm	Enhanced neuroblastoma cells proliferation	[20]
		Controlled porosity by hyaluronan content		
	Cell adhesive peptide (GRGDSP) modified alginate nanofibers	Uniform nanofibrous structure	Enhanced fibroblast cell attachment, spreading, and proliferation	[21]
		Peptide did not influence the electrospinning process	Potential tissue engineering applications	
	Cell adhesion ligands (RGD sequence) modified alginate nanofibers	Biodegradable, photo-crosslinkable biopolymer	Promoted the adhesion of primary human dermal fibroblasts	[22]

(*continued*)

Table 1 (continued)

Main application	Carbohydrate nanofiber	Structural properties	Highlights	References
Antibacterial applications	Chitosan nanofiber	Porous nanofiber structures	Enhanced antibacterial, antifungal, and antioxidant activity	[23]
		Chitin and chitosan source can influence on surface morphologies		
	Thiol-chitosan and chitosan iodoacetamide nanofibers	Thermally stable structure	Antibacterial activity against negative bacteria *Escherichia coli*	[24]
			Wound dressing applications	
	Chitosan/PEG[b]/PLGA[c] nanofibers	3D mats with random distribution of nanofibers	Antibacterial functionality with 1 or 2.5%	[25]
		Fiber diameter range of 981–1139 nm	Chitosan	
	Chitosan nanofibers containing AgNPs[d]	Well dispersion of 10 nm AgNPs in nanofibers	High degree of antibacterial effectiveness	[26]
		Diameters decreased by increase of AgNPs	Increase in quantity of AgNPs induced increased antibacterial properties	
	Electrospun chitosan/PEO nanofibrous containing AgNPs and chlorhexidine	Homogeneous distribution of NPs throughout the fibers	Active antibacterial against *Staphylococcus aureus*	[27]
	Chitosan/gelatin nanofibers containing Fe_3O_4 NPs	Well-dispersed Fe_3O_4 NPs in the composite nanofibers with effective interactions	NPs enhanced mechanical properties	[28]
			Antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*	
Drug delivery systems	Chitosan nanofiber	PTX core and chitosan cell structure	High PTX loading content	[14]
			Well-controlled drug release	
			Few platelets adhesion	
	PEO, SA[e], and sodium ibuprofen	3D structures	Fabrication of tunable pulsatile drug release system	[29]
		Responsive to pH		
	Cellulose nanofiber and SA	pH and electric field stimulus responsive	Increased ibuprofen release	[30]
	CA[f] nanofibers	Uniform structures and smooth surface	Sustained drug release profiles for ketoprofen	[31]
		Morphologies		
Filters and adsorbents	Cellulose nanofibers	5 nm diameter	Excellent permeation flux	[32]
		Average pore size diameter of 20 nm	99.5% rejection ratio	
			High virus adsorption capacity	

(*continued*)

Table 1 (continued)

Main application	Carbohydrate nanofiber	Structural properties	Highlights	References
	Cellulose nanofibers	5–10 nm diameter	Adsorption and removal of radioactive UO_2^{2+} in water	[33]
	Chitosan nanofiber	Continuous and randomly oriented morphology	Pb(II) removal from aqueous/acid solutions with good adsorption selectivity	[34]
		Fiber average diameter decrease with increase in glutaraldehyde content		
	Chitosan nanofibers	Average diameter of 75 nm	Chemical filtration of Cr (VI)	[35]
	Chitosan/ polycaprolactam nanofibers	Flexible nanofibers with 97 nm diameter	High adsorption and reduction of toxic chromium (VI)	[36]
		Average pore diameter of 301 nm		
	Chitosan hybrid nanofibers with AgNPs	Stable microstructure	Excellent water durability	[37]
		Smooth uniform morphology	Filtration efficiency of more than 99%	
		25–60 nm diameters		
	Iron functionalized chitosan nanofiber	─NH, ─OH, and C─O functional groups are responsible for arsenate uptake	Arsenate removal from water	[38]
	Ferric hydroxide ($(Fe(OH)_3$) coated cellulose nanofibers	Fibers diameters of 40–100 nm	Removal of phosphate from wastewater	[39]
		Fe weight percentage of 38.8%		
	Poly(acrylic acid) (PAA) and poly (glycidyl methacrylate) modified cellulose nanofibers	Fiber diameter range of 200–500 nm	Removal of Cd from water	[40]
Sensing applications	Chitosan nanofibers/ gold NPs	ChOx[g] immobilized on nanofibers	High sensitivity and selectivity to cholesterol	[41]
		Uniform formation of nanofibers		
		50–100 nm diameter		
	Acetylcholinesterase immobilized chitosan-PVA nanofibers	Homogenous fibrous lattice structure	Pirimiphos- methyl detection in olive oil	[42]
		Diameters of 100 nm		
	Cellulose nanofiber containing red cabbage	Porous structure with biocompatibility and tensile strength	pH monitoring	[43]
	Cellulose nanofibers with AgNP coating	3D flexible nanofibers network	Rapid and sensitive detection of TBZ[h] pesticides	[44]

(*continued*)

Table 1 (continued)

Main application	Carbohydrate nanofiber	Structural properties	Highlights	References
Enzyme immobilization	Chitosan nanofibers	Trypsin immobilized by covalent binding	Long-term storage stability and high reusability	[45]
	Chitosan nanofibers	150–200 nm diameter Immobilization of lysozyme via cross-linking	Long-term activity	[46]
	Alginate nanofibers with PVA or PEO	Immobilization of lipase	Effective and enhanced stability	[47]
	Chitosan nanofiber	Fiber diameter of 80–150 nm Lipase immobilized using glutaraldehyde coupling reagent	High lipase loading, activity retention, thermal stability, reusability, and storage stability	[48]

[a]Three-dimensional
[b]Poly(ethylene glycol)
[c]Poly(DL-lactide-coglycolide)
[d]Silver nanoparticles
[e]Sodium alginate
[f]Cellulose acetate
[g]Cholesterol oxidase
[h]Thiabendazole

On the other hand, carbohydrate-based nanofibers have been processed by various methods in which electrospinning is the most common practical method because of its simplicity and capability to fabricate large-scale continuous fibers. This method could be used for various materials with different nature and structure from natural to synthetic polymers. Final product can be achieved with micro- to nanoscale components and high-throughput production. Electrospun nanofibers provide properties including very rapid formation process, large specific surface area per unit mass, high porosity, and appropriate mechanical properties [1]. These characteristics make them promising candidates in applications like tissue engineering scaffolds, antibacterial materials, drug delivery systems, wound dressing, sensors, and environmental purification applications. In addition, some other synthesis methods have also been used to fabricate carbohydrate nanofibers. For example, Nasri-Nasrabadi et al. [12] produced porous starch/cellulose nanofiber composite via combination of film-casting, salt-leaching, and freeze-drying methods; ultimately, final ultrasonic mechanical treatment used for extracting nanofibers. Another study fabricated chitosan/silica hybrid nanofibers using sol-gel-derived hybrid nanofibers containing chitosan solution and then electrospinning [13]. Furthermore, self-assembly has been introduced as a simple and efficient method for nanofiber fabrication. Paclitaxel (PTX) core and chitosan shell nanofiber structure are formed by ultrasonication of mixed solution, dialyzation of concentrated solution, and finally freeze-drying; the hydrophilic and flexible product used to prepare drug-eluting stent [14]. This method showed more convenience in synthesis method especially for slow drug release applications compared to electrospinning.

Carbohydrate Nanofibers Applications

Tissue Engineering

In this section applications of carbohydrate nanofibers like alginate, chitin, chitosan, and cellulose in engineering of various tissues are summarized. Structural properties and biocompatible nature of carbohydrates especially in nanofiber forms could be advantageous for this promising field. In tissue engineering, major trend is fabrication of cell scaffold that mimics the extracellular matrix (ECM) of cells for tissue and organ defects. Many types of natural and synthetic polymers have been used for scaffold fabrication and in result tissue engineering applications. Successful results of scaffold-based tissue engineering depend on better simulation of ECM in regard to 3D porous structure, facilitating cell attachment and growth, appropriate biocompatibility and biodegradability, and controllable physicochemical properties. Carbohydrate nanofibers can successfully mimic the fibrous structure of cells' ECM. In addition, their 3D porous structure could be useful for creating in vivo-like environment. Relative biocompatibility and biodegradability of carbohydrates make them safe scaffold sources; however their physicochemical properties must be customized in specific tissue. Alginate nanofiber scaffolds significantly supported attachment, spreading, and proliferation of human dermal fibroblast cell, particularly in cell adhesive peptide (GRGDSP) modified nanofiber group with minimal cytotoxicity [21]. Emulsion electrospinning of SA (dispersion phase) and PLA (continuous phase) has been conducted for fabrication of composite nanofiber membranes with good hydrophilic and mechanical properties [49]. In addition, bone tissue regeneration was achieved by rat calvarial osteoblast culture on hydroxyapatite/alginate nanocomposite fibrous scaffolds. Cells showed multiple filopodial formation with natural morphology, and attachment was more stable on composite nanofibers compared to alginate nanofibers [50].

Usually application of chitosan electrospun nanofibers is in combination with other polymers like PEO [7], PLA [8], and collagen [8]. For example, chitosan/PVA nanofiber scaffold is fabricated as a wound dressing for diabetes mellitus-induced skin ulcers [19]. In vitro experiments showed that composite structure had high moisture vapor transmission rate and good antimicrobial activity without cytotoxicity. Treatment of rats with nanofiber scaffolds showed significant acceleration in diabetes wound healing (Fig. 1). Another study fabricated a hybrid scaffold including electrospinning of chitosan with 3.6 wt.% PEO and silica precursors for bone repair and regeneration. Bone-forming 7F2 cell culture on scaffold showed cytocompatibility and enhancement in cell attachment and proliferation for more than 7 days [13].

Electrospun CA mats are synthesized and then hydrolyzed to cellulose nanofibers [18]. Alternative chitosan and alginate are coated on nanofibers by layer-by-layer (LBL) self-assembly technique. Characterization experiments showed loosely packed cylindrical fibers with average diameter of 383 nm and successful bilayer coating and existence of chitosan and alginate on the structure. Biological experiments with Beas-2B human bronchial epithelial cells reported good biocompatibility. In

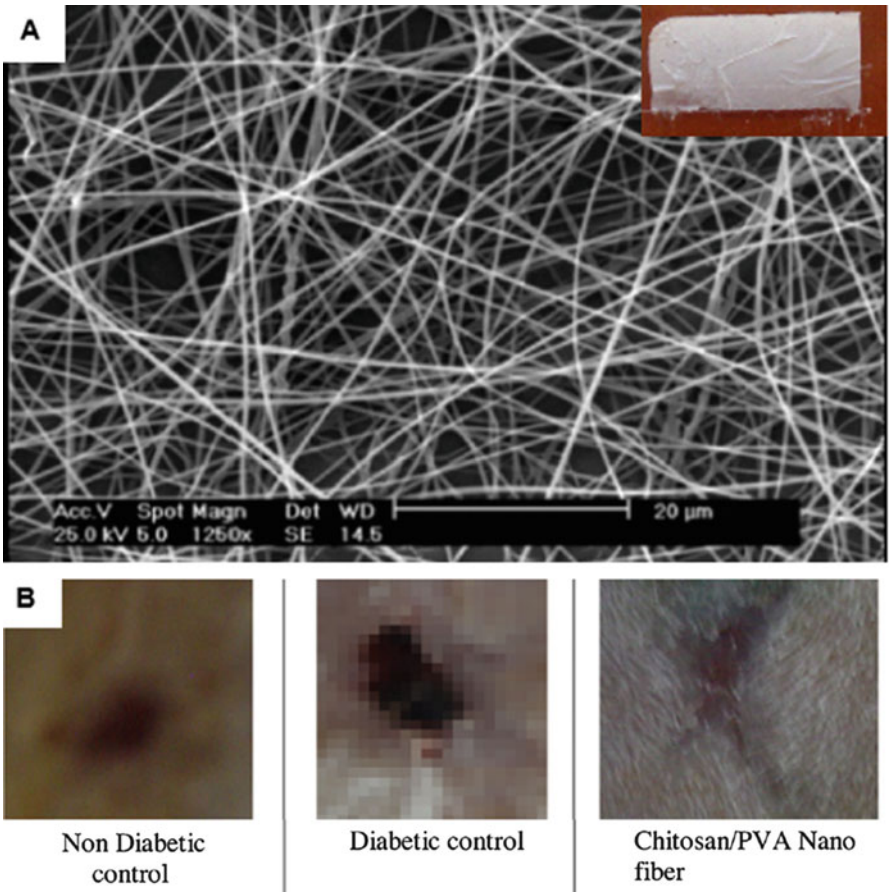

Fig. 1 Characterization and application of chitosan/PVA nanofibers. (**a**) SEM image of nanofibers (inset shows the dressing). (**b**) Photographs of macroscopic appearances of wounds in different groups after 14 days (Reproduced from [19] with permission from Elsevier)

addition, better adhesive and 3D constructions with uniform cell cluster distribution are reported in the outermost layer of chitosan group in comparison with the outermost layer of alginate and cellulose groups. Starch/cellulose nanofiber composite was synthesized by salt-leaching technique with 40–90 nm diameter and interconnected porous morphology [12]. In vitro experiment on isolated rabbit chondrocytes showed improved cell attachment and proliferation with good biodegradability. In regard to evaluate the advantages of carbohydrate-derived materials in tissue regeneration, a comparative study has been conducted on neural tissue engineering of chitosan, CA, and polyethersulfone (PES) electrospun nanofibers with rat PC12 cell line and human neural stem cell culture [17]. Although there was no cytotoxicity in all groups, proliferation was higher in carbohydrate-derived scaffold compared to PES, showing

advantageous properties of carbohydrate materials in tissue regeneration. In addition neuronal differentiation of cell types was higher in chitosan group. In spite of suitable results in cellulose scaffolds, chitosan can be a better choice in neural tissue engineering applications.

Antibacterial Applications

For decades, microbial infections are one of the most challenging problems in medical and nonmedical fields, from lab experiments to clinical treatments. Prevention of infections could be useful in food industry, textiles, and clinical problems like wound and urinary infections. Several approaches have been proposed for fabrication of antibacterial products like wound dressing, stents, textiles, food packages, and metal coatings. Alongside, different natural and synthetic materials have been used in the related fabrication process. However, still microorganism infections are challenging issue in different industries and clinical fields. This section aims recent applications of carbohydrate nanofibers for antibacterial products. Several carbohydrates have been introduced for their antibacterial properties or potential applications in delivery of antibacterial/antioxidant agents. Among them chitin and chitosan show appropriate antibacterial nature and extensive potential applications in this field. Several studies have been used from chitosan itself as an antimicrobial agent against bacteria, fungi, and yeasts and as an antioxidant. Blue crab's shell-derived chitosan nanofibers showed antimicrobial and antioxidant activities. Inhibition zone diameter assay showed antibacterial activity of about 20 mm for human bacterial pathogens (like *Escherichia coli* and *Staphylococcus aureus*), about 16 mm for fungal, and 15 mm for fish bacterial pathogens. Antimicrobial activity of chitosan comes from the presence of free amino groups and degree of chitosan deacetylation which depend on derivation methods. Chitosan deacetylation degree variation is between 30% and 95%; higher degree causes more antibacterial activity [23]. Two methods commonly used in food industry, ferric ion reducing power activity results of EC_{50} 6.16 and free radical scavenging activity of DPPH (IC_{50}, 5.99), showed antioxidant activity of the chitosan. Altogether, these results show that chitosan can be used as a natural, nontoxic antioxidant and antibacterial agent, particularly in food industry. However, optimum deacetylation degree and concentration of chitosan should be achieved for most appropriate results in every specific application.

Regarding the fact that pathogens always use new defense mechanisms against antibacterial agents, development of more efficient agents is necessary. In this regard, a promising approach is using synergistic antibacterial effects of carbohydrate nanofibers with other antibacterial materials like AgNPs or delivery of antibacterial agents. For a long time, Ag materials have been used as an antibacterial agent in traditional and industrial manners. Several studies have been reported on preparation of chitosan nanofibers in combination or coating with AgNPs for antibacterial applications. Different ratios of AgNPs mixed with chitosan solution and electrospun nanofibers of the composite are obtained and freeze-dried (Fig. 2) [26]. SEM and TEM images showed homogeneous nanofibrous structures with

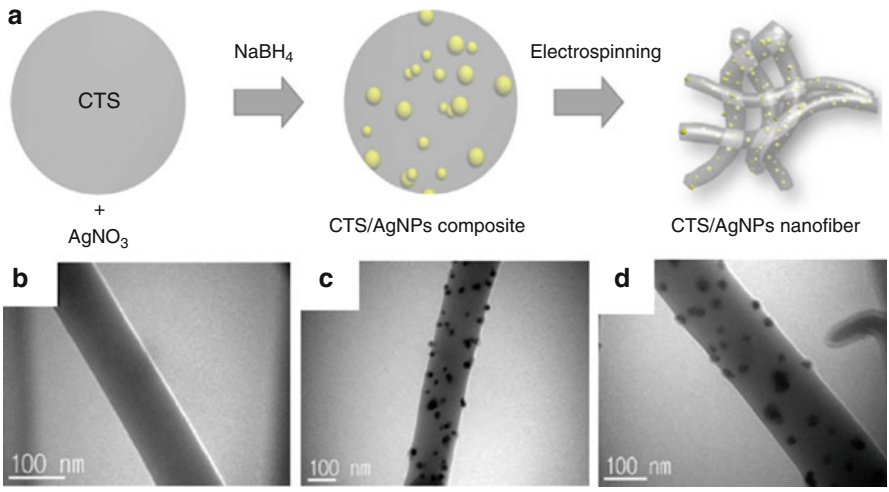

Fig. 2 Chitosan-AgNP nanofibers for antibacterial applications. (**a**) Schematic synthesis of chitosan-AgNP nanofibers, (**b**–**d**) TEM images of chitosan nanofibers and chitosan-Ag nanofibers: (**b**) chitosan nanofibers, (**c**) chitosan/chitosan/AgNPs = 50:50, (**d**) chitosan/chitosan/AgNPs = 50:50 after neutralization (Reproduced from [26] with permission from Elsevier)

about 126 nm diameter and well distribution of NPs without any abnormal morphology (Fig. 2). Antibacterial activity evaluation of the composite nanofibers on gram-negative *Pseudomonas aeruginosa* and gram-positive methicillin-resistant *Staphylococcus aureus* (MRSA) showed significant effectiveness against both types compared to pure chitosan nanofibers. In addition, increase in AgNP quantity allowed enhancement of antibacterial activity. Extensive researches have been conducted in combination of different types and concentrations of Ag nanomaterials with chitosan nanofibers with excellent antibacterial activity against different microorganisms. These studies are important in challenging clinical issues like antibiotic-resistant infections and for fabrication of more efficient medical instrument like wound dressing and stents.

Another study used AgNPs containing electrospun chitosan/PEO nanofibers as an implantable delivery vehicle of chlorhexidine and Ag ions. Short- and long-term treatments proved antibacterial effect by release of chlorhexidine and AgNO3 against *Staphylococcus aureus* (Fig. 3) [27]. Moreover, in vitro antibacterial effects conducted on fabricated honey, PVA, chitosan nanofibers (HPCS) were investigated by loading of alone *Allium sativum* aqueous extract (AE) alone or in combination with *Cleome droserifolia* (CE). HPCS-AE and HPCS-AE/CE nanofibers showed biocompatibility and complete inhibition of *Staphylococcus aureus*, while HPCS-AE/CE had mild antibacterial activity against MRSA, both compared to commercial dressing Aquacel Ag. In addition, in vivo studies showed enhanced wound healing process by both nanofibers in comparison with untreated control, and HPCS-AE showed enhanced wound closure rate compared to Aquacel Ag [51].

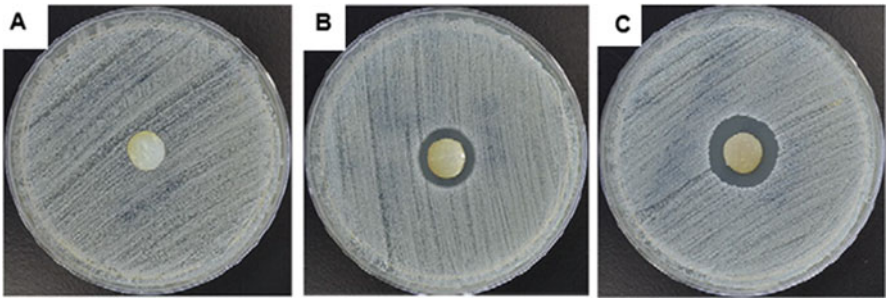

Fig. 3 Antibacterial effects of AgNPs containing electrospun chitosan/PEO nanofibrous structure. (**a**) Control group (without any antibacterial agent), (**b**) 5 wt% AgNO3 after 4 days, (**c**) both 60 μg chlorhexidine and 5 wt% AgNO3 (Reproduced from [27] with permission from Elsevier)

Drug Delivery Systems

In recent years, pharmaceutical researchers have been faced with new challenges like controlled drug delivery and control on fabrication methods of drug vehicles, which lead them to introduction of unprecedented drug delivery systems. Researchers seek controllable way for fabrication of drug vehicles and control of drug delivery and release. Emergence of nanotechnology proposed novel nanomaterials with potential applications in biomedical fields including pharmaceutical science. Various kinds of nanomaterials, such as nanofibers with different physicochemical properties, and various synthesis methods make them interesting choices for drug and other biomolecule delivery systems. Nanofibers, including carbohydrate ones, have been used extensively in drug delivery applications in implant, stents, wound dressing, and transdermal drug delivery systems. Electrospinning as the main approach of synthesis of carbohydrate nanofibers introduces a simple, cost-effective, and versatile synthesis method. This versatility can be used for fabrication of nanofibers with different morphology, diameter, porosity, composition, and surface area by changing the process parameters. Thus, these benefits make electrospinning and carbohydrate nanofibers advantageous for drug delivery to specific site using different ways [52]. In this section, various carbohydrate nanofibers with different composition and structures and their applications for delivery of drugs to specific tissue or organ will be reviewed.

The mixture of PTX and chitosan solutions under sonication allowed nanofiber synthesis and non-covalent interactions of PTX and chitosan [14]. Core-shell structures of chitosan-PTX were confirmed by characterizations, locating PTX in the core and chitosan on it as the shell (Fig. 4). Low cytotoxicity and good hemocompatibility of the structures confirmed the idea of potential applications in drug-eluting stents. More experiments showed successful coating of nanofibers on metal stents with enough flexibility and few platelet adhesions. In addition high drug loading content of more than 40% wt is obtained with controllable drug release (Fig. 4). A mixture of PEO, SA, and sodium ibuprofen (SI) was used to fabricate electrospun nanofiber-based pulsatile drug delivery system [29]. SI crystallites embedded PEO-SA matrix obtained. Two-stage mechanism of model drug release was shown at pH 3, first rapid burst release,

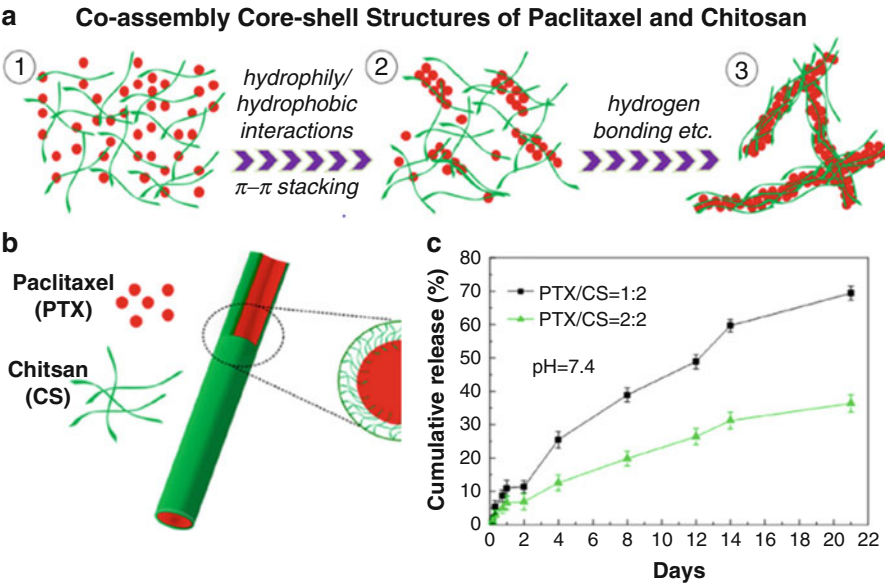

Fig. 4 Chitosan-PTX nanofiber drug delivery system. (**a**, **b**) Molecular co-assembly mechanism of PTX and chitosan with core-shell structure, (**c**) slow drug release profile of PTX/chitosan (1:2, 2:2) nanofibers in PBS buffer solution (pH 7.4) over 21 days (Reproduced from [14] with permission from Elsevier)

120–150 min with no release, and final stage of remaining drug release. SI contents of nanofibers controlled burst release, and the amount of SA controlled period between the first and final drug release, resulting in a tunable pulsatile drug release system.

An interesting novel approach of drug delivery is triggering of carrier by one or multiple internal and/or external stimuli. In recent years, several stimuli responsive materials and their drug delivery systems have been proposed. Triggering of carrier by pH, temperature, redox conditions, or electrical, magnetic, and mechanical stimuli causes disassembly of the structure followed by cargo release. Stimuli-responsive drug delivery could also be useful for loading and release of multiple diagnostic and/or therapeutic agents [53]. Bacterial cellulose nanofiber and SA are combined to fabricate a drug delivery system with pH- and electro-responsive characteristics. Changing of pH from 1.5 to 11.8 and electric field changing from 0 to 0.5 V increased Ibuprofen release. Decreased and increased drug release could be possible by alginate protonation, low swelling ratio and alginate deprotonation, and high swelling ratio of the structure, respectively [30].

Filters and Adsorbents

Air and water pollution produce many risks for mankind health and survival. Pollution of environment will be more dangerous due to unlimited industrial

development of the world. Pollution of air and water sources by different contaminants, like radioactive species such as U^{238}, Cs^{137}, and I^{131}; transuranium elements such as plutonium, curium, and neptunium; and biological contaminants like viruses needs emergency attention of scientists and principals. In this regard different kinds of water adsorbents and air filters have been introduced. Different adsorbent materials like clay (such as montmorillonite and kaolinite), polymers containing adsorbents, and copolymer hydrogels are used as water adsorbents [33]. On the other hand, air pollutants like haze are serious concern in different countries. In addition, ultrafine particles, like NPs, are becoming common air contaminant with dangerous health problems. Because of these concerns, fabrication and using of efficient adsorbents and filters are primary requirement for future clean environment [33, 37]. Different nanofibers particularly electrospun fibers are used for fabrication of effective environmental adsorbents and filters. Properties of nanofibers particularly carbohydrate fibers like appropriate physicochemical characteristics, high surface area, high aspect ratio, and cost-effective and environmentally friendly fabrication methods make them ideal choices for purification applications. However, functional properties of nanofibers must be optimized, such as reducing diameter while maitaining the effective performance [37].

In this section different methods of application of carbohydrate nanofibers for filters and adsorbents and their examples are discussed. Different approaches have been used for applying of carbohydrate nanofibers in fabrication of adsorbents and filters. One approach is fabrication with carbohydrate nanofibers alone. Cellulose nanofibers with 5 nm diameter and average pore size diameter of 20 nm were fabricated by oxidation treatment of carbohydrate pulps/powders for ultrafiltration of oil/water emulsions [32]. Excellent permeation flux was reported by cellulose nanofibers with tenfold higher than commercial ultrafiltration membranes (PAN10 and PAN400) with above 99.5% rejection ratio. Additional assay of MS2 bacteriophage testing confirmed functional properties of cellulose nanofibers like negatively charged surface and high surface-to-volume ratio allowed high virus adsorption capacity. Similarly, cellulose nanofibers with 5–10 nm diameter were used for adsorption and removal of radioactive UO_2^{2+} in water [33]. In another study of this approach, chitosan/polycaprolactam nanofibrous filter paper is fabricated by electrospinning method. The structures contained asymmetric, flexible nanofibers with 97 nm diameter and average pore diameter of 301 nm and porosity of 69.5%. Nanofibers showed high adsorption of toxic chromium (VI) (Cr (VI)) (maximum of 114.7 mg g^{-1}), and amino groups of chitosan reduced Cr (VI) to the less toxic form Cr (III) (Fig. 5) [36].

Another main approach is fabrication of filters and adsorbents with combination of carbohydrate nanofibers and other materials like NPs. Combination of chitosan hybrid nanofibers with AgNPs is fabricated in production rate of 50 g/h by needleless electrospinning method for air filtration applications. Nanofibers had smooth uniform morphology with 25–60 nm diameters and 2.9 nm deposited AgNPs. Hybrid nanofibers showed excellent water durability, stable microstructure, filtration efficiency of more than 99% for NP aerosol removal, and daily productivity of above 1.2 kg [37]. Similarly, removal of trace arsenate from water was achieved

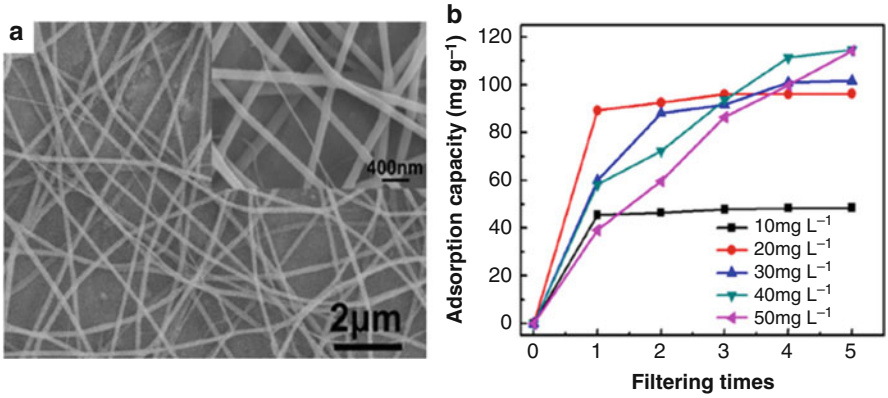

Fig. 5 Chitosan/polycaprolactam nanofibrous filter paper. (**a**) SEM images of nanofibers (inset is the high magnification), (**b**) relation between the adsorption capacity of the filter with the increase of Cr (VI) initial concentration (Reproduced from [36] with permission from Elsevier)

with iron functionalized chitosan electrospun nanofiber [36]. In another study, ferric hydroxide ((Fe $(OH)_3$)-coated cellulose nanofiber was used for the removal of phosphate from wastewater [39]. Adsorption capacity of 142.86 mg/g is obtained by this structure which was superior compared to traditional adsorbents. This adsorbent performs in different pH conditions by electrostatic attraction and ligand exchange mechanism. Similarly, PAA and poly (glycidyl methacrylate)-modified cellulose nanofiber membrane were used for removal of Cd from water with maximum capacity of 160 mg/g [40].

Sensing Applications

Sensor devices are designed to study the presence of specific species and measure their quantity in different media. Similarly, biosensors are designed for recognition of target by using biological entities like antibody or sensing of a biomolecule. For example, glucose biosensors are the most famous examples of commercialized biosensors in the last 50 years. Most optimized behavior of sensors depends on different factors like sensitivity, response time, signal stability, reproducibility, and reversibility. In addition, the effects of working environment are important like industrial factories or biological samples like blood [43, 54]. Some advantages of nanofibers including carbohydrate nanofibrous structures could be useful for fabrication of sensors and biosensors. They show distinct tunnel and 3D porous structure, high specific surface area, and excellent mechanical strength. Chemical compounds can easily diffuse and interact with recognition moieties in highly porous nanofiber structure. In addition, specific characteristics of carbohydrate nanofibers could be helpful in this field, for example, biocompatibility, water holding capability, high hydrophilicity, and appropriate physicochemical properties [43]. Thus, carbohydrate nanofibers can perform as solid support material for fabrication of sensing devices.

Different kinds of carbohydrate nanofibers have been used in sensing applications that are discussed in this section. The main strategy is application of nanofiber structure with addition of a sensing material like natural indicators or NPs. Nanofibers work as a solid substrate for introduction of sensing agents to the target environment. For example, Gomathi et al. studied on cholesterol sensor due to its importance in the diagnosis and assessment of coronary heart disease, arteriosclerosis, thrombosis, and myocardial infarction using nanofibers [41]. They fabricated ChOx immobilized chitosan nanofibers/gold NPs (CSNFs/AuNPs). Chitosan nanofibers are fabricated by oil/water emulsion method and gold NPs loaded by electrochemical deposition. SEM images showed uniform formation of nanofibers with bead-free bundle shape, interconnectivity, and 50–100 nm diameter. In addition spherical NPs on nanofibers with size rage of 500 nm–1 μm were shown (Fig. 6). Results of cyclic voltammetry, hydrodynamic voltammetry, and amperometry showed high sensitivity (1.02 μA/μM) with low response time (5 s) and good reproducibility. In addition, linear response to cholesterol with high selectivity was obtained by this composite.

Another study used cellulose nanofiber containing red cabbage for pH monitoring [43]. Red cabbage is a natural pH indicator that its color changes in pH range. Addition of red cabbage is optimized in regard to concentration and color response efficiency without significant morphological and structural changes. In addition, porous structure of cellulose nanofibers and their good biocompatibility and tensile strength can help in the functional application of this structure. Color variation with CIELab methodology showed high responsibility in pH 2–10 (Fig. 7a). These results could be useful in food smart packaging of spoilage process in perishable foods.

A composite of cellulose nanofibers with AgNP coating was fabricated as a substrate for surface-enhanced Raman spectroscopy (SERS). Rapid and sensitive detection of TBZ pesticides in apples was achieved with this structure (Fig. 7b). SERS method enhances Raman signals of analyte molecules and produces distinctive spectral features. Traditional SERS substrates are rigid, expensive, and not environmentally friendly; thus biocompatibility, flexibility, and cost-effectiveness of nanofiber structures could be advantageous for this field. Large surface area and porous-3D nature of nanofiber networks allow increase reaction of target molecule with surface NPs and in results increase SERS signal intensity [41].

Enzyme Immobilization

Enzyme immobilization with different approaches like covalent binding, encapsulation, and entrapment has been introduced for potential application of enzymes in different fields. Activity of enzymes may be limited by environment and reaction product, resulting in decrease in activity. In addition, stability and reusability are other challenges of practical application of enzymes. Enzyme immobilization methods provide situation for reducing these limitations. Enzyme immobilization separates enzymes from their products and in result facilitates enzymatic activity. In addition, long-time usability of enzymes would be possible by using enzyme

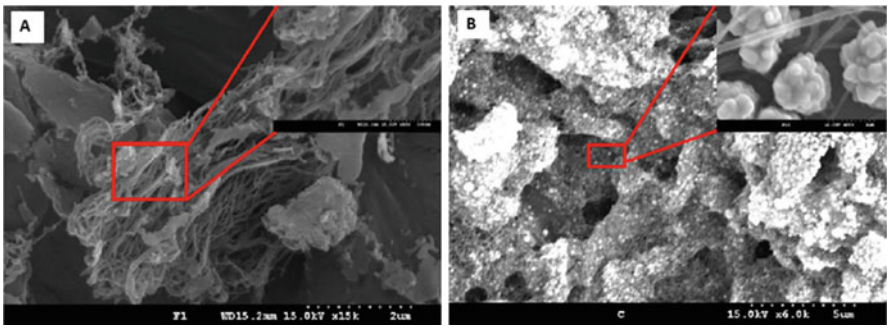

Fig. 6 FE-SEM images of (**a**) nanofibers and (**b**) nanofiber-NP structures with ChOx (Reprinted from [41] with permission from Elsevier)

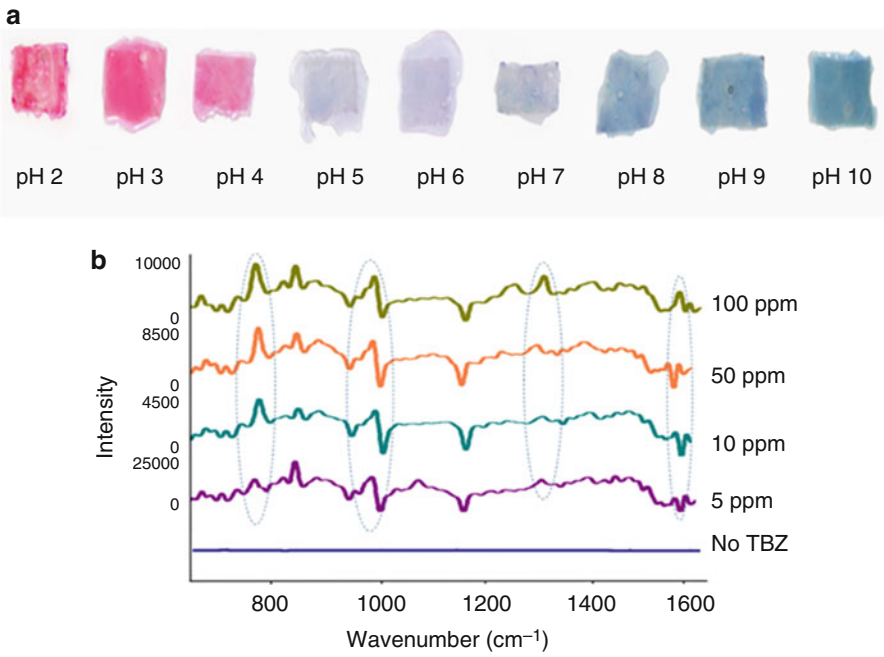

Fig. 7 Cellulose sensing devices. (**a**) pH indicator labels show different colors at different pH values (Reprinted from [43] with permission from Elsevier). (**b**) SERS spectra of different concentrations of TBZ solutions (Reprinted from [41] with permission from Elsevier)

immobilization methods [55]. In regard to avoiding immobilization problems like reducing enzyme activity, application of appropriate immobilization method and structural support is necessary. In addition, reducing chemical nature change of enzymes and optimization of immobilization and enzyme activity situation should be considered [55]. Therefore, seeking for proper structural support with lowest

inappropriate interaction with enzyme in a cost-effective manner is an interesting research field.

Properties of the matrix for immobilization like material composition and physicochemical characteristics influence on the process. Proper mechanical properties of support material induce better stability and long-term application. Excellent properties of nanomaterials and nanofibers allow enhanced stability and enzyme activity. Significant high surface-to-volume ratio of nanofibers allows a minimum decrease in enzyme activity under immobilization process. These properties and nanoscale size of enzymes induce synergistic collaboration for better outcomes. Furthermore, 3D porous nature of nanofibers including carbohydrate nanofibers allows enhanced diffusion of enzyme molecules, while other nonporous materials and NPs represent serious limitation in this issue [55]. In regard to interaction types, covalent binding presents more appropriate outcomes in comparison to other interactions like entrapment and encapsulation. Covalent binding represents stable enzyme immobilization due to reducing enzyme leakage. In this regard, nanofibers show excellent potential properties due to large specific ratio. Therefore, more functional groups are present on nanofiber surface for interaction with enzyme molecules. For example, hydroxyl groups of cellulose nanofibers and amine and/or hydroxyl groups of chitosan nanofibers have been used for covalent immobilization of enzyme molecules [45, 55, 56].

Different carbohydrate nanofibers have been used in enzyme immobilization technique using mentioned properties of nanomaterials that are reviewed in this section. Biocompatibility, nontoxicity, and hydrophilicity of chitosan nanofibers have been used as a large surface to volume membranes for immobilization. Electrospun chitosan nanofibers are prepared by Nanospider™ technology and trypsin immobilized by covalent binding [45]. In this regard, two methods of immobilization are used, oxidation of chitosan and carbodiimide coupling in addition with immobilized trypsin (Fig. 8). A one-step EDC+sulfo-NHS method (carbodiimide one-step protocol) showed maximum trypsin activity of 209.8 ± 0.6 IU/cm^2, while trypsin adsorption showed 2.49 IU/cm^2. Using this structure, long-term storage stability and high reusability are achieved with no cytotoxicity on growth of HeLa cells. In addition, no undesirable skin reactions are showed by in vivo tests.

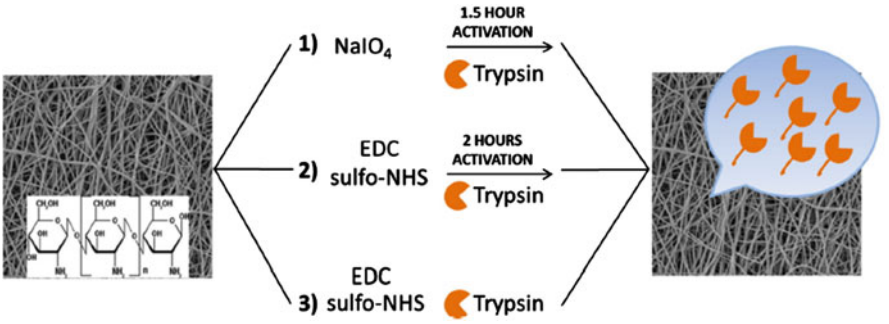

Fig. 8 Different trypsin coupling methods to the chitosan nanofibers (Reprinted from [45] with permission from Elsevier)

Similarly, chitosan nanofibers with 150–200 nm are used for immobilization of lysozyme via cross-linked enzyme aggregate method with 62.3 mg/g maximum amount of nanofibers (Fig. 9) [46]. In addition, 75.4% and 76% of initial activity are retained after 80 days and 100 consecutive uses, respectively.

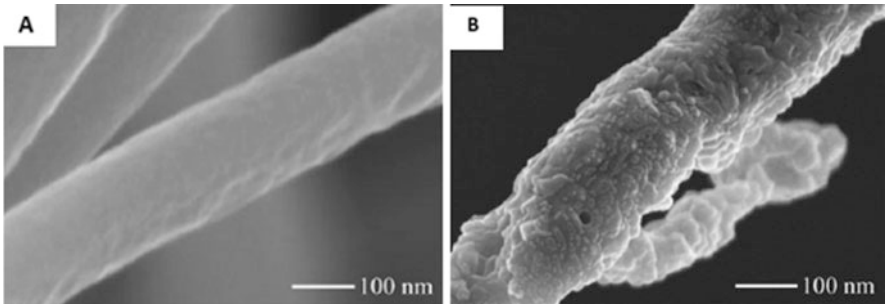

Fig. 9 FESEM images of the (**a**) chitosan nanofibers and (**b**) lysozyme immobilized on chitosan nanofibers (Reproduced from [46] with permission from Elsevier)

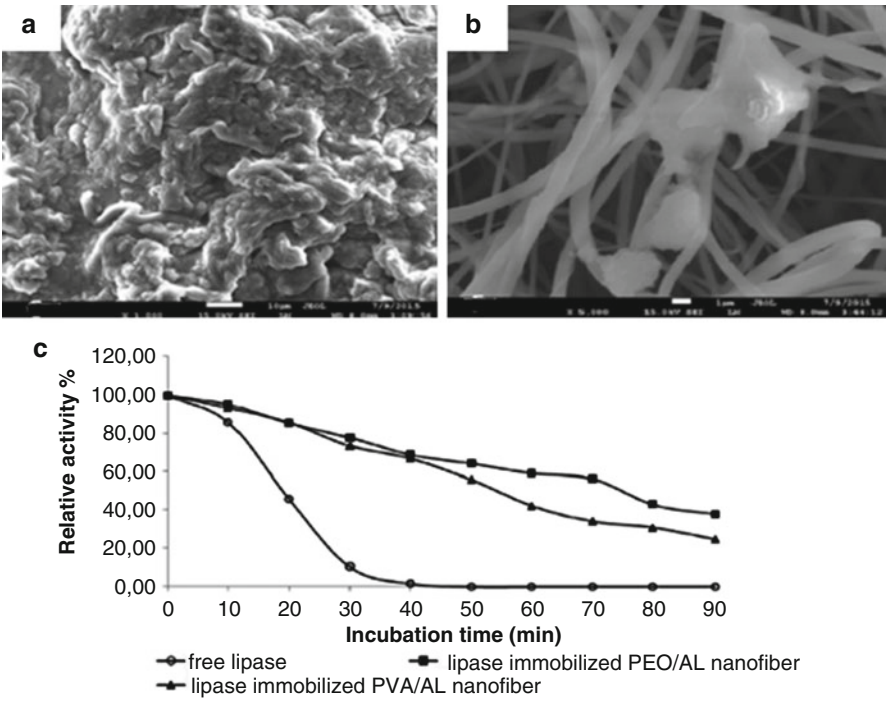

Fig. 10 Lipase immobilized alginate nanofibers. Immobilization of lipase on electrospun (**a**) PEO-alginate and (**b**) PVA-alginate nanofibers (**c**) Thermal stability of lipase in different groups at 70 °C (Reproduced from [47] with permission from Elsevier)

Several studies developed immobilization with other carbohydrate nanofibers and enzymes. For example, immobilization of lipase is obtained on electrospun alginate nanofibers with PVA or PEO. Both groups showed almost 65–70% activity in 40–60 min, while free lipase lost its activity. Both groups retained all activity until pH 9, and 60% of activity in PVA and PEO groups is maintained after 14 and 7 reuses, respectively (Fig. 10) [47]. The results of this study introduce a simple, versatile, and economical approach for industrial applications of enzyme immobilization. Application of cellulose nanofibers in enzyme immobilization has been reviewed by Sulaiman et al. with advantages like high surface area-to-volume ratio, different functional groups, and high flow rate of enzymes [55].

Conclusion

Carbohydrates have attracted extensive attentions in different fields of biology, medicine, and engineering. Carbohydrate nanofibers have properties that are related to their material characteristics and fabrication methods. Carbohydrates are inexpensive materials, easily available, and renewable resources with hydrophilicity and biocompatibility. Electrospinning is the major approach of carbohydrate nanofiber fabrication mainly due to its simplicity and capability of large-scale production. These advantages make them ideal choices for different applications including tissue engineering, antibacterial materials, drug delivery systems, and environmental purification. First, the fibrous structure of carbohydrate nanofibers represents the in vivo-like scaffold for tissue regeneration with appropriate biocompatibility. Second, natural antibacterial properties of chitosan and combination of carbohydrate nanofibers with other antibacterial materials could be useful in medical and nonmedical applications as natural, nontoxic antioxidant and antibacterial agents. Third, carbohydrate nanofibers with advantages like simple, cost-effective, and versatile synthesis methods and versatility in physicochemical properties are promising in controlled drug delivery systems. Fourth, carbohydrate nanofibers with high surface area, high aspect ratio, and cost-effective and environmentally friendly fabrication methods are advantageous for fabrication of water adsorbents and air filters. Fifth, 3D porous structure, high specific surface area, and appropriate biocompatibility of carbohydrate nanofibers could be useful in fabrication of industrial and medical sensors. Additional in vivo experiment studies especially by large-scale production of electrospun fibrous scaffolds would be useful for clinical applications. Application of carbohydrate nanofiber-based products in antibacterial food packaging and medical device, water adsorbents, and air filters is a promising field of research and industry. On the other hand, more extensive researches are needed for applying of carbohydrate nanofibers in drug delivery systems, industrial detection sensors, and medical biosensors. However, functional application of abovementioned potentials needs comprehensive research studies and collaboration between university engineers and industrial factories.

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