



Applications of Cellulose Nanocrystals: A Review

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Cellulose Nanocrystals (CNCs) have a great potential as an excellent nanomaterial for synthesizing advanced materials. To date a lot of research has been done both in terms of the modification of CNCs as well as in developing the CNCs applications. This work is a review of widespread CNCs applications in papermaking industry, reinforcing filler for polymers, shape memory polymers, healable polymeric materials, food industry, drug carrier in pharmaceutical industry, supporting matrix for catalysts, and nanomedicine. The properties of the unmodified CNCs and modified CNCs, the CNCs-free and CNCs-containing materials, and the CNCs use patterns are also described.

Keywords: Cellulose nanocrystals; application; reinforcing filler; materials; matrix

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1. Introduction

During the past decade, with the overexploitation and exhaustion of fossil resources and serious environmental deterioration, there is an increasing interest in the development of applications of low-cost and renewable resources.¹ Cellulose, one of three main components in botanic field, is the oldest and richest natural polymer on earth. The special and superior properties of cellulose and cellulose derivatives include low density, biodegradability, renewability, biocompatibility, extensive chemical modification, etc. Cellulose nanocrystals (CNCs) can be produced from the natural cellulose by acid hydrolysis or enzymatic method.

CNCs, also known as “cellulose whiskers”, “cellulose nanowhiskers” and “nanocrystalline cellulose”, have structural dimensions in nanoscale width and length.² The cellulose sources include bacterial cellulose, cotton, ramie, tunicate, soft wood and hard wood, etc. Although the sources of CNCs are different, the rod-like CNCs display a high surface area with a high amount of hydroxyl groups that give CNCs some extra natural properties, such as hyperfine structure, high transparency, high purity, high crystallinity, high strength and Young’s modulus, and high reactivity.³ These properties differ greatly from those of the regular cellulosic fibers, which enables CNCs to extend more widespread applications,⁴⁻⁶ as shown in Figure 1. In this review, the emerging applications of CNCs in papermaking, polymer, food, and pharmaceutical industries, as well as in catalysis, are summarized and the future directions are predicted.

2. Applications of CNCs

2.1. Applications in papermaking industry

CNCs are featured with high crystallinity, high degree of molecular orientation, and high mechanical strength, and display a high surface area with a high amount of hydroxyl groups, thus are commonly used in papermaking applications, as shown in Figure 2.⁷ After being added to the pulp, they form strong hydrogen bonds with the pulp fiber, and thus can be strongly bound with the fiber. The additions of CNCs together with or without cationic polyacrylamide and cationic starch in deinked pulp improved the retention of fillers and fines, and strength properties.⁷ For instance, modified CNCs improved the cationic starch-emulsified alkenyl succinic anhydride (ASA) emulsion stability. After the introduction of cationic CNCs-ASA in the paper, it was found that there was a 6 % increase in the tensile index and 11 % increase in the burst index.⁸ CNCs isolated from cotton cellulose powders reinforced the starch-based composite suspensions which were used as surface sizing agents for cellulosic paper.⁹ Salam et al. prepared CNCs from pure cellulose (Whatman paper #4) by acid hydrolysis and modified the surface with diethylenetriamine pentaacetic acid (DTPA) followed by cross-linking with chitosan (Ch).¹⁰ Then the CNCs-DTPA-Ch was introduced into the recycled paper OCC (old corrugated containerboard) as an additive to improve its tensile and other mechanical properties.

However, in spite of their strength-reinforcing effects, the high water retention capacity of CNCs limits their uses in certain applications such as paper coating materials.¹¹ This limitation is attributed to the high number of hydroxyl groups in CNCs. Thus chemical surface modification should be carried out to reduce the number of hydroxyl interactions in order to increase the hydrophobicity of paper coating. In addition, extremely high tensile strength (wet and dry

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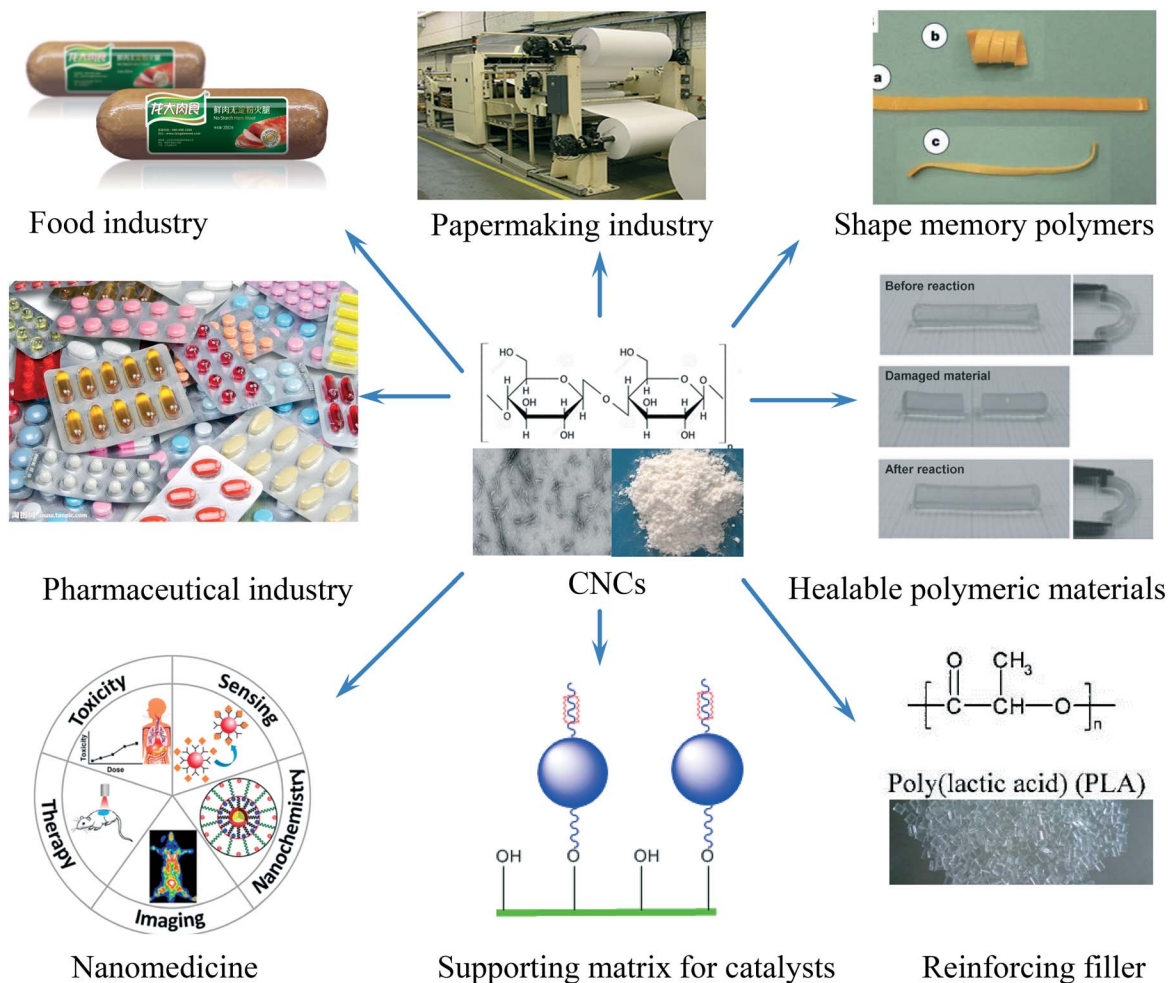


Fig. 1 A variety of CNCs applications. Adapted with permissions from (Chen, G., Roy, I., Yang, C., Prasad, P.N., 2016. Nanochemistry and Nanomedicine for Nanoparticle-based Diagnostics and Therapy. *Chem. Rev.* 116, 2826-2885), Copyright (2016) American Chemical Society; (Fiore, G.L., Rowan, S.J., Weder, C., 2013. Optically healable polymers. *Chem. Soc. Rev.* 42, 7278-7288.), Copyright (2013) Royal Society of Chemistry; (Lendlein, A., Jiang, H., Jünger, O., Langer, R., 2005. Light-induced shape-memory polymers. *Nature* 434, 879-882.), Copyright (2005) Springer Nature.

strength) and tearing resistance in machine direction, as well as air permeability are important requirements for some specialty papers (e.g. battery diaphragm paper, hand tissues, kitchen towels, packaging boards, and bottle labels).¹² Unfortunately, the wet tensile indexes of paper sheets with and without the unmodified CNCs were almost the same, which were not affected by the increase in the unmodified CNCs dosage. The oxidation of CNCs can generate aldehyde groups for crosslinking reactions or for further surface modification of CNCs. The oxidized CNCs by sodium periodate enhanced not only the dry tensile index (32.6 % higher than the control sample), but also the wet tensile index dramatically by 4 fold.¹³ Carboxylated CNCs (CCNCs) effectively improved the mechanical properties of paper made of cellulosic fiber or PVA fiber.¹⁴ Another specialty application is electro-conductive cellulosic paper. Cellulosic fiber is non-conductive, but the introduction of electro-conductive fillers such as carbon nanotubes (CNTs) in the production process imparted it with electro-conductivity. Graphene oxide (GO) with the hydrophilic oxygen-containing functional groups can improve the aqueous dispersion of CNTs while CNCs derived from cotton fibers were

used for enhancing the dispersion of CNTs/GO nanocomposites as a binder.¹⁵

2.2. Applications in polymer industry

2.2.1. Reinforcing filler for polymers. The introduction of CNCs has a very significant impact on the mechanical properties of polymer nanocomposites over the corresponding matrix materials, such as the remarkable improvements of stiffness and strength. CNCs are attractive as reinforcing fillers due to the inexhaustible supply and high specific modulus (modulus/density).¹⁶ Table 1 shows the effect of CNCs loading on the mechanical properties of CNCs-based polymer nanocomposites.

CNCs with high aspect ratios, isolated from tunicates, display the exceptionally enhanced mechanical properties in aerogels made from cellulose nanofibers and poly(vinyl alcohol) (PVA) at low filler concentrations.²³ Similarly, the superior properties of the tunicate-derived CNCs were also demonstrated by the high level dispersion of unmodified hydrophilic CNCs in the hydrophobic low-density polyethylene (LDPE).²⁴ However, CNCs with high-aspect-ratio from

Table 1 Effect of CNC loading on the mechanical properties of CNC-based nanocomposites.

Matrix	CNC addition	subadditive	Increase		Reference
			tensile strength (MPa)	Young's modulus (GPa)	
PLA	5 wt%	30 wt % PVA	-6 %	10 % (dry)	17
poly(ethylene oxide-co-epichlorohydrin)	10 wt%	5% PVA	231 %	206%	18
poly(3-hydroxybutyrate-co-3-hydroxyvalerate)	5 wt%	3 wt% PEG	85 %	115 %	19
PLA	1 wt%	Fatty acid	-7 %	5 %	20
PLA	1 wt%	-	4 %	2 %	21
unsaturated polyester	1 wt% CNCs	-	37 %	6 %	22
	1 wt% m-CNCs	-	77 %	11 %	

-Not given, m-CNCs: modified CNCs

tunicates are not a viable commercial source for CNCs due to the limited supply.²⁵ The commercially available CNCs with low-aspect-ratio, such as those derived from cotton (c-CNCs), showed the unimproved mechanical properties in dry PVA/CNC nanocomposites at even much higher CNC filler concentrations, which was attributed to the CNC aggregation.²⁶ Therefore, surfactants or surface-modified CNCs were necessary to improve the compatibility during the preparation of nanocomposites.

PVA has long been used as a surfactant to improve the dispersion of CNCs in the biodegradable polylactic acid (PLA) matrix.¹⁷ Recently, the addition of PVA improved the mechanical properties of poly(ethylene oxide-co-epichlorohydrin)/CNC nanocomposites remarkably,¹⁸ which was related to the improved dispersion of the CNCs by solution-casting. CNCs were also used to try to reinforce poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) with the low molecular-weight polyethylene glycol (PEG) as a compatibilizer through melt processing.¹⁹ However, these composites exhibited decreased strength and constant glass transition temperature. In contrast, homogeneous dispersion of CNCs by solution casting achieved better performance of the composites, e.g. improved tensile strength and modulus and increased glass transition temperature, indicating that the dispersibility of CNCs by solution casting was superior to that by melt processing.

The organic modification on the surface of CNCs essentially reduces the amount of hydroxyl groups, thus lightens the agglomeration of CNCs to ensure good dispersion of the filler in the host polymer matrix. For instance, dodecanoyl chloride esterified CNCs,²⁰ as well as the surface modified CNCs by using 2-(carbomethoxy)ethyltrimethoxysilane (2CETMS)²¹ or grafting (3-Mercaptopropyl)trimethoxysilane (A-189) via hydrogen bonding and Si-O-C covalent bonds,²⁷ were good examples for reinforcing the PLA materials. The surface modification of the CNCs improved the interfacial bonding between the filler and the matrix, and thus reinforced the PLA composite with an enhancement in mechanical properties. Introduction of reactive vinyl groups on CNC surface was also demonstrated to reinforce the unsaturated polyester matrix.²²

2.2.2. Shape memory polymers. Shape memory polymers (SMPs) are resilient materials that can recover their original permanent shape on exposure of external stimuli, such as heat, light, water, pH, etc., from a temporarily deformed shape. The addition of CNC was proved to not only enhance the stiffness of the polymer composite but also improves the shape memory properties of the polymer matrix, as shown in Figure 3. For instance, Nicharat et al. found that either phosphorylated CNCs (P-cCNCs, P-mCNCs), iso-

lated from cotton and microcrystalline cellulose (MCC), respectively, were able to enhance the stiffness and the shape memory properties of the thermoplastic polyurethane (TPU) elastomer.²⁸ A bio-nanocomposite was designed by blending the poly(ester-urethane) matrix and the functionalized CNCs by grafting poly(L-lactic acid) (PLLA) chains onto their surface. This nanocomposite exhibited excellent thermally-activated shape memory effects at 35 °C, which was mainly attributed to the enhancement of the interactions between the biocompatible PLLA functionalized CNCs and the poly(ϵ -caprolactone)(PCL)-based polymeric matrix.²⁹ Only 5 wt of CNCs content were also able to overcome the rather low strength and stiffness of poly(polyol sebacate) (PPS) materials.³⁰ It can be seen in Figure 4 that the nanocomposites with a high degree of crosslinking, e.g., poly(glycerol sebacate urethane) (PGSU) and CNCs, exhibited a unique water-active shape memory effect at temperatures between 15 and 45 °C.³¹ The water-responsive shape-memory performance was dependent on the content of CNCs. A polycaprolactone (PCL) and PEG nanocomposite network cross-linked by CNCs chemically showed excellent thermo-induced and water-induced shape-memory effects in water at 37 °C.³² In contrast, similar water-active shape-memory effects of cellulose nano-whisker/TPU elastomer (CNW/TPU) nanocomposites could be realized only under the severe conditions, i.e., wetting for 5 days and drying for 24 hours during stretching and recovery.³³

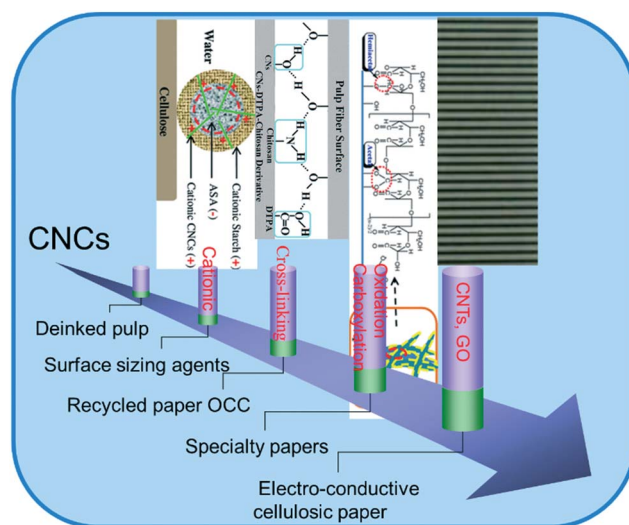


Fig. 2 Applications of CNCs in papermaking industry.^{8-10,13,15} Adapted with permissions from American Chemical Society, and Springer Nature.

Compared with water-active SMPs, the pH-induced SMPs are more suitable for the drug delivery and tissue engineering systems due to the physiological environment.³⁴ However, cellulose itself is not pH-sensitive, and thus must be functionalized with pH-sensitive moieties. Chitosan-modified cellulose whiskers (CS-CWs) were used as the stimuli-response reinforcing phase to prepare biomimetic polymer composites with TPU as the resilient matrix.³⁵ The CS-CWs/TPU composites showed shape-memory behavior in different pH environments. As shown in Figure 5, another pH-responsive shape memory polymer nanocomposite was prepared by blending poly(ethylene glycol)-poly(ϵ -caprolactone)-based polyurethane (PECU) with pyridine/carboxyl groups functionalized CNCs (CNC-C₆H₄NO₂, CNC-CO₂H).³⁶ The introduction of pyridine/carboxyl groups endowed the pH-responsiveness of CNCs via the association and disassociation of hydrogen bonding interactions among CNCs that served as the switch units of SMPs. The addition of the modified CNCs in PECU polymer matrix not only obviously improved the mechanical properties of nanocomposite network, but also transferred the pH-responsive shape memory function to the nanocomposite network.

2.2.3. Healable polymeric materials. Self-healing materials with the enhanced reliability, functionality, lifetime and remarkable mechanical performance gained an increasing interest from researchers in both academia and industry. Various stimuli-responsive attributes, such as the crack, heat, light, etc. can recombine the mechanically damaged network efficiently.

Previously, CNCs isolated from natural products which formed percolating networks within the polymer matrix were used as reinforcing fillers for self-healing polymers.^{37,38} However, these unmodified CNCs showed poor self-healing properties because their surfaces covered with only the hydroxyl groups. The unmodified CNCs were used to reinforce the supramolecular healable polymer blend via the π - π interactions between a π -electron-donating pyrenyl end-capped oligomer and a chain-folding oligomer containing pairs of π -electron-accepting naphthalene-diimide (NDI) units.³⁹ The healing rate declined with an increase in the CNC content that dem-

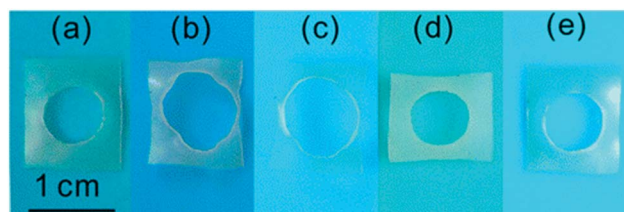


Fig. 4 Water-active shape-memory effects of pretreated PGSU6: the original shape (a), wet PGSU6 after immersed in distilled water for 1 h, the fixed deformed shape (b), dried PGSU6 after the wet PGSU6 was punched using a rod and distorted and subsequently dried at ambient temperature for 4 h, the deformed shape at the beginning of immersion in water (c), the recovered shape after a 1 h immersion in water (d), and the recovered shape after removal from water (e).³¹ Adapted with permissions from American Chemical Society.

onstrated that the unmodified CNCs only exhibited reinforcing property to afford enhanced mechanical properties but not led to self-healing. Because of the CNC aggregation, the unmodified CNCs addition should be kept at no more than 10 wt%, whereas heterogeneous nanocomposites were obtained.

Therefore, the surface of CNCs must be modified with active moieties to enable these functional properties. The modified CNCs were used to reinforce optically healable supramolecular polymers,⁴⁰ suggesting that the CNCs flow back into the healed zone as the filler. This light-healable nanocomposite was formed via the combination of a telechelic poly(ethylene-co-butylene) that was functionalized with hydrogen-bonding ureidopyrimidone (UPy) and CNCs decorated with the same binding motif, as shown in Figure 6.⁴¹ Herein the decoration of CNCs not only showed significantly improved mechanical properties but also revealed their self-healing features based on the hydrogen-bonding UPy motif. The modified CNCs and the supramolecular matrix with the same surface groups help to remedy the CNC aggregation. Thus, even the nanocomposites with a rather high CNC-UPy concentration, in which the mechanical reinforcement is very significant, exhibited very efficient and rapid optical healing.⁴¹ The comparison of unmodified CNCs and modified CNCs helps

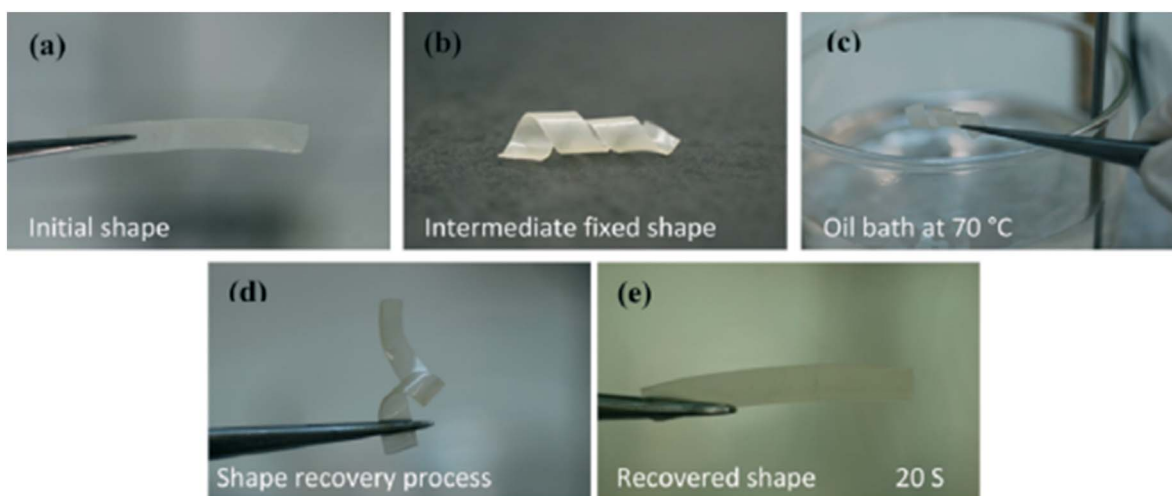


Fig. 3 Thermally-activated shape memory properties of TPU/CNC Nanocomposites, pictures showing the shape memory behavior of a TPU/10% P-mCNC nanocomposite film. (a) The initial sample was heated to 70 °C and formed into a spiral shape, and the temporary shape was fixed by cooling to ambient temperature (b). The original shape was recovered (c,d,e) upon heating the sample again to 70 °C in silicon oil.²⁸ Adapted with permissions from John Wiley and Sons.

understand the importance of the specific design of CNCs-reinforced healable polymers.

In another application, CNCs isolated from cotton were modified with diarylbibenzofuranone (DABBF)-based dynamic covalent mech-anophore to enable the self-healing property. A self-healable cross-linked polymer with DABBF was efficiently reinforced upon introducing the modified CNCs through the formation of reversible covalent bonds between the highly mobile DABBF units in the modified CNCs and the highly mobile DABBF units in the cross-linked polymer matrix.⁴² Unlike the hydrogen-bonding that offer self-healing of polymers, the healable property of this self-healing polymer composites depends on the reversible covalent bonds between two DABBF units that enable the modified CNCs and polymer matrix to retain the healing ability.^{43,44}

2.3. Applications in food industry

2.3.1. CNCs as food additives. People pay more and more attention on the application of cellulose to the food industry owing to

its odorless, colorless, high-security, and unique physiochemical properties. Cellulose does not influence the food quality so that it is used as food additives such as emulsifier, thickener, foam stabilizer, functional food ingredient, etc. CNCs can act as a stabilizer because these solid particles accumulate at the oil-water interface to form "Pickering emulsions". It is demonstrated that highly stable oil-in-water Pickering emulsions stabilized by native CNCs from different sources have been obtained.^{45,46} CNCs derived from wood pulp and the esterified CNCs by chemical modification with lauroyl chloride (C12) were able to stabilize oil-in-water and water-in-oil emulsions, respectively.⁴⁷

2.3.2. CNCs in food packaging. Food packaging as an essential part of food production keeps food fresh and avoids physical, chemical, and biological damages during distribution of the food products from the factory to the hands of millions of consumers. Among starches, proteins, PLA, cellulose, and other biodegradable polymers,⁴⁸ CNCs show the great potential because they can improve the mechanical, thermal and barrier properties of other bio-based

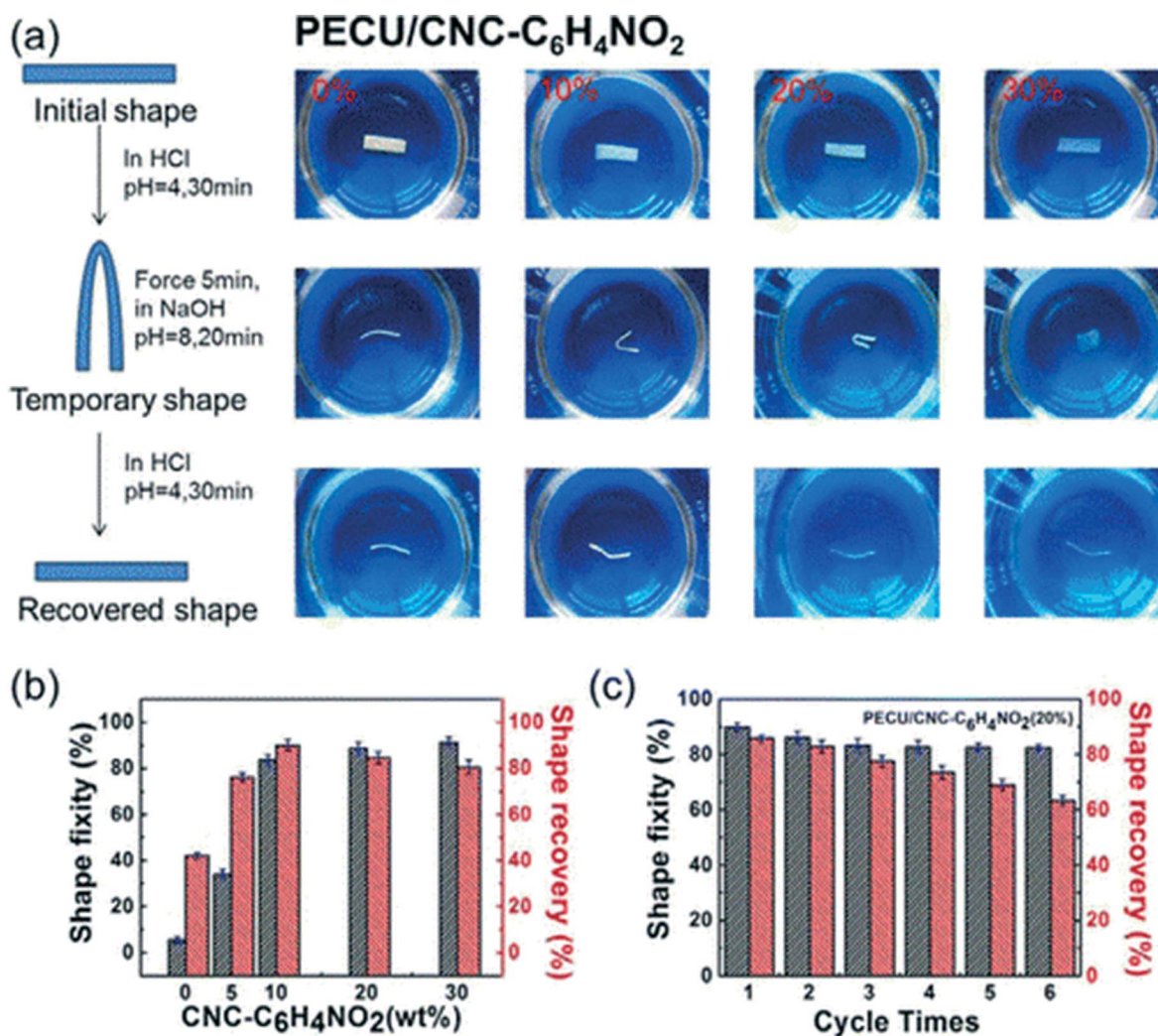


Fig. 5 pH-responsive shape memory effect of PECU/CNC-C₆H₄NO₂ film (a) Digital photos showing the shape memory process of PECU/CNC-C₆H₄NO₂ film (15 × 4 × 0.2 mm) with different CNC-C₆H₄NO₂ loading immersed in HCl solution (pH = 4) and NaOH solution (pH = 8) at room temperature. (b) Shape memory properties of PECU and its nanocomposites as a function of CNC-C₆H₄NO₂ content. (c) Shape memory properties of PECU/CNC-C₆H₄NO₂ (20 wt %) versus cycle times.³⁶ Adapted with permissions from American Chemical Society.

materials with otherwise poor properties. In particular, the barrier property of food packaging materials prevents food from direct contact with microbes, moisture or oxygen. Table 2 shows the effect of CNC loading on the mechanical properties and water vapor permeability (WVP) of biodegradable nanocomposite films. The addition of CNC increased the tensile strength and tensile modulus of the films and significantly decreased the WVP of the films. The high crystallinity of CNCs and the formation of a rigid network of bio-based matrix with CNCs through the hydrogen bonding provide physical barriers to the permeation of water.

The addition of CNCs improved not only the water vapor barrier but also the oxygen barrier properties of the bio-based food packaging materials. The influence of the nature of the CNCs on the water vapor and gas (CO₂, N₂ and O₂) permeability of films composed of CNCs was investigated.⁵⁵ The CNCs reinforced film showed weak WVP and gases barrier properties, which was ascribed to its high porosity. However, the oxygen barrier property of CNC-based biodegradable nanocomposites was improved significantly in comparison with the CNCs-free films, as shown in Table 3. This significant change may be ascribed to the CNCs-containing denser composite film with higher tortuosity factor, smaller average pore diameter, and higher bulk density.⁵⁶ Using surfactant(acid phosphate ester of ethoxylated nonylphenol)-modified CNCs (s-CNCs) could also achieve an improvement on the oxygen/water barrier of PLA-based nanocomposite films,⁵⁷ which was ascribed to the good dispersion of s-CNCs.⁵⁸ In addition, the promising food packaging nanocomposites could be created by layer-by-layer assembly of two biopolymers^{59,60} or coating of the bacterial CNCs (BCNCs) film via electrospun PLA fibres.⁶¹

2.4. Applications in pharmaceutical industry

There is a long history of using cellulose in the pharmaceutical industry. The form of current commercialized medicinal cellulose includes powered cellulose, microcrystalline cellulose (MCC), and MCC derivatives, such as carboxymethyl cellulose (CMC), ethyl cellulose, and methyl cellulose. However, the commercial use of CNCs in the pharmaceutical industry is still in the nascent stage.

2.4.1. Drug delivery carrier. Researchers have attempted several utilization forms of CNCs as the drug carrier in pharmaceutical

industry, such as the direct binding with drug, the hydrophobic associating with drug, the covalent attachment of drug, encapsulating drug, etc. as shown in Figure 7. Recently, new approaches have been developed to control drug release at the molecular level via binding interactions between the ionized drug molecules and negatively charged CNCs. The hydrolysis of the microcrystalline cellulose (MCC) using the sulfuric acid hydrolysis produces a stable colloidal water suspension of CNCs with a negative surface charge.^{66,67} It was demonstrated that CNCs were able to bind significant quantities of the ionizable hydrophilic antibiotics tetracycline and doxorubicin which were rapidly released completely in 1 day.⁶⁸ Cetyl trimethylammonium bromide (CTAB) was capable of neutralizing the negative zeta potential. Thus the CTAB-modified CNCs bind significant quantities of the hydrophobic anticancer drugs, e.g. docetaxel, paclitaxel, and etoposide, which were released in a controlled manner over several days.⁶⁸ Binding chitosan, a cationic polysaccharide to the surface of CNCs led to the formation of a novel polyelectrolyte macro-ion complex (PMC) for the potential applications in drug delivery.⁶⁹ Cationic b-cyclodextrin (CD) was bound to the surface of CNCs by ionic association to form CD/CNCs complexes that can encapsulate the hydrophobic drug curcumin.⁷⁰ Compared with pure curcumin, these nanoparticles showed enhanced cytotoxic activity against colorectal and prostatic cancer cell lines.

The covalent attachment of folic acid molecules to the surface of CNCs is another effective method for the targeted delivery of chemotherapeutic agents to folate receptor-positive cancer cells.⁷¹ The primary alcohol moieties of CNCs could be selectively oxidized to carboxyl groups which were then reacted with amino groups of chitosan oligosaccharide (CS_{OS}).⁷² CNC-CS_{OS} particles loaded with procaine hydrochloride revealed a fast release of drug in 1 h, which demonstrated that CNC-CS_{OS} particles have the potential applications as fast response drug carriers in wound-dressings and local drug delivery to the oral cavity, such as treatment of periodontal cavities.

Besides, CNCs were able to be incorporated into alginate-based nanocomposite microspheres with the aims of enhancing mechanical strength and regulating drug release behavior.⁷³ CNCs increased the stability of the cross-linked network structure, and thus the alginate-based microspheres exhibited prominent sustained release profiles,

Table 2 Effect of CNC loading on the mechanical properties and water vapor permeability (WVP) of biodegradable nanocomposite films.

Matrix	CNC addition	Increase		Decrease WVP	Reference
		tensile strength	tensile modulus		
Agar	1-10 wt%	25 % (5 wt% CNC)	40 %	25 % (3 wt% CNC)	49
Cassava starch	0.1-5 wt%	92 % (0.2wt%CNC)	> 400%	Water activity <0.5	50
Alginate	1-8 wt%	37 % (5 wt% CNC)	75 %	31 % (5 wt% CNC)	51
Chitosan	1-10 wt%	26 % (5 wt%CNC)	87 %	27 % (5 wt% CNC)	52
PVA	1-5 wt%	19.5 % (3 wt% CNC)	16.6 %	16.4 (3 wt% CNC)	53
Xylan	10 %	-	-	42.8 %	54
-Not given					

Table 3 Oxygen barrier property of CNC-based biodegradable nanocomposites.

Matrix	CNC addition	Subadditive	Increase in oxygen barrier property	Reference
Xylan	5-50 wt%	50 wt% Sorbitol	99.4 % (5 wt% CNC)	56
Guar gum	5-60 wt%	-	65.3 %	62
PLA	0.5-2 wt%	-	62 % (1 wt% CNC)	63
PLA	1-5 wt%	-	9 % (1 wt% CNC)	57
			34 % (1 wt% s-CNC)	
			34 % (1 wt% s-CNC)	
PLA	5 wt%	15 wt% of acetyl(tributylcitrate), 25 wt% Poly(hydroxybutyrate)	24 %	58
PLA	5 wt%	25% Poly(hydroxybutyrate)	56 %	64
PLA	1-5 wt%	1 wt% Ag	46 % (1 wt% CNC)	65
PLA	1-5 wt%	1 wt% Ag	46 % (1 wt% CNC)	65
			54 % (1 wt% s-CNC)	
poly(ethylene terephthalate)	-	-	94 %	59
BCNCs	-	Electrospun PLA coatings	97%	61

-Not given, s-CNC represents surfactant-modified CNC.

as demonstrated by inhibited diffusion of theophylline. Ternary bio-nanocomposites were investigated by the combination of PVA, CNCs and poly (d,l-lactide-co-glycolide) (PLGA) nanoparticles (NPs) loaded with bovine serum albumin fluorescein isothiocyanate conjugate (FITC-BSA).⁷⁴ CNCs increased the elongation properties of the ternary PVA/CNC/NPs bio-nanocomposites. The bio-nanocomposite films have been demonstrated to vehiculate biopolymeric nanoparticles to adult bone marrow mesenchymal stem cells successfully, and thus would represent a new tool for drug delivery strategies.

2.4.2. Nanomedicine. Although CNCs were not popular in the biomedical applications,³⁸ CNC derivatives have been used in certain nanomedical applications, such as the antibacterial agents, tissue replacements, biosensors and bioimaging agents.

2.4.2.1. Antibacterial agents. AgNPs showed excellent antimicrobial properties by killing both Gram-positive human pathogens (*Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli*).⁷⁵ The incorporation of AgNPs or Ag-ZnO NPs into CNC matrix endowed the dressings with antimicrobial properties.⁷⁶⁻⁷⁸ The CNC-supported Ag-ZnO NPs were well-dispersed, and thus showed greater antibacterial activity when compared with CNC-free ZnO-Ag heterostructure nanoparticles of the same particle size.⁷⁸

2.4.2.2. Tissue replacement. The formats of the CNC-based functional biomaterials for tissue engineering include dense films and membranes, hierarchical three-dimensional (3D) porous constructs (micro/nanofibers mats, foams and sponges), and hydrogels.⁷⁹

CNCs were embedded in cellulose acetate propionate as a matrix to fabricate a fully biobased scaffold in vascular tissue engineering.⁸⁰ Myoblasts (muscle cells) could respond to the submonolayer surfaces of tunicin CNCs with a high degree of orientation,⁸¹ and thus highly oriented multinuclear myotubes formed.⁸² CNCs was used to reinforce poly(ϵ -caprolactone) (PCL) nanofibers by chemically grafting low-molecular-weight PCL diol onto the CNCs,^{83,84} fibrous nanocomposite mats,⁸⁵ or uniaxially aligned cellulose nanofibers.⁸⁶ Besides the improvements in mechanical properties and the thermal stability, the nontoxicity to human cells, and the strong effect on directing cellular organization made the nanofibers particu-

larly useful for various artificial tissues or organs. Naïve CNCs and aldehyde-functionalized CNCs (CHO-CNCs) were also employed as nano-fillers in a fully biobased strategy for the production of reinforced injectable hydrogels.⁸⁷⁻⁸⁹ Especially, CHO-CNCs played dual role by acting as a filler and chemical cross-linker.

2.4.2.3. Biosensors. The reactive hydroxyl groups on the large specific surface area of CNCs can be decorated with sensing nanomaterials to endow CNCs with sensing capabilities. Ag-Pd alloy nanoparticles were synthesized by using carboxylated CNCs as the matrix and were used as labels for electrical detection of DNA hybridization.⁹⁰ The Ag/carboxylated CNCs bio-nanocomposites could also be employed as the labeled DNA probe to identify the complementary target DNA sequence.⁹¹ The hydroxyl surface groups of CNC/PVA bio-nanocomposite films can react with 2-(acryloxy)ethyl (3-isocyanato-4-methylphenyl) carbamate to further carry out the nucleophile-based thiolene Michael addition with thiolated fluorescein-substituted lysine.⁹² This fluorescent CNC derivative was used to detect protease activity and 250 $\mu\text{g/mL}$ of trypsin, suggesting that this biosensor can be applied in wound diagnosis and other biomedical applications. In another application, a human neutrophil elastase (HNE) tripeptide substrate, n-Succinyl-Alanine-Alanine-Valine-para-nitroanilide (Suc-Ala-Ala-Val-pNA), was covalently attached to the glycine esterified cotton CNCs to prepare an HNE biosensor.⁹³

2.4.2.4. Bioimaging agents. CNCs were considered as a new generation of bioimaging probes because of their sizes in the range of 200-300 nm long and 5-50 nm wide, and the specific surface area of up to 150 m^2/g .^{94,95} The negative charge of CNCs would cause cellular damage whereas the suitable modification of CNCs prohibited this side effect. Fluorescein-5'-isothiocyanate (FITC) moieties were covalently attached to the surface of CNCs via three-step reaction pathways.⁹⁶ Thus CNC-FITC was endowed with fluorescence characteristics. Cellular uptake and cytotoxicity of CNC-FITC and newly synthesized CNC-rhodamine B isothiocyanate (CNC-RBITC) gained further study.⁹⁷ The results revealed that CNC-RBITC did not affect the cell membrane integrity and showed no noticeably cytotoxic effect.

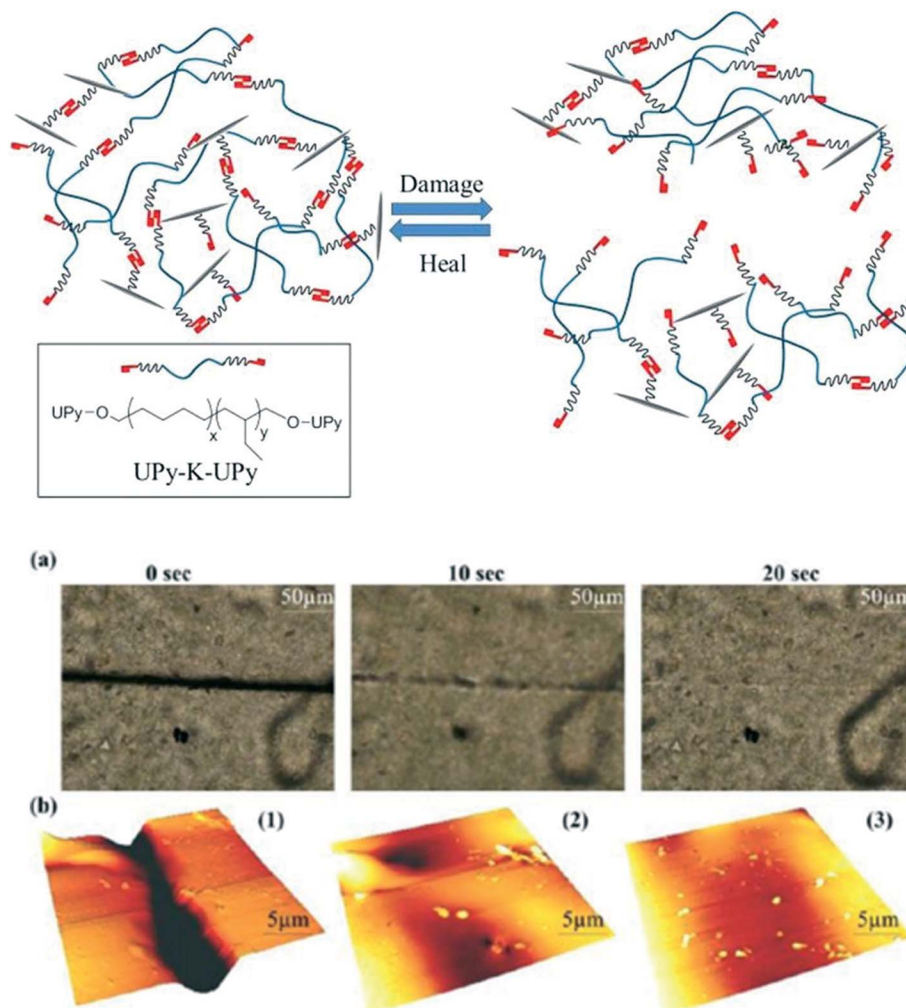


Fig. 6 Schematic representation of the formation of a supramolecular nanocomposite based on UPy-K-UPy and UPy-decorated CNCs and (a) Optical microscope images of deliberately damaged UPy-K-UPy/CNC-UPy 10% w/w nanocomposite films before, during, and after exposure to UV light (320–390 nm, 350 mW/cm², 20 s); (b) Atomic force micrographs of UPy-K-UPy/CNC-UPy 10% w/w nanocomposite films in the deliberately damaged (1), partially healed (2), and completely healed (3) state (color range; black = 7 μm.⁴¹ Adapted with permissions from American Chemical Society.

2.5. Applications in catalysis

Immobilization of homogeneous catalyst on solid supports combines the advantages of homogeneous catalysis and heterogeneous catalysis. CNCs are ideal support matrix for catalysts because they display the well-defined size and high specific surface area.⁹⁸ As seen in Figure 7, the high specific surface area of CNCs can: (1) support nano-catalysts directly; (2) be functionalized with other moieties to support the catalysts; (3) be grafted with the catalysts for selective catalysis. Table 4 shows the catalytic reactions in the presence of the unsupported catalysts and CNC-supported catalysts. It is demonstrated that CNCs are excellent support matrix for the metal nanoparticles or the heterogenization of homogeneous catalysts. The CNC-supported nanocatalysts exhibited the advantages over the supported nanocatalysts such as mild reaction conditions, excellent yields, short reaction time, easy work-up procedure, product purity, and effortless separation and reusability of nanocatalysts.

2.5.1. Supporting nano-catalysts directly. The abundant electron-rich hydroxyl groups on the surface of CNCs played dual

roles in the reduction and immobilization of catalyst under hydrothermal conditions.¹⁰¹ The CNC-supported catalyst displayed much greater catalytic activity and stability than the unsupported catalysts. The CNCs supports not only metal nanoparticles, but also other metallic nanostructures. The obtained CNCs were used as a matrix for the synthesis of zinc oxide (ZnO) NPs^{105,115} and mesoporous TiO₂^{106,116} which exhibited superior catalytic activity than unsupported pure NPs. The unique assembly of NPs bound to CNCs enabled the NPs with a large specific surface area for enzyme immobilization.¹¹⁷ A new immobilization matrix, Fe₃O₄@CNCs nanocomposite was prepared for immobilizing a novel cold active and salt tolerant esterase, EstH,¹¹⁸ which showed better temperature stability, prolonged half-life, higher storage stability, improved pH tolerance, and reusability.

2.5.2. Functionalized with other moieties to support the catalysts. Co(II)-ethylenediamine functionalized CNCs displayed the same catalytic activity with unsupported Co(II) in the selective oxidation of various primary and secondary benzylic alcohols to the corresponding

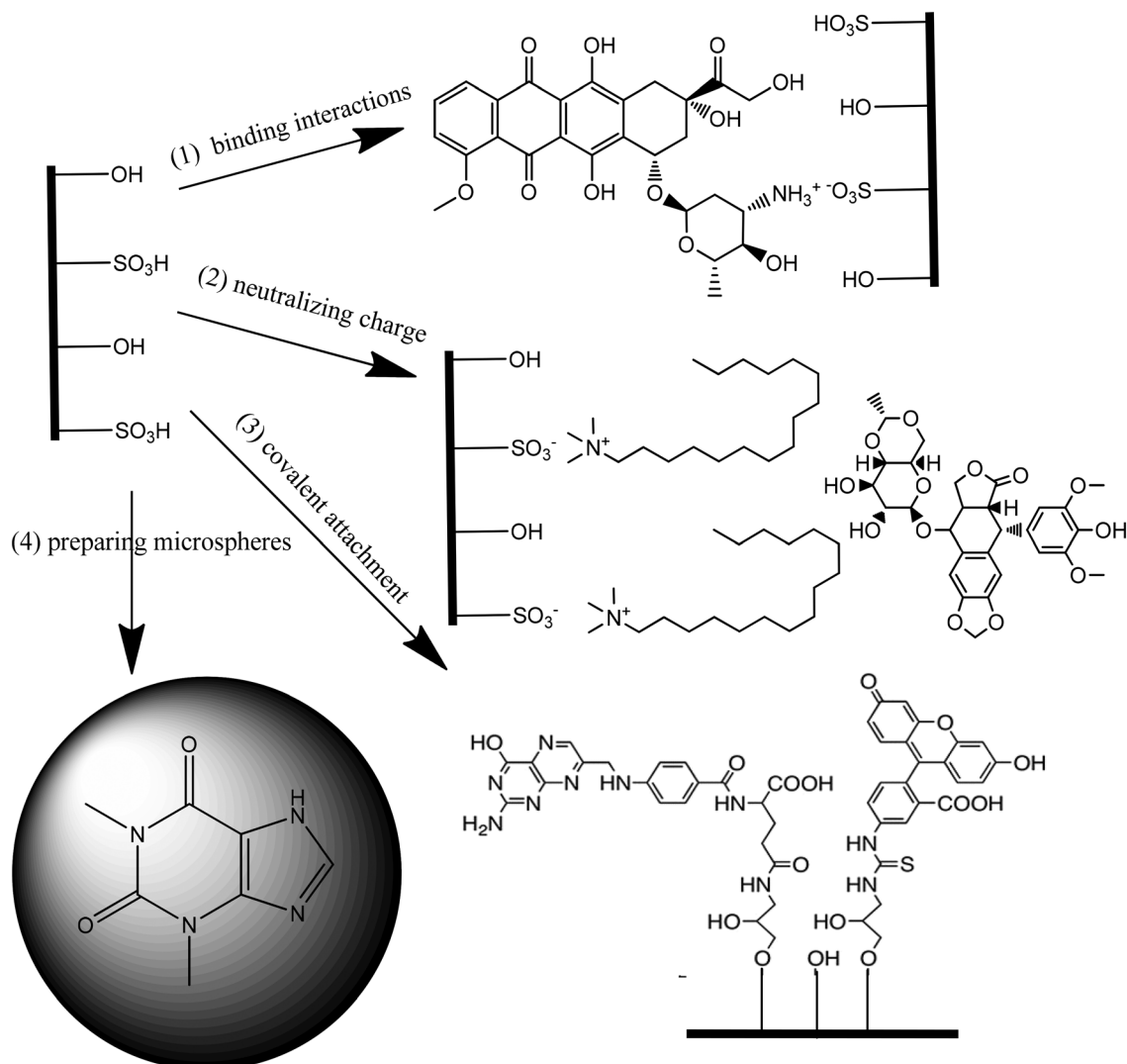


Fig. 7 Utilization forms of CNCs as the drug carrier in pharmaceutical industry.

aldehydes and ketones.¹⁰⁷ Generation 6.0 polyamidoamine (G6 PAMAM) dendrimer-grafted CNCs (CNC-PAMAM) were synthesized and employed as supports for AuNPs.¹¹⁹ Alkynyl-dendrons of the PAMAM family were covalently incorporated on azide-functionalized CNCs by click chemistry to support monodispersed gold nanoparticles in aqueous media for the reduction of 4-nitrophenol to 4-aminophenol.¹⁰⁸ The well-dispersed CNC-PAMAM-supported AuNPs or CNC-G^{AT}₂@AuNPs exhibited remarkable catalytic effect on the reduction of 4-nitrophenol to 4-aminophenol.

2.5.3. Grafted with the catalysts for selective catalysis. Heterogeneous CNC-dirhodium(II) catalysts (CNC-Rh₂) were synthesized by ligand exchange between carboxyl groups on the CNC surface and Rh₂(OOCCH₃)₄.¹⁰⁹ The successful grafting of copper-tetrasulfonate phthalocyanine on CNCs enabled it to act as a selective heterogeneous catalyst for the aerobic oxidation of alcohols.¹¹⁰ Nano-cellulose-OSO₃H was successfully prepared through the reaction of hydroxyl groups of CNCs with chlorosulfonic acid and used as a new solid acid catalyst.¹¹¹ Nano-TiCl₂/cellulose was prepared as the biopolymer solid acid catalyst

by the C–O–Ti bonding.¹¹² The surface OH groups on nano-Fe₃O₄ reacted with TiCl₄ via Ti–Cl bonds to form nano-Fe₃O₄/TiCl₂/cellulose.¹¹³ Treatment of Fe₃O₄@CNCs with TiCl₄ also leads to the formation of Fe₃O₄@nano-cellulose/TiCl₄.¹¹⁴ These facile, green, and efficient heterogeneous catalysts accelerated the reactions distinctively with much efficient yield under milder conditions.

3. Conclusion remarks and outlook

Cellulose, the most ancient and important natural polymer on earth revives and attracts a lot of attention in the new form of “CNCs” which can be used as a novel and advanced materials and matrix. Widespread applications of CNCs in papermaking industry, reinforcing filler for polymers, shape memory polymers, healable polymeric materials, food industry, drug carrier in pharmaceutical industry, supporting matrix for catalysts, and nanomedicine were summarized in this paper. With a high amount of hydroxyl groups on the high surface area to be modified chemically, CNCs will be

Table 4 Catalytic reactions in the presence of the unsupported catalysts and CNC-supported catalysts.

Catalyst	Reactant	Product	Yield ^a	Yield ^b	Reference
(1)					
PdNPs@CNCs	phenol	cyclohexanone	0	90 %	99
PdNPs@CNCs	ketones	Alcohols	-	67 % 65 % ee	100
AuNPs@CNCs	4-nitrophenol	4-aminophenol	35.1 % (14 min)	84.4 % (14 min)	101
AgNPs@CNCs	benzaldehyde	benzyl alcohol	0 (AgNO ₃)	96 %	102
CNC@PDA-AgNPs	4-nitrophenol	4-aminophenol	x	6x	103
RuNPs@CNCs	toluene	methylcyclohexane	-	100 %	104
ZnO@CNCs	methylene blue	-	23 % (30 min)	94.4 % (30 min)	105
TiO ₂ @CNCs	rhodamine B	-	77.3 % (1 h, P25)	96.9 % (1 h)	106
(2)					
Co(II)- ethylenediamine functionalized CNCs	primary and secondary benzylic alcohols	aldehydes and ketones	95 %	95 %	107
CNC-G ^{AT} ₀ @AuNPs	4-nitrophenol	4-aminophenol	x	8x	108
(3)					
Synthesized CNC-Rh2 catalyst	Styrene + ethyl diazoacetate	cyclopropanation of styrene	95 %	70–80 %	109
CNC-phthalocyanine	benzyl alcohol	oxidized derivatives	25 %	99 %	110
Nano-cellulose-OSO ₃ H	4-hydroxy-6-methyl-2H-pyran-2-one, malononitrile, and aldehydes	pyrano [4,3-b] pyran	-	94 % (10 min)	111
nano-TiCl ₂ /cellulose	2-aminobenzothiazole, 4-nitrobenzaldehyde, and ethyl acetoacetate	4H-pyrimido[2,1-b]benzothiazole derivatives	-	97 %	112
nano-Fe ₃ O ₄ /TiCl ₂ /cellulose	aldehydes and 2-aminobenzamide	2,3-dihydroquinazolin-4(1H)-one derivatives	-	96 %	113
Fe ₃ O ₄ @nano-cellulose/TiCl	2-aminobenzothiazole, 4-nitrobenzaldehyde, and ethyl acetoacetate	4H-pyrimido[2,1-b]benzothiazole derivatives	-	96 %	114

^a (unsupported), ^b (supported), ^c X represents the yield of products before the complete conversion, ^d -Not given

endowed with more mystical properties that is worthy of getting more applications.

Different natural sources of CNCs, the production methods for CNCs, the modifications of CNCs, together with their applications as advanced matrix and materials, have attracted a lot of attention due to the high surface area of CNCs with a high amount of highly reactive hydroxyl groups.¹²⁰ Derivatization of CNCs is an effective solution to overcome the poor chemical resistance and mechanical properties of CNCs, such as grafting the functionalized moieties to endow them with the shape memory effect, healable effect or other particular effects.^{29,42,96} However, the energy consumption and production costs are urgent problems that need to be solved at present. The poor chemical resistant property and limited mechanical property also limited the scope of applications. As discussed in the application section, the preparations of CNCs and CNCs-derived materials are the cores for further processing CNCs into high-performance composites and hybrid materials.¹²¹

Firstly, the preparation of special CNCs is the first consideration in some applications. CNCs were investigated as stabilizers for oil-water Pickering emulsion.¹²² Needle-like CNCs were found to play a dominating role to the stabilization of Pickering emulsion while the individual granules with ellipsoid shapes were good candidates as stabilizer. In other words, the specific morphology of CNCs should be designed for different application situation. This special feature is embodied in the length. For example, CNCs could act as a better nucleating agent for poly(3-hydroxybutyrate-co-3-hydroxy-

valerate) (PHBV) than CNFs with higher aspect ratio, which led to a higher tensile modulus of CNCs/PHBV composites.¹²³ Thus the design of CNCs morphologies are absolutely necessary for large-scale applications.

Secondly, people are more inclined to develop CNCs-derived materials as value-added materials. The development of CNC applications is very fast in many new directions,¹²⁴ such as high-performance thermal insulating materials,¹²⁵ biopolymer composite coatings on plastic films,¹²⁶ etc. For instance, the deposition of CNCs films on the flexible electrodes may also reinforce the mechanical properties of electrodes of editable supercapacitors and prevent short circuit.¹²⁷ In addition, multicellular cancer spheroids growth and on-demand release from nanofibrillar thermoreversible hydrogels formed by CNCs carrying surface-grafted molecules of the temperature-responsive polymer poly(N-isopropylacrylamide) (PNIPAM) has been reported where CNCs were used as the nanofibrillar elements of the hydrogel.¹²⁸ After modifying the surface of CNCs with a photoactive bis(acyl)phosphane oxide derivative, CNCs can act as highly efficient initiators for radical polymerizations, cross-linkers, as well as covalently embedded nanofillers for nanocomposite hydrogels.¹²⁹ 3D printing of CNCs also offers an attractive pathway for fabricating sustainable structures.^{130,131} Therefore, the high-cost CNCs prefers to hunting for “high value targets”. However, the strong hydrophilic property, the aggregation, and the degradation of CNCs should be addressed during the new applications and have to be further evaluated with extensive studies.

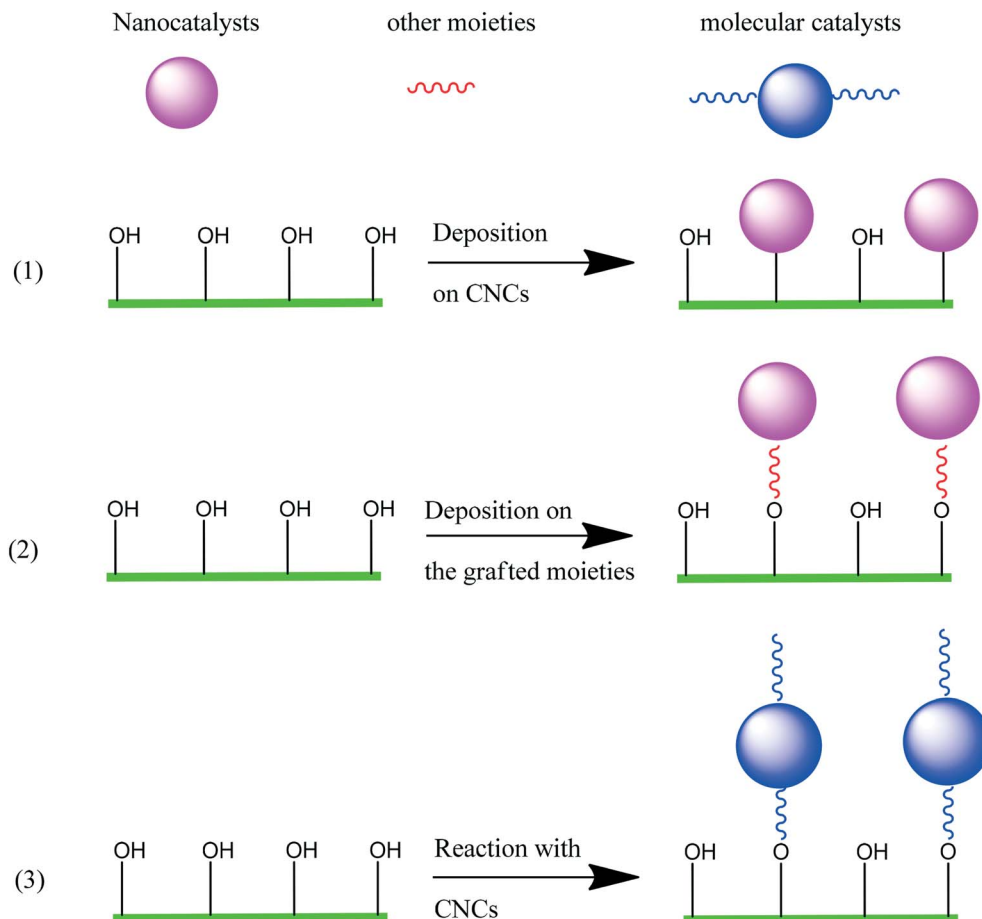


Fig. 8 The loading process of catalysts on the surface of CNCs.

Notes

The authors declare no competing financial interest.

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参数错误