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Application of Nanocellulose for Controlled Drug Delivery

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1.1 Introduction

The therapeutic effectiveness of a pharmacological treatment depends upon the availability of the active drug at the site of action in a concentration that exceeds the minimum effective concentration. However, more often than not, this ideal condition for therapeutic activity is not met due to several inherent pharmaceutical and pharmacological properties of the drug. In fact, it has been generally recognized that for many disease states, there are substantially good numbers of therapeutically effective compounds available on offer [1]. The obvious cause of therapeutic failure with several of these otherwise promising compounds when used in a clinical setting is that they are unable to reach the site of action. The potential reasons for the poor bioavailability of the drugs at the required site include (i) poor water solubility, (ii) poor permeability across the biological membranes, and (iii) rapid metabolism and clearance from the body [2]. The aim of controlled drug delivery is, therefore, to overcome these limitations to effective drug therapy by localizing drug release at the site of action, reducing the dose required, and providing constant drug release. As a result, controlled drug delivery systems offer several advantages over conventional system in reducing the toxicity, enhancing the activity, and ultimately improving the patient convenience and compliance [3]. Several dosage forms, conventional and nonconventional, have been developed and continuously improved over the years to achieve better drug therapy. One of the newer approaches for improved drug delivery that received enormous interest in recent times is nanomedicine. The applications of nanotechnology for treatment, diagnosis, monitoring, and control of biological systems have recently been referred to as *nanomedicine* by the National Institutes of Health [4]. Drug delivery is the dominant area of nanomedicine research as it accounts for 76% and 59% of all recent scientific papers and patents on nanomedicine, respectively [5].

Polymers are the backbone of controlled drug delivery systems. Over the past few decades, there has been considerable interest in the development of effective drug delivery devices based on biodegradable nanoparticles [6]. Both natural and

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synthetic polymers with a wide range of safety and functionalities are extensively investigated in designing controlled delivery systems. The investigations into the novel synthetic and fabrication methods, and mathematical models to study the mechanisms of controlled drug release, have resulted in the ability to create tunable polymeric nanoparticulate drug delivery systems that are capable of taking care of the spatial and temporal aspects of controlled drug delivery [7]. Due to their cytocompatibility, biodegradability, and availability of reactive sites amenable for ligand conjugation, cross-linking, and other modifications, natural polymers have been successfully used in controlled drug delivery [8, 9]. Plant-derived nanostructures such as starch, cellulose, zeins, legume proteins, and others are particularly attractive sources as they are cost effective, sustainable, and renewable with excellent tunable properties [10].

Nanocellulose obtained from cellulose – the most abundant biopolymer on Earth – is an emerging renewable polymeric nanomaterial that holds promise in many different applications including food and pharmaceuticals [11, 12]. Due to its excellent biocompatibility, biodegradability, and low ecological toxicity risk and low cytotoxicity to a range of animal and human cell types [13], nanocellulose is currently a subject of interdisciplinary material of interest. Excellent discussions on the chemistry, preparation, and the general properties of nanocellulose are available from several literatures [12, 14–17]. Nanocellulose can be obtained from a wide variety of sources and their properties were also found to depend on the source from which they are prepared (Figure 1.1). Broadly, they are divided into three categories such as bacterial cellulose (*BC*), cellulose nanocrystals (*CNC*s) (also called as *cellulose nanowhiskers* or *nanocrystalline cellulose*), and cellulose nanofibrils (CNFs) depending on their source and methods of production [18]. Those obtained from acid or enzyme hydrolysis are commonly called as CNC, while those obtained through mechanical treatments are termed as cellulose nanofibrils (CNFs). Bacterial nanocellulose is another highly crystalline form

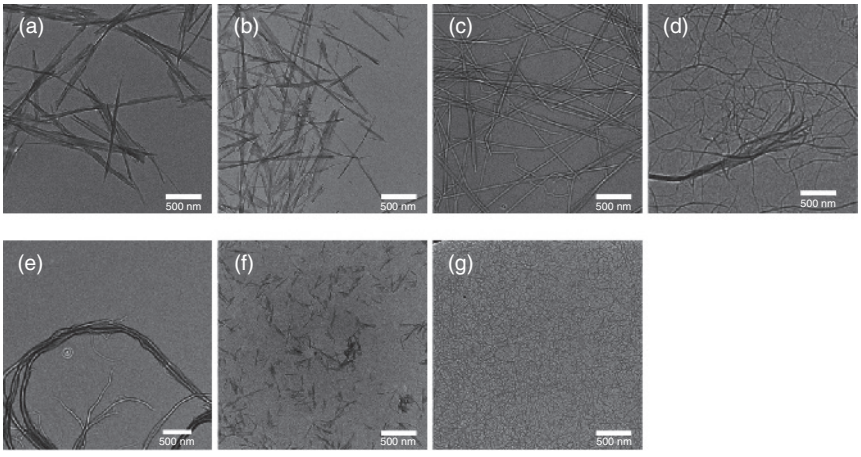

Figure 1.1 TEM images of (a) bacterial HCl, (b) bacterial sulfate, (c) tunicate sulfate, (d) wood enzymatic, (e) wood mechanically refined, (f) wood sulfate, and (g) wood TEMPO. (Sacui *et al*. 2014 [17]. Reproduced with permission of American Chemical Society.)

of cellulose, which is obtained mainly from *Gluconacetobacter xylinus* [19]. The presence of free reactive hydroxyl group exposed at the surface and its nanometer size dimension rendered nanocellulose a good candidate for imparting different functionalities through chemical derivatization. Since cellulose is stable to a wide range of temperatures, it can also be subjected to heat sterilization methods, which is often required in biomedical applications [20]. All the different categories of nanocelluloses have been widely investigated in drug delivery systems. Also, since BC can be purified using sodium hydroxide to the US Food and Drug Administration (*FDA*) acceptable range of endotoxin values for implants, that is, <20 endotoxin units/device, they are also potentially safe for use in intravenous applications [21].

Different cellulose derivatives including ethylcellulose, methylcellulose, carboxymethyl cellulose, and hydroxypropylmethyl cellulose are indispensable in drug delivery and pharmaceutical technology. They are listed as generally recognized as safe (*GRAS*) by the FDA and are widely used in the preparation of drug products [22]. Even though it was way back in 1949 that Ranby [23] successfully produced a micellar cellulose solution, it is only in the last few years that the potential of nanocellulose in drug delivery has been realized and research into this material has began to pick up. Current research into the application of nanocellulose in drug delivery includes formulation of nanoparticles, microparticles, tablets, aerogels, hydrogels, and transdermal drug delivery systems. This chapter will describe the current and recent research activities in the application of nanocellulose in the preparation of different dosage forms.

1.2 Biodegradability, Cytotoxicity, and Cellular Internalization of Nanocellulose

Choosing a suitable polymer that is biocompatible, able to encapsulate, control, and target the release of the drug and yet biodegradable is highly critical for the successful formulation of nanomedicine. The ability of nanomedicines to target specific sites depends upon the particle size, surface charge, surface modification, and hydrophobicity, which in turn determine their interaction with the cell membrane and their penetration across the physiological drug barriers [24]. Therefore, it is important that the biodegradability, cytotoxicity to a range of human cell types, and the mechanism of cellular uptake of nanocellulose-based delivery systems are investigated (Table 1.1). When investigated against nine different cell lines such as HBMEC, bEnd.3, RAW 264.7, MCF-10A, MDA-MB-231, MDA-MB-468, KB, PC-3, and C6 following the MTT and LDH assay methods, the filamentous CNCs showed no cytotoxic effects against any of these cell lines in the concentration range (0–50 $\mu g\,ml^{-1}$) during the exposure time (48 h) [25, 26]. Low nonspecific cellular uptake was observed when cellular uptake was evaluated through fluorescein-5′-isothiocyanate labeling, which indicates that CNCs are good candidates for nano drug delivery applications. In another study, the cellular uptake of negatively charged fluorescein isothiocyanate (*FITC*)-labeled CNCs was evaluated and compared against the positively charged rhodamine B isothiocyanate-labeled CNCs (*RBITC*) in human embryonic kidney 293 (*HEK 293*) and *Spodoptera frugiperda*

Table 1.1 Cellular uptake mechanisms of different formulations.

Formulation type	Release mechanism	Cells used	Cellular uptake
Nanocrystals	—	HBMEC, bEnd.3, RAW 264.7, MCF-10A, MDA-MB-231, MDA-MB-468, KB, PC-3, and C6	Low nonspecific cellular uptake [25, 26]
Negatively charged fluorescein isothiocyanate-labeled CNCs (FITC)	—	HEK 293 and *Sf*9	No significant uptake [27]
Positively charged rhodamine B isothiocyanate-labeled CNCs (RBITC)	—	HEK 293 and *Sf*9	High uptake, due to favorable electrostatic interaction between cationic RBITC and anionic cellular membrane [27]
Folic acid-conjugated CNCs	—	DBTRG-05MG, H4, and C6	Caveolae-mediated endocytosis and clathrin-mediated endocytosis in H4 cells [28]
Acid-hydrolyzed CNCs	Slow release over 4 days	KU-7 bladder cancer cells	Evidence of cellular uptake may be due to partitioning following cell binding [29]
Curcumin–cyclodextrin/CNC nanocomplex	Slow release	Colorectal and prostatic cancer cell lines (PC-3, DU145, and HT-29)	Endocytosis [30]
Polyphosphoester-grafted CNC	pH-Dependent, slow and controlled release	HeLa cells and L929 cells	Endocytosis [31]

(*Sf9*) cells [27]. This study reports that the positively charged *CNC–RBITC* conjugate was uptaken by the cells without affecting the integrity of the cell membrane and there was no noticeable cytotoxic effect observed (Figure 1.2), whereas the negatively charged *CNC–FITC* conjugate resulted in no significant internalization at physiological pH but the effector cells were surrounded by CNC–FITC, leading to eventual cell rupture showing the importance of the surface charge of CNC for bioimaging and drug delivery.

Due to the availability of reactive groups on the surface of nanocelluloses, they are often functionalized with functional groups to improve their physicochemical and functional properties. In recent study, nanofribrillated cellulose (*NFC*) was surface-functionalized with anionic and cationic groups, and the effect of this functionalization on the monocyte/macrophage (*MM*) reaction was investigated along with the unmodified form to have a better understanding on the

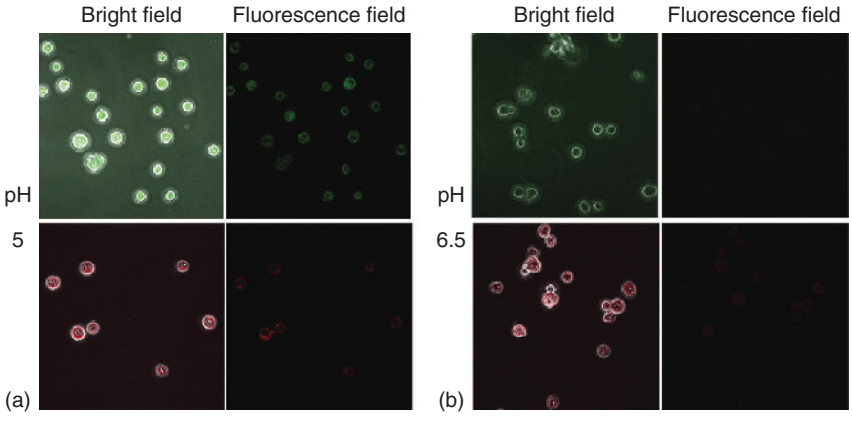

Figure 1.2 Mixed-field and fluorescence microscopy images comparing the uptake of CNC–FITC (upper) with CNC–RBITC (lower) by *Sf*9 cells at (a) pH 5 and (b) pH 6.5. Cells were incubated with CNC–FITC or CNC–RBITC during 3 h at respective pH and then fixed for confocal microscope measurement. (Mahmoud *et al*. 2010 [27]. Reproduced with permission of American Chemical Society.)

effect of physicochemical properties of nanocellulose on its interactions with biological systems [32]. Cell response was evaluated in terms of cell adhesion, morphology, and secretion of TNF-α, IL-10, and IL-1ra after THP-1 monocytes were cultured on the surface of the films for 24 h in the presence and absence of lipopolysaccharide. A pro-inflammatory phenotype was found to activate the anionic carboxymethylated NFC films, while the unmodified forms promote a mild activation and cationic hydroxypropyl-trimethylammonium groups does not resulted in the activation of MMs at all. This study significantly enhances our understanding on the importance of surface charges on the nanocellulose derivatives when they are intended to be used for biomedical applications (Figure 1.3).

With the advent of nanotechnology and the availability of a multitude of nanomaterials synthesized from innumerable numbers of materials, concerns over an ecotoxicological risks associated with their exposure and biodegradability loom large. Toxicity test of CNCs with rainbow trout hepatocytes and nine aquatic species showed that CNCs exhibit a low toxicity potential and environmental risk [33]. When the biodegradability of CNC in aqueous environment was also studied as per the OECD standard and compared with other nanomaterials, CNCs and starch nanoparticles were found to biodegrade at similar levels but faster than their counterparts such as fullerenes and functionalized carbon nanotubes, which was attributed to their higher surface area [34].

1.3 Nanocellulose in Nanoparticulate Drug Delivery

Drug delivery research over the years has become highly interdisciplinary. Researchers from diverse fields such as biomedical engineering, pharmaceutical sciences, and life sciences investigate into a plethora of research questions pertaining to their background. One of the interesting findings, as a result, is the effect of

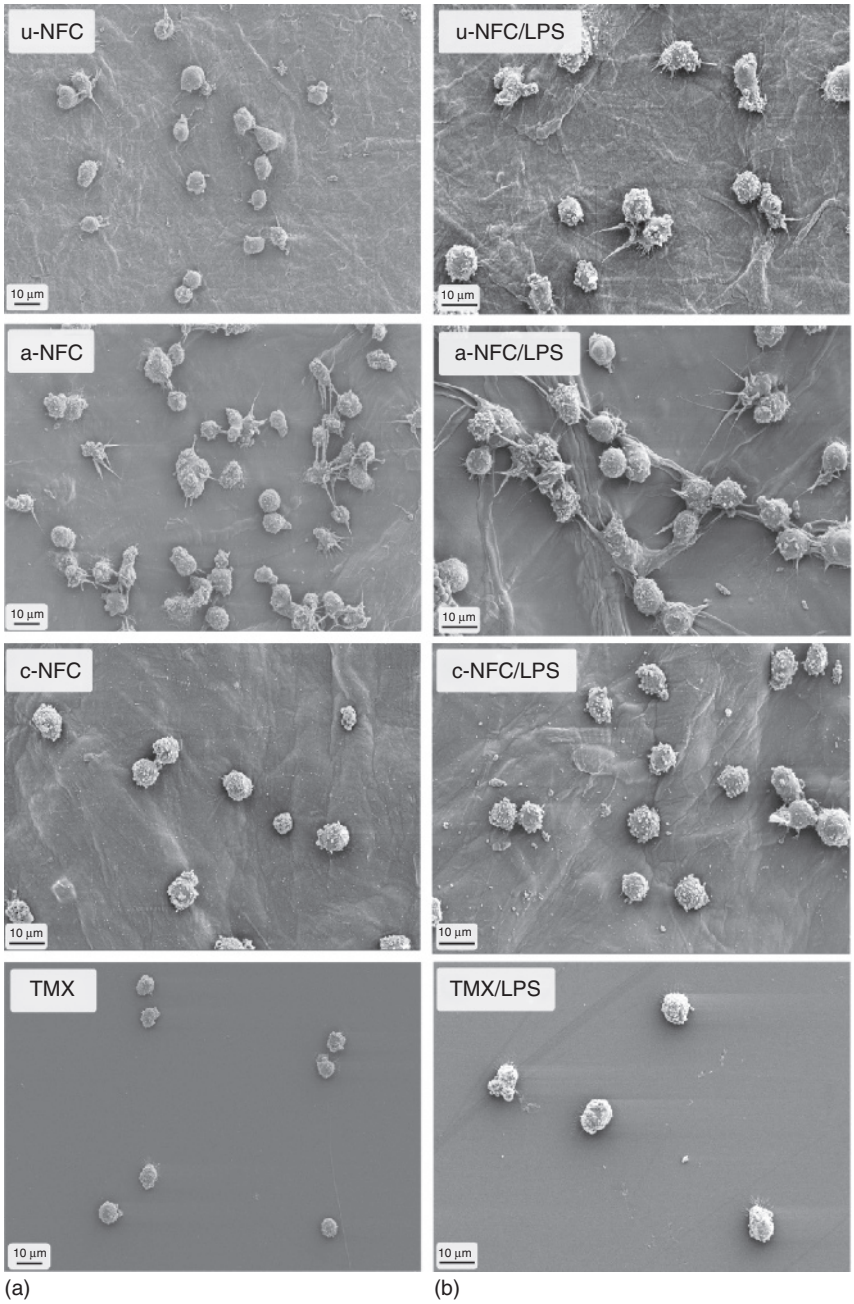

Figure 1.3 Representative SEM micrographs at ~1000 times magnification of THP-1 monocytes cultured for 24 h on u-NFC, a-NFC, c-NFC, and TMX in the presence (b) and absence of LPS (a). Mainly rounded single cells are found on c-NFC and TMX. Cells on a-NFC tended to form clusters and presented many short filopodia, while u-NFC presented both single cells and small cell clusters, with few and short filopodia. This figure represents the importance of surface charge on the CNCs. (Hua *et al*. 2015 [32]. Reproduced with permission of American Chemical Society.)

nanoparticles' geometry on the effectiveness of the delivery system. When polymeric micelles of flexible filament types were compared with the spherical types, the filament types exhibit 10 times longer circulation time and are also taken up more readily by cells as a result of their extended flow [35]. The anticancer drug paclitaxel was effectively delivered, which resulted in the shrinking of the human-derived tumors in mouse model. Other elongated novel carriers such as elongated liposomes, carbon nanotubes, and others are also reported to exhibit much longer clearance time when compared with the spherical systems [36]. These findings coupled with the outstanding surface area-to-volume ratio of filamentous nanocelluloses have attracted researchers to develop a novel nanoparticulate drug delivery system based on nanocellulose. Folic acid-conjugated CNCs were synthesized for cellular uptake and folate receptor-positive cancer targeting of chemotherapeutics [28]. When tested on such folate receptor-positive human (DBTRG-05MG, H4) and rat (C6) brain tumor cells, the cellular binding and uptake of the conjugate were 1452, 975, and 46 times higher in the DBTRG-05MG, H4, and C6 cells than the non-conjugated cellulose nanoparticles, respectively. The uptake mechanism of the conjugate by DBTRG-05MG and C6 cells was also found to be primarily through caveolae-mediated endocytosis and through clathrin-mediated endocytosis in H4 cells.

One of the earliest reports on the application of acid-hydrolyzed CNCs was published in 2011 [29]. The study reported the binding of the water-soluble, ionizable drugs tetracycline and doxorubicin to the CNCs, which resulted in the rapid release of drugs over a period of 1 day. When the CNCs were treated with cetyltrimethylammonium bromide, a significant increase in zeta potential was observed, which bound significant quantities of hydrophobic drugs such as docetaxel, paclitaxel, and etoposide. The bound drugs were shown to be released over a 2-day period in a controlled manner, and an evidence of cellular uptake of the nanocomplex by the KU-7 bladder cancer cells was also observed. A polyelectrolyte–macroion complex between anionic CNCs and a cationic chitosan was also prepared for controlled drug delivery (Figure 1.4), which resulted in nearly spherical nanoparticles with positive charge at amino/sulfate group molar ratios >1 and nonspherical nanoparticles with negative charge when particles were formed at the ratios <1 [37]. Another ionic nanocomplex prepared between cationic β-cyclodextrin (*β-CD*) and the CNCs was also used to encapsulate curcumin for controlled drug delivery. The CNCs were obtained by sulfuric acid hydrolysis, while cationic β-CDs were obtained by the reaction of glycidyltrimethylammonium chloride with β-CD in alkaline aqueous medium. When tested *in vitro*, the nanocomplex was shown to exhibit an antiproliferative effect on colorectal and prostatic cancer cell lines where the IC_{50} was found to be lower than that of curcumin alone [30].

A novel polyphosphoester-grafted CNC was developed by the "grafting onto" process through "click" reaction, which possessed a negatively charged surface suitable for binding doxorubicin and delivers it to the HeLa cells. The system showed a good biocompatibility to both HeLa cells and L929 cells, internalized through endocytosis, and exhibited an anticancer activity against HeLa cells where the drug released was caused by the disruption of the electrostatic interaction in the acidic environment inside the tumor cells [31]. The novel modified

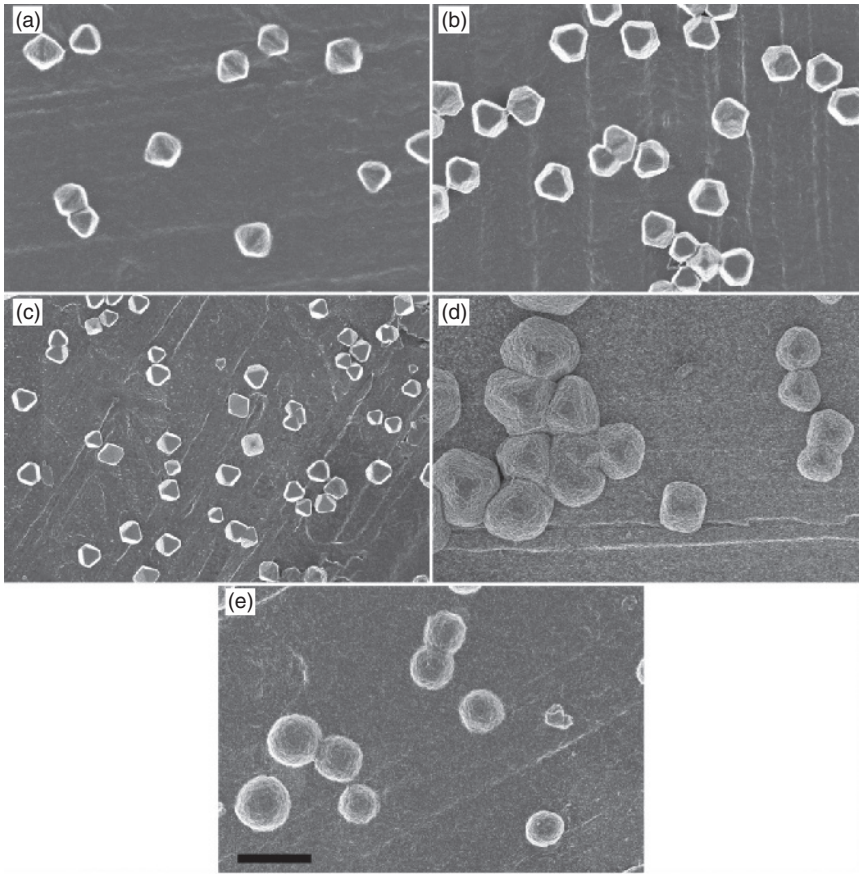

Figure 1.4 FE-SEM images of PMC particles formed by the addition of a 0.001% (w/v) chitosan solution to a 0.02% (w/v) CNC suspension at reaction mixture N/S ratios of (a) 0.33, (b) 0.66, (c) 0.99, (d) 1.33, and (e) 1.66. Scale bar: 3 μm (applies to all images). (Wang and Roman 2011 [37]. Reproduced with permission of American Chemical Society.)

CNC was found to show a good pH response, making it a promising delivery vehicle for anticancer drugs.

1.4 Nanocellulose in Microparticulate Drug Delivery

The importance of encapsulating drugs, food actives, flavors, or even cell for improved performance and preservation has been well appreciated across different scientific fields. A wide range of natural and synthetic polymeric materials are available for encapsulation, the choice of which mainly rested upon the desired performance of the end products. Nanocellulose is an emerging natural polymer that has received considerable interest in recent years as the encapsulating polymer for drug delivery. It has also been widely investigated to enhance the

mechanical properties and influence drug delivery behavior of microcapsules prepared with other natural polymers. A study was conducted to evaluate the influence of three polysaccharide nanocrystals (*PN*s) such as CNCs, starch nanocrystals, and chitin whiskers on the mechanical and drug release properties of sodium alginate microspheres [38]. All the three PNs resulted in improved mechanical properties and pH sensitivity of the microspheres. All the PNs were found to restrict the motion of the sodium alginate polymer chains and inhibit diffusion of the drug, resulting in the slow dissolution of theophylline from the microspheres, and diffusion transport was found to be the drug release mechanism from the systems.

An electrostatic interaction between negatively charged CNCs and positively charged chitosan has also been employed to prepare layer-by-layer assembled thin film and microcapsules for controlled drug delivery [39]. Both the water-soluble anticancer drug doxorubicin hydrochloride and lipophilic curcumin were successfully incorporated into the system for sustained drug delivery. Self-assembled nanocellulose and indomethacin structures were prepared for sustained release of the encapsulated drug [40]. A high encapsulation efficiency of up to 97% of the water-insoluble drug indomethacin was achieved with drug release sustained over 30 days. Drug release was found to take place through diffusion, and fitting the drug release curves into various equations to determine the drug release mechanism showed that first-order model was the best fit.

Matrix-type microparticles were prepared by spray drying of nanofibrillar cellulose for sustained delivery of different drugs such as indomethacin, nadolol, atenolol, metoprolol tartrate, verapamil hydrochloride, and ibuprofen [41]. Spherical particles of diameters around 5 μm were obtained by encapsulating the active drug mainly in the amorphous form. Final drug loading was quite low, up to 15.1% in indomethacin and 8.2% in verapamil hydrochloride. This low drug loading was attributed to the result of the low affinity between the drug and the cellulose fibers. When drug release from the microparticles was assessed by dissolution study, it was observed that after initial burst release, drug release was extremely slow taking over a 2-month period as a result of the tight binding between the drugs and the cellulose fibers. Drugs were released by diffusion through the matrix system, and when dissolution curves were fitted into different equations, different drugs were found to follow different release kinetics, mainly attributed to the inherent properties of the drugs. Microparticles based on BC were also prepared by spray-drying method where the particles obtained were semispherical in shape [42]. The resulting particles demonstrate good redispersibility, with better water retention capacity and higher thermal stability than microcrystalline cellulose (*MCC*). Beads tailored from dissolved cellulose to release the encapsulated drugs in a controlled manner were also showed to be a promising controlled delivery system [43].

In another application in microencapsulation, nisin-loaded beads prepared with alginate–CNC were evaluated against its ability to inhibit growth of *Listeria monocytogenes* in ready to-eat (*RTE*) ham [44]. Nisin-loaded beads were able to prevent the growth of the microorganism for at least 28 days.

1.5 Nanocellulose in Tablet Formulations

Cellulose and its derivatives in different forms have been indispensable components in the preparation of tablets for a long time. Cellulose derivatives such as MCC, hydroxypropyl methylcellulose, ethylcellulose, carboxymethylcellulose, and others are extensively used in conventional as well as controlled-release tablet formulations. With the practical edge provided by nanocellulose in numerous functional properties being realized and appreciated, a few investigations have explored its potential as functional excipients in tablet formulations. The potential of spray-dried cellulose nanofibers as novel tablet excipients was evaluated and compared against two commercial MCC, Avicel PH-101 and Avicel PH-102, which are the two most commonly used direct compression excipients [45]. Cellulose nanofibers were found to possess excellent compressibility and were amendable to both wet granulation and direct compression methods of tablet preparations. Cellulose nanofibers prepared through direct compression method showed faster disintegration and drug release showing its potential as direct compression excipients. Freeze-dried CNC prepared from water sugarcane bagasse was also shown to enhance the dissolution of diltiazem hydrochloride tablets prepared with the nanocellulose [46].

Disintegrants are added into tablet formulations to ensure that the tablet breaks up into fragments in the GI fluid tract to facilitate dissolution, which in turn results in enhanced bioavailability [47, 48]. Nanocrystalline cellulose was reported to exhibit two potentially advantageous properties when used as disintegrant in calcium carbonate tablet preparation [49]. First is the reduced disintegration time and second is the increased hardness, which was observed with increase in the nanocrystalline cellulose concentration in the tablet formulation, confirming its potential disintegrant property. Along with pectin and sodium alginate, CNCs are also used in the successful probiotic tablet preparation [50].

1.6 Aerogel Systems

Aerogels are lightweight materials with outstanding surface area and open porosity, suitable for high loading of active compounds [51]. They are nanoporous systems obtained from the wet gels or hydrogels through a suitable drying technology that keeps the porous texture of the wet material intact. Due to their weblike structure, high porosity, and high surface reactivity, aerogels prepared from nanocelluloses possess a high mechanical flexibility and ductility with ability for water uptake, which makes them an excellent candidate for the removal of dye pollutants, thermal insulation materials, and drug delivery system [52]. As a result, different types of nanocelluloses, due to their excellent and suitable properties, have become the subject of keen interest in the preparation of aerogels for drug delivery.

Freeze-drying method was applied to prepare highly porous aerogels from nanofibrillar cellulose obtained from four different sources and compared with MCC as nanoparticulate oral drug delivery systems [53]. Release of the beclomethasone dipropionate drug nanoparticle integrated into the aerogel system was found to be quick and immediate for red pepper-based aerogel and MCC, while BC,

quince seed (*QC*), and TEMPO-oxidized birch cellulose-based (*TC*) aerogels show sustained drug release. A controlled release of the drug was achieved, which was modulated by the interactions between the drug nanoparticles and the cellulose matrix, making it a promising carrier for controlled drug delivery.

Three different systems such as hydrogels, aerogels, and films of CNFs were prepared and functionalized with silver nanoparticles through the interaction of the negatively charged CNFs, obtained by TEMPO oxidation method and the positively charged silver, Ag^+ [54]. A stiff hydrogel was formed after the reaction, which was free-dried to obtain the aerogel with a potential for drug delivery applications.

1.7 Hydrogels

Hydrogels are prepared by cross-linking of polymer chains through the interactions that may be of ionic, physical, or covalent, having the ability to absorb water [55]. Hydrogels swell in water but do not dissolve in it. Due to their ability to display sol–gel transitions that can be induced by a slight changes in the environmental conditions such as temperature, pH, ionic strength, phase separation, wavelength of light, crystallinity, and others, smart polymeric hydrogels are extensively used in biomedical fields such as in the development of controlled-release drug delivery systems, tissue engineering, and regenerative medicine [56]. Several smart hydrogels such as injectable hydrogels [57], shape-memory bacterial nanocellulose hydrogels [58], supramolecular hydrogels [59], double-membrane hydrogels [60], temperature-sensitive hydrogels [61], and many others with potential for drug delivery have been developed, which were based on nanocellulose.

PNs from natural sources such as CNCs, chitin whiskers, and starch nanocrystals have been shown to impart pH sensitivity to sodium alginate microparticle hydrogels, thereby exhibiting a pH-dependent drug release [38]. About 12 h of drug release was achieved, and the drug was released through diffusional transport mechanism. A biocompatible double-membrane hydrogel was also developed based on CNCs and sodium alginate for controlled drug delivery of two drugs [60]. Two drugs, ceftazidime hydrate and human epidermal growth factor, were incorporated into the first and second membranes, respectively (Figure 1.5). Controlled release lasting form more than 6 days was achieved for the incorporated drugs. A supramolecular hydrogel prepared through the *in situ* host–guest inclusion complex between modified CNCs and β-CD was prepared with pluronic polymer for drug delivery [59]. Doxorubicin hydrochloride was taken as a model drug for studying the drug release behavior. Drug release was extended over 7 days, and when the release curves were fitted into Ritger–Peppas equation, a special drug release mechanism was observed. The study showed that with a neat pluronic/α-CD-Dox hydrogel system, drug release follows Fickian diffusion, but the *in situ* CNCs/CD-pluronic-Dox hydrogels were found to exhibit an anomalous transport release mechanism.

Hydrophilic and high biocompatible bacterial nanocellulose was investigated for its potential in controlled delivery taking serum albumin as a model drug [62]. The model drug was loaded into both never-dried bacterial nanocellulose hydrogel and the free-dried, re-swellable sample. Both the samples showed controllable

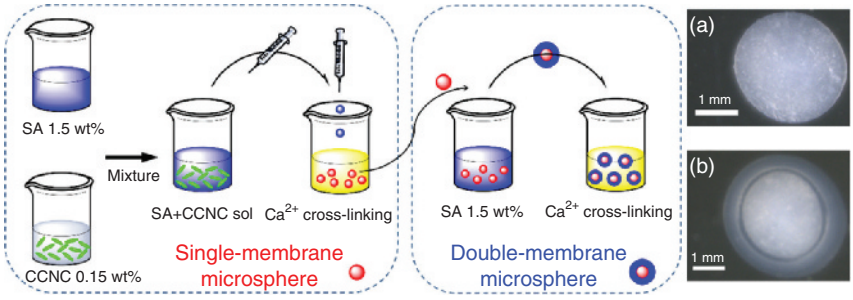

Figure 1.5 Preparation routine of single-membrane and double-membrane microsphere hydrogels; optical microscope images of (a) the SA/CCNC single-membrane microsphere hydrogel and (b) the SA/CCNC-1h double-membrane microsphere hydrogel. (Lin *et al*. 2016 [60]. Reproduced with permission of American Chemical Society.)

loading and release of the drug, and when drug release was fitted into Ritger–Peppas equation, an overlay of diffusion and swelling controlled processes was observed. The same group had also evaluated the potential of shape-memory three-dimensional (3D) bacterial nanocellulose structures for drug delivery [58]. The re-swelling behavior was found to be influenced by the tested additives such as magnesium chloride, glucose, sucrose, sorbitol, trehalose, lactose, mannitol, polyethylene glycol, and sodium chloride. The drawback that bacterial nanocellulose suffers after simple air-drying technique was solved in a simple manner by incorporation of the above additives. The characteristic fast release of the incorporated red dye azorubine was observed with the control air-dried bacterial nanocellulose as about 98% of the drug was released within the first hour. However, after modification of the nanocellulose with the hydrophilic additives, controlled re-swelling and drug release over a prolonged times could be achieved (Table 1.2).

CNF–gelatin structure for controlled release of nanocurcumin to be used for wound dressing and antimicrobial applications was developed through a

Table 1.2 Drug release mechanism.

Nanocellulose type	Dosage form	Drug release mechanism
CNC–alginate	Microspheres Hydrogel microparticle	Diffusional transport [38] Diffusional transport [38]
CNC–chitosan	Microspheres	Fickian diffusion [39]
Cellulose nanofibers	Self-assembled	First-order model [40]
CNFs (spray dried)	Matrix microspheres	Diffusion, but differ as per the drug [41]
Dissolved cellulose	Beads	Diffusion-controlled release [43]
Spray-dried CNF	Tablets	Fast drug release, fast disintegration [45]
CNC–β-cyclodextrin	Supramolecular hydrogel	Fickian diffusion [59]
Bacterial nanocellulose	Hydrogel	Diffusion and swelling [62]

green process [63]. CNF–gelatin system impregnated with nanocurcumin was reported to be superior in its antimicrobial activity against *Escherichia coli* and *Staphylococcus aureus* when compared with the non-formulated curcumin-impregnated structure. Nontoxic, injectable, and biodegradable hydrogels capable of higher nanoparticle loading was were developed using CNCs as reinforced fillers, which have great potential in drug delivery applications [57]. Bacterial nanocellulose–alginate hydrogels were also investigated for encapsulation of cells in biomedical engineering [64].

1.8 Nanocellulose in Transdermal Drug Delivery

Delivery of drugs through the skin offers several advantages over other routes including elimination of first-pass metabolism, minimization of pain, prolonged release of the drug, and the potential to terminate drug absorption by removing the patch from the skin [65]. Nanocellulose, especially bacterial cellulosic sources, has attracted a great deal of interest in the development of controlled transdermal drug delivery and wound healing preparations [66–69].

Bacterial nanocellulose-based 3D network was fabricated for controlled transdermal delivery of berberine [66]. A significant extension of drug release was achieved even when compared with the commercially available system (Figure 1.6). Drug

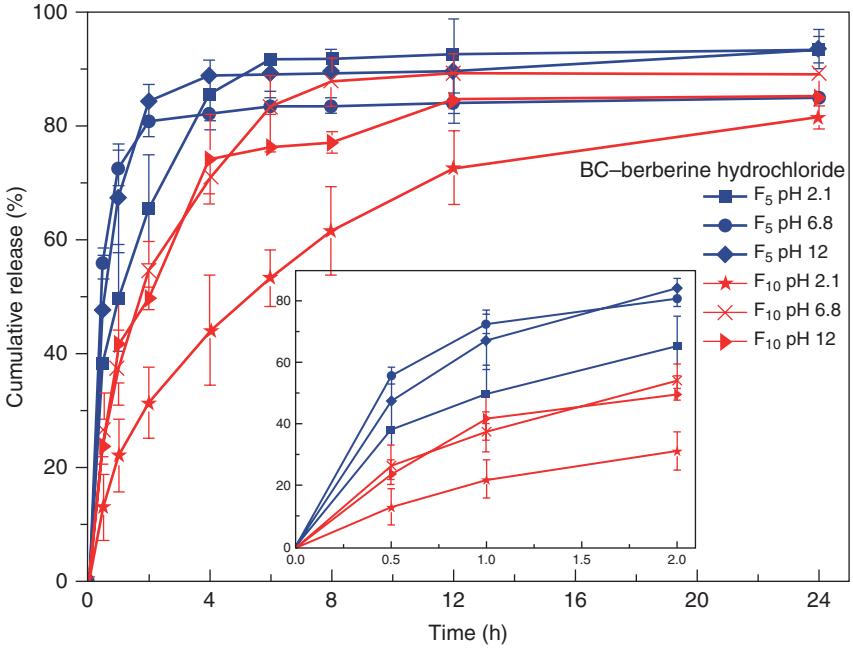

Figure 1.6 Influence of medium composition on the release from F_5 and F_{10} membranes of BC–berberine hydrochloride at 37 °C. The inset graph is an enlarged view from 0 to 2 h. Each data point is the average of six experiments ± standard deviation. (Huang *et al*. 2013 [66]. Reproduced with permission of Royal Society of Chemistry.)

release showed pH dependence, with diffusion being the most prominent drug release mechanism. An active wound dressing system based on bacterial nanocellulose was also developed, which was impregnated with an antiseptic drug, octenidine [68]. The system was found to possess physicochemical strength, high biocompatibility, and properties suitable for transdermal drug delivery. It also demonstrated antimicrobial activity against *S. aureus* and remains biologically active over a period of 6 months. A highly biocompatible system with good antiseptic property was also prepared by impregnating bacterial nanocellulose with polyhexanide and povidone-iodine [69]. Drug release was found to depend on diffusion and swelling. Bacterial nanocellulose has also been investigated for controlled transdermal delivery of other drugs such as diclofenac sodium [70, 71], and they may also be physically modified using methods such as gamma irradiation treatment [67] for transdermal applications.

A few research works on CNCs for transdermal delivery have also been dedicated in recent years. A transdermal delivery system for hydroquinone was developed to inhibit the production of melanin and prevent discoloration of the skin [72]. CNCs were prepared by sulfuric acid hydrolysis, and drug loading was done through complexation method, yielding particle size of about 310 nm. Sustained release of hydroquinone was achieved with 80% of the bound drug released in 4 h. A biocompatible and biodegradable transdermal carrier for procaine hydrochloride delivery was prepared using chitosan-functionalized oxidized CNCs [73]. At pH 8, a fast release of the drug in 1 h was obtained.

1.9 Conclusion

Nanocellulose in different forms obtained from various sources has been widely investigated as controlled drug delivery vehicle. Even though it was isolated way back in 1949, CNCs and other nanocellulosic forms have received interest in drug delivery only in the last few years. Their biocompatibility, biodegradability, and exceptional physicochemical properties definitely made them an excellent candidate in a wide range of biomedical applications. The reports available at present indicate that nanocelluloses possess the required biocompatibility and biodegradability criteria for the development of different pharmaceutical dosage forms. Investigations of different nanoparticulate preparations based on nanocellulose indicate that they interacted well with the cells and the cellular uptake mainly takes place through endocytosis. Evaluation of drug release from such controlled delivery system shows that drug release is mainly diffusion dependent and prolonged drug delivery can be achieved through proper formulation development.

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