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REVIEW ARTICLE

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Potential of magnetic nanocellulose in biomedical applications: Recent Advances

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ABSTRACT

Biopolymers have attracted considerable attention in various biomedical applications. Among them, cellulose as sustainable and renewable biomass has shown potential efficacy. With the advancement in nanotechnology, a wide range of nanostructured materials have surfaced with the potential to offer substantial biomedical applications. . The progress of cellulose at the nanoscale regime (nanocelluloses) with diverse forms like cellulose nanocrystals, nanofibres and bacterial nanocellulose) has imparted remarkable properties like high aspect-ratio and high mechanical strength, and biocompatibility. The amalgamation of nanocellulose together with magnetic nanoparticles (MNC) could be explored for a synergistic effect. In this review, a brief introduction of nano cellulose , magnetic nanoparticles and the synergistic effect of MNC is described. Further, the review sheds light on the recent studies based on MNCs with their potential in the biomedical area. Finally, the review is concluded by citing the remarkable value of MNC with their futuristic applications in other fields like friction layers for triboelectric nanogenerator (TENG), energy production, hydrogen splitting, and wearable electronics.

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Introduction

With the advancement in nanotechnology, continuous progress and innovation have been witnessed in numerous industrial and biomedical applications (Singh et al., 2019). Materials in the nano regime (1-100 nm) obtained from different natural and synthetic materials have been engineered to obtain unique physical and chemical characteristics compared to their bulk or macroscale material (Nasrollahzadeh et al., 2019). Materials in the nanoscaled dimensions can offer significant features absolute for biological functions and treatments (Wang & Wang, 2014). Therefore, the last decade has witnessed the fabrication and usage of various precisely engineered nanomaterials (Heidarian et al., 2021) for different potential biomedical applications such as tissue engineering (Barroso et al., 2020; Fathi-Achachelouei et al., 2019), wound healing, cancer treatments (Sood, Arora, et al., 2021), bioimaging (Nune et al., 2009), protein separation (Gu et al., 2006), and enzyme immobilisation (Lee & Au-Duong).

The progress in the field of technology and development has uncovered severe concerns for the environment (Mahapatra et al., 2021; Rana, Gupta, et al., 2021. This has led to evolvement in the employment of renewable and sustainable biomass for many fields, including its potential in biomedical applications (Li, 2019). For this, biobased feedstocks such as forest/agricultural residues, wood, and food waste have been considered an attractive choice to produce value-added materials (Kumar et al., 2012; Thakur & Thakur, 2015). Here, plants composed of lignocellulosic biomass (i.e., cellulose, hemicellulose, and lignin) are considered a more promising alternative due to their most abundant biopolymer system and renewable nature (Ning et al., 2021; Beluns et al., 2021). Cellulose has been considered as extremely produced sustainable biomass on earth, and structurally it is a linear chain of homo-polysaccharide glucose residues linked

through a β-1,4-glycosidic linkage (Thakur et al., 2022; Thakur & Voicu, 2016). Each monomer residue contains hydroxyl groups that form extensive intra- and inter-molecular hydrogen bonds with adjacent glucose residues in the same and nearby chains (Barhoum et al., 2020; Li et al., 2018; Moon et al., 2011; Shen et al., 2020). The mechanical stability of material plays an important role which could be explored in various applications (Verma et al., 2018). Cellulose-based biomaterials offer the advantage to fall under the category of mechanically stable and environmentally friendly.

A nano-scaled form of cellulose obtained by the disintegration of the significant cellulose residues has been reported to provide more effective opportunities in terms of biomedical applications. Therefore, cellulose has been utilised extensively in this area due to its renewability, biodegradability, hydrophilicity, biocompatibility, remarkable mechanical strength and adjustable surface modification (Heidarian et al., 2021; Patil et al., 2021)**.** Likewise, metal nanomaterials have also been flagged as an imperative candidate in the biomedical area due to their significant features compared to their bulk counterparts (Zhu et al., 2018). Different forms of metal nanomaterials, including nanoparticles, nanoclusters, nanowires, and other related nano-structures, have gained considerable attention owing to their distinctive electrical, thermal, magnetic, and catalytic characteristics (Gul et al., 2019). Among them, magnetic nanomaterials (e.g., iron oxide NPs) have remarkably attracted many research groups in the past few decades in the field of biomedicines due to their superparamagnetic properties, high magnetic susceptibility, low curie temperature, and no coercivity value (Sood et al., 2017). Therefore, a combination of nanocellulose and magnetic nanoparticles can offer a synergistic effect (Gennari et al., 2019) by representing a functional biomaterial with diverse biomedical applications. The current review focuses on the fundamental characteristics of nanocellulose and magnetic nanomaterials and sheds light on their efficacy as a synergistic material for various biomedical applications. Finally, the future implications of the blends of nano cellulose and magnetic nanomaterials is also highlighted.

1.1 Nanocellulose

Nanocellulose is a biodegradable polymer with a highly crystalline nature and is composed of a linear condensation polymerization of α-D-glucose residues linked through 1-4 glycosidic bonds (Platnieks et al., 2021; Rana, Frollini, et al., 2021; Zielińska et al., 2021). This structure of nanocellulose leads to high mechanical strength, elevated surface area, enhanced aspect ratio, and abundance of hydroxyl groups readily available for functionalisation (Klemm et al., 2020; Neibolts et al., 2020). Nanocellulose is a critical member of the nano-polysaccharide family and can be isolated from plants, bacteria and some animals (e.g., tunicates, a marine animal) in various morphologies like nanocrystalline cellulose (NCC), cellulose nanocrystals (CNCs), cellulose nanofibres (CNFs), cellulose nanowhiskers (CNWs) and other cellulose-based nanoparticles by using bacterial, chemical, mechanical and/or chemo-mechanical methods (Isogai, 2021; Platnieks et al., 2020). Nanocellulose obtained from bacteria is acknowledged as bacterial nanocellulose (BNC) with *acetobacter xylinum* being the most efficient bacteria explored in producing BNC's. BNC's are highly pure as compared to nanocellulose derived from other sources and are effortlessly differentiated from other nanocellulose forms.

CNCs are highly crystalline and needle-like structured with typical dimensions of 4-20 nm in width and 100-500 nm in length and are mainly obtained from cellulose-rich sources via acid treatment (Shankaran, 2018). On the other hand, CNFs are a concoction of crystalline and amorphous cellulose with a typical length of 1 μm and are synthesised by chemical treatment, followed by mechanical disintegration (Niaounakis, 2015). Whereas, BNCs are synthesised from different microorganisms and ranges from 20-100 nm diameter and several micrometres in length (Patil et al., 2021).

Further, CNFs constitutes of amorphous and crystalline fibrils (5-60 nm diameter) and are extracted with the help of strong mechanical process like homogenisation and ultrafine grinding or in combination with mild chemical treatments. CNFs exhibits superior flexibility and gel-like uniformity due to their amorphous regions compared to CNCs, which is highly crystalline in nature (De France et al., 2017; Du et al., 2019; Heidarian et al., 2021).

1.2 Magnetic nanomaterials

Magnetic nanoparticles (MN) constitute an important class of materials explored for biomedical applications due to their biocompatibility, upscalability, facile synthetic route and magnetic properties (Arora et al., 2020). The magnetic properties of MN are highly dependent on their size, as with the decrease in size, the surface effect dominates, which further influences its magnetic properties (Sood et al., 2016). The biomedical applications of MN mainly include magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) but ferrites have also been explored by many researchers (Wang et al., 2020). Diverse routes for synthesising MN have been reported in the literature, including co-

precipitation, sol-gel, ultrasonication, irradiation, laser ablation, microwave and electrochemical, and physical vapour deposition etc. (Mosayebi et al., 2017). The physicochemical properties of MN, such as shape, size, charge, hydrophilicity and hydrophobicity, could be modulated to escape the elimination from the body's immune system and can endure the endocytosis process (Veiseh et al., 2010).

1.3 Magnetic nano cellulose (MNCs)

Magnetic nanoparticles find their applicability in a wide range of fields like water purification (Moosavi et al., 2020; Zhang et al., 2016), Magnetic Resonance Imaging (MRI) (Jain et al., 2008; Sood, Dev, et al., 2021), biosensors (Du et al., 2019; Rocha-Santos, 2014), cancer treatment (Dürr et al., 2013; Wu & Huang, 2017), and drug delivery (Anderson et al., 2019; Arruebo et al., 2007). Although MN features numerous advantages, however, few shortcomings can also be associated with MN. Although MN can be collected under the influence of magnetic fields after completing any designated process, its removal from suspension is a challenging task as MN are very prone to aggregation and tends to oxidise very easily. This limits their saturation magnetisation due to interparticle dipolar forces' dominance (Saville et al., 2013). To address the aggregation issue related to MN, researchers use different approaches such as polymeric templates to synthesise in situ MN, functionalisation of MN and designing polymer composites (Amiralian et al., 2020). Among different materials used to protect MN, nanocellulose offers remarkable opportunities due to its remarkable characteristics. The presence of an abundance of the hydroxyl group in the structure of nanocellulose plays a vital role in providing a nanofiber network (through hydrogen bonding) to condensate MN. Magnetic nanocellulose has shown a noteworthy aptitude to be used as a next-generation material for diverse applications.

2. Potential applications of MNC

2.1 Tissue engineering

Constant efforts are being made to search for effective biomaterials that can contribute to the regeneration of injured biological tissues. Metals and graft that were used traditionally are now being replaced by polymer-based constructs that have shown commendable results (Ferreira et al., 2020). To facilitate this issue, MNC has acquired the attraction of many researchers due to its biocompatibility, non-porous network and high water retaining ability. To take advantage of this remarkable biomaterial, Pastrana *et al.* fabricated magnetite (Fe_3O_4) reinforced BNC nanofibers. BNC as a biomaterial has attracted a great attraction due to its distinctive nanoporous network with high water retention and mechanical properties and biocompatibility (Fig. 1). Therefore, BNC as a scaffolding biomaterial has widely been applied in tissue engineering applications. For specific cell attraction, the Fe_3O_4@BNC matrix is supposed to drive magnetically labelled cells to specific tissues for healing damaged tissue. Fe3O4@BNC matrix fibres' diameter was 33% smaller than that of only BNC fibres, whereas pore areas were 25% larger (pore size for BNC: 121 m^2, Fe_3O_4@BNC:161 m^2). Further, the cytotoxicity analysis showed 96% viability of porcine aortic smooth muscle cells for BNC, Fe3O4@BNC, and poly (ethylene glycol) (PEG)-coated Fe_3O_4@BNC and exhibited 9% reactive oxygen species (ROS) production PEG-Fe_3O_4@BNC. In contrast, 25% of cells when exposed to Fe3O4@BNC were apoptotic due to their damaging effect even when cells were metabolically active (Pastrana et al., 2016).

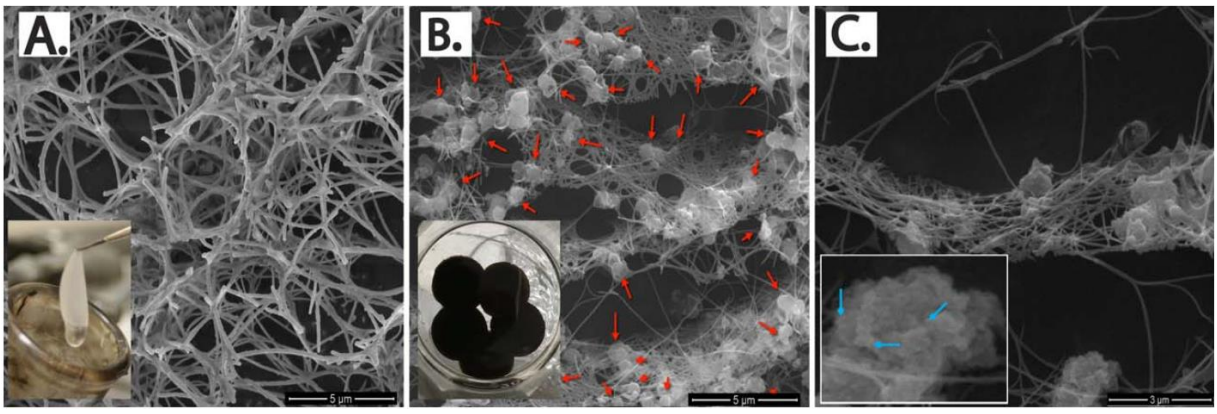

Figure 1. Synthesised BNC without and with Fe_3O_4 NPs. (A) Cryo-SEM images of the cross-section of BNC before adding Fe_3O_4 NPs (inset: BNC produced by *G. xylinus*), (B) BNC fibres attached with Fe_3O_4 NPs clusters (inset: Fe_3O_4@BNC samples), and (C) magnified SEM image of Fe_3O_4 NPs clusters attached to BNC fibres (Inset: the cluster of Fe_3O_4 NPs) Reproduced with permission from [Pastrana et al., 2016]. Copyright 2016 Wiley

MNC has also found its utility in brain-related pathological conditions. Aneurysms are pockets of blood (hematomas as blood pools under the skin) that are collected outside the layer of blood vessel walls and weaken the walls. In this case, brain aneurysms are more critical and their current treatments are invasive, traumatic, and not appropriate in most of the patients having enhanced risks. Therefore, scaffold stents facilitate a local and focal attraction force of the cells for an *in-situ* resetting of the tunica media. For this purpose, a nanostructured bioactive coating to furnish an asymmetric domain for stent scaffold to be biomimetic and magnetic, where BNC is used as platform for both magnetic and cell attraction, and thereby proliferation. In this regard, Echeverry-Rendon *et al.* synthesised *in-situ* BNC hydrogel membrane impregnated with superparamagnetic Fe_3O_4 NPs (Fe_3O_4/BNC) and further coated the hydrogel with PEG to enhance its biocompatibility (Fig. 2). This multifunctional hydrogel was evaluated for neuroendovascular application by using a stent scaffold and showed good viability and migration of porcine aortic smooth muscle cells and exhibited minimal cytotoxicity (Echeverry-Rendon et al., 2017)

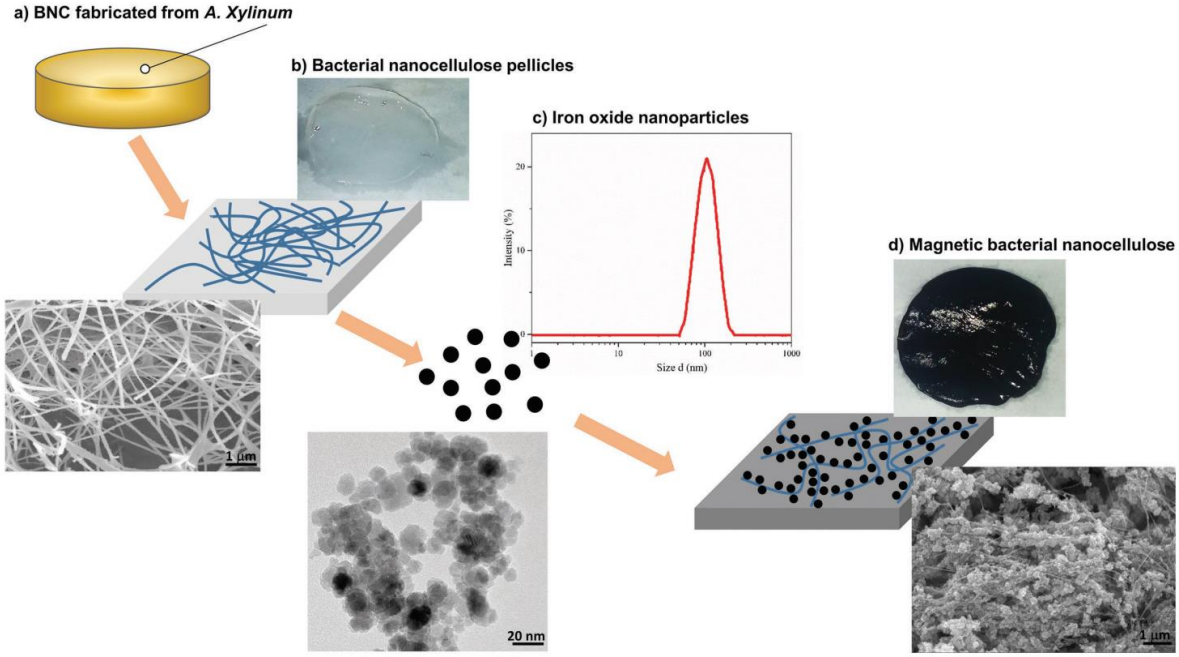

Figure 2. (a) BNC synthesised by *A. xylinum* bacteria, (b) digital and SEM images of BNC hydrogel membrane, (c) TEM and DLS assessments of Fe3O4 NPs, and (d) Digital image of Fe3O4/BNC and its detailed SEM evaluation (SEM analysis exhibits strong bonding of Fe3O4 NPs on BNC fibres). Reproduced with permission from [Echeverry-Rendon et al., 2017]. Copyright 2017 Wiley.

Moreover, Pavón *et al.* targeted the use of MNC for brain injury aneurysms as conventional clinical methods such as surgical clipping and endovascular coiling have shown partial success in penetrating brain injury aneurysms. This study focused on in-situ diagnosis of nano-mechanical behavior of BNC membranes (in aqueous surroundings) applied as tissue regenerative substrates for cerebral aneurysmal neck orifice. BNC hydrogel membrane with local attachment of Fe_3O_4 NPs to a stent scaffold at the aneurysms neck orifice for improving revascularisation modality was developed and presented. A very low normal load from 0.01 to 0.5 mN was observed in the presence of water (deionised). Further, BNC serves similar to blood vessel walls having a very low Young's modulus (E: 0.0025-0.04 GPa) and a noticeable creep effect (26.01±3.85 nm s^{-1}) (Pavón et al., 2019). These studies have shown the potential of MMC based scaffolds in neural diseases conditions. With the aid of MNC, thrombus formation and rupturing of aneurysms near arterial walls are also targeted. Therefore, the coating as flexible and resilient magnetic.

In another study, BNC was synthesised *in-situ* using the bacteria *G. xylinus* strain and impregnated *in-situ* with Fe_3O_4 NPs to develop magnetic Fe_3O_4/BNC pellicle by Arias *et al.* Further to improve its biocompatibility, Fe_3O_4/BNC was coated with PEG. Fe3O4 NPs were located preferentially in the fibril interlacing spaces in this BNC matrix, and some of them were found along the BNC ribbons. Also, the results exhibited the presence of magnetic regions under weak and high-intensity magnetic field and mechanical properties (i.e. reasonable agreement of

Young's modulus values with previously reported values for various blood vessels) (Arias et al., 2016). In addition, tissue-engineered vascular grafts (TEVG) cells with or without scaffold are required to realize tissue remodeling and expansion of damaged blood vessels. This process may take many weeks due to hemodynamic shear stress at the injured site, which causes cellular vulnerability and diminishes tissue ingrowth. In this case, magnetic BNC demonstrated the capability to produce a force to speed-up re-endothelisation at the vascular defect by smoothing high cell density coverage, especially during first 24 h after implantation. Therefore, *in-situ* precipitated Fe_3O_4/BNC and then coated by dextran to protect Fe_3O_4 from oxidation.

Further, this composite system was applied to target cells locally (*in-vitro*) under dynamic flow conditions (a pulsatile fluid flow: 0.514 dynes cm^2) and significantly enhance smooth muscle cell homing at TEVG without using blood cessation. The obtained magnetic hydrogel system showed magnetisation upto 10 emu/g (higher than the relevant value (0.05 emu/g) for tissue engineering). Moreover, these characteristics are dependent on Fe_3O_4 amount (Arias et al., 2018). However, for bone tissue engineering, hydroxyapatite (HAp) and Fe_3O_4 NPs have been uniformly dispersed into the BNC matrix through ultrasonic irradiation and improved physicochemical and mechanical properties superparamagnetic properties, and excellent thermal stability of the scaffold system. In this study, after deposition of HAp with superparamagnetic character, a reduction in saturation magnetisation of HAp-Fe_3O_4/BNC (porosity: ~80%) was observed from 15.84 to 3.94 emu/g at ±10KOe as well as. Moreover, the obtained exhibited non-toxicity to mouse fibroblast L929 cells and showed positive attachment and proliferation potential of human osteoblast MC3T3 cells onto the scaffold (Torgbo & Sukyai, 2019). It could be concluded that BNC based matrix could play the dual role of condensing magnetic nanoparticles and offer the ability for cell attachment, which makes it a persuasive contender for tissue engineering applications.

2.2 Drug delivery

With the rapid evolution of nanotechnology, nanomaterials have been utilised tremendously in drug delivery applications (Patra et al., 2018). Further, magnetic nanoparticles, particularly Fe_3O_4 NPs have -remarkably provided supplies in designing scaffolding systems for controlled and targeted drug delivery due to their excellent anti-microbial property and relatively low toxicity to human beings (El-Boubbou, 2018; Vangijzegem et al., 2019). However, biological performances of magnetic NPs are dependent on their shape, size, surface functionality, and hydrophobicity (Nypelö et al., 2014; Prabhu et al., 2015; Zhang et al., 2019). For example, the self-standing films and electrospun fibres composed of poly(vinyl alcohol), CNCs (150 nm in length), and cobalt-iron NPs (Co-Fe_2O_4, 10-80 nm in diameter) have been fabricated and examined by Nypelö *et al.* The obtained system was ferromagnetic with a saturation magnetisation of 20 emu/g and demonstrated efficacy for the applications such as fluid hyperthermia and other biomedical applications (Nypelö et al., 2014). In another study, Supramaniam *et al.* prepared hydrogel beads from the assembly of alginate and Fe_3O_4/CNCs for drug delivery applications. In this study, CNCs were extracted from the rice husks and then Fe_3O_4/CNCs were prepared by co-precipitation method. Further, Fe_3O_4/CNCs were added into alginate-based hydrogel beads for better mechanical properties and regulated the release behavior of Ibuprofen as model drug. The obtained composite hydrogel beads exhibited the drug's controlled release profile and drug release mechanism was analyzed, analysed, and discussed with mathematical models (Supramaniam et al., 2018).

Moreover, Tade *et al.* undertook similar study by developing Fe_3O_4/CNFs composite system through *in-situ* co-precipitation method and Nystatin (Nyst) as model drug was loaded into Fe_3O_4/CNFs composite. The resulted composite system was observed to be porous and aggregated structure of CNFs. The BET surface area and BJH pore size were measured as 13.42 m^2g^{-1} and 104.48 Å, respectively. Due to the porous nature of CNFs network, high loading capacity of approximately 17.8% could be achieved with Nyst-loaded Fe_3O_4/CNFs composite exhibited controlled drug delivery for upto 8h compared to the release of pure drug. In addition, the composite showed prominent antifungal activity as evaluated on *Candida Albicans* (Tade et al., 2018). However, Chaabane *et al.* developed a novel magnetic composite material composed of tetraaza macrocyclic Schiff-base BNC ligands and Fe_3O_4 NPs through a multi-step process for anti-microbial, cytotoxic properties chemotherapy in cancer treatment. Here, 2,3-dialdehyde BNC (DABNC) was prepared using sodium periodate and was furtherfunctionalised by ethylenediamine (EDA) and benzyl (Bzl) in the presence of ferrous ions. Finally, Fe_3O_4 NPs were prepared inside the complex system [Fe(DABNC-EDA-Bzl)Cl_2)] through *in-situ* co-precipitation method. This magnetic complex system Fe_3O_4-INS (DABNC-EDA-Bzl) exhibited stronger anti-microbial and cytotoxic activities against a wide range of species and cells with no cytotoxicity towards normal cells (peripheral blood mononucleocyte (PBMC) cells). Furthermore, this magnetic complex effectively inhibited the growth of CT26 tumor model in BALB/c mice (Chaabane et al., 2020). To design an effective system for drug delivery applications, the

size, morphology, charge, encapsulation efficiency and degradation rate plays a crucial role. MNC offers the right platform to be used as a drug delivery system to be further upgraded for theranostic applications.

2.3 Gene delivery

Safe and well-ordered delivery of genes into cells is a vital goal in the evolution of nucleic acid therapeutics. Therefore, Anirudhan *et al.* developed a novel gene carrier composed of aminated *β*–cyclodextrin-modified-carboxylated magnetic cobalt/nanocellulose composites (ACDC-Co-/NCC) for the efficient gene transfection into tumor cells. ACDC-Co-/NCC exhibited enhanced DNA condensing ability with increased content of ACDC-Co-/NCC. The incorporation of 84.9% DNA (1.0 µg/mL) was observed in 6.0 µg/mL ACDC-Co/NCC, and minimal cytotoxicity was observed even at high concentration with respect to the model transfecting agent. Moreover, 88.2% of the gene was transfected at a high DNA dose (Anirudhan & Rejeena, 2014). The area is still unexplored and further research in the applicability of MNC for gene delivery could aid in the development of a cost-effective methodology with high efficiency.

2.4 Wound healing

Various efficient strategies have widely been developed to treat and improve the healing process of chronic wound healing and thereby are associated with social impacts. In this advancement, 3D cell cultured-scaffolds prepared by pre-seeding drug-loaded scaffolds with undifferentiated cells in order to achieve *in-situ* functional neotissue is a modern tissue engineering approach. Therefore, Galateanu *et al.* prepared Fe_3O_4/BNC bio-nanocomposite membranes by directly dispersing various amounts of Fe3O4 NPs into the cellulose bacterial culture medium during the biosynthesis process. The obtained composite membranes exhibited good cytocompatibility properties like cellular morphology, viability, proliferation and cytotoxicity (Galateanu et al., 2015). Enhanced understanding of wound healing, gene interaction and routes involved in healing process has been achieved through molecular biology. In this advancement, Moniri *et al.* developed Fe_3O_4/BNC nanocomposite films as wound dressing and investigated physicochemical, cytotoxicity, anti-microbial properties, and gene expression involved in wound healing after treating films. In this study, Fe_3O_4 (15-30 nm) were biosynthesised by the extract of Aloe vera in newly isolated BNC. The Fe_3O_4/BNC films exhibited non-toxicity (IC50.500 µm/mL) with remarkable wound healing efficiency (after 48 h) and good antibacterial property (from 6±0.2 to 13.40±0.10 mm) against *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Pseudomonas aeruginosa*. Further, Fe_3O_4/BNC films showed an effect on microRNA by diminishing its expression and thereby caused gene expression enhancement of other genes that eventually occurred in wound healing (Moniri et al., 2018). Antibacterial property of a material could be explored for a number of applications (Kummara et al., 2017), including wound healing. Wound healing is a complex process and involves many steps (Haider et al., 2018). The application of MNC based constructs could further aid in achieving a high successful rate of wound healing. Incorporation of growth factors along with Fe_3O_4/BNC films could further refine the process and aid in attaining wound healing at a higher pace.

2.5 Protein separation and segregation

Protein is an essential component of life and constitutes the framework and plays the role of main constituent of human tissues and organs. The applicability of proteins can be perceived in almost every activity of an organism. Protein separation from biomaterials and their structural and functional analysis holds inordinate importance in comprehending the law of life phenomena. Therefore technological advancement in protein separation plays a momentous role(Liu et al., 2020). In this regard, Anirudhan *et al.* prepared a multicomponent superabsorbent composite made of poly (methacrylic acid-co-vinyl sulfonic acid)-grafted-magnetite/nanocellulose (P(MAA-co-VSA)-g-MNC) for the selective recovery and separation of the antibody as an immunoglobulin (IgG) from aqueous solutions. The swelling of the superabsorbent composite was observed to be increased with pH and time. Also, the antibody was adsorbed onto a superabsorbent composite and 3.0 g/L adsorbent dose was sufficient for complete recovery of IgG from the aqueous solutions. Here, the maximum adsorption was measured at pH 6.8 with 3 h as equilibrium time. The kinetic rate was adequately described by pseudo-second order kinetic model and the experimental adsorption isotherms of IgG were efficiently fitted with Sip model. The maximum adsorption capacity as 200.21 mg/g (30^{o}C) was measured based on Langmuir model, where adsorption of IgG was highly dependent on ionic strength. Furthermore, the results on IgG separation from the mixture of proteins showed its better utilisation in biomedical areas. Moreover, spent adsorbent was regenerated without any remarkable loss in adsorption capacity by treating with 0.01M KOH (Anirudhan & Rejeena, 2013).

Further, Guo *et al.* synthesised *in-situ* hybrids of Fe_3O_4 NPs and CNCs through co-precipitation process. In this study, CNCs were oxidised by using 2,2,6,6-tetramethylpiperidine-1-oxyl radical

(TEMPO) and amine-containing Fe_3O_4 NPs were prepared by using dopamine ligand exchange (NH_2-Fe_3O_4 NPs), and then both were reacted to prepare hybrids of Fe_3O_4@CNCs through carbodiimide reaction. As-obtained Fe_3O_4@CNCs hybrid system was further complexed with Cu(II) ions to develop specific protein binding sites (**Fig. 3**). This developed Cu-Fe_3O_4@CNCs hybrid showed a significant binding ability with lysozyme (860.6±14.6 mg/g), whereas almost full recovery (~98%) was attained by simple elution. Also, Fe_3O_4@CNCs hybrids were regenerated and reused for protein separation effectively. Moreover, lysozyme was separated from the matrices having egg white (Guo et al., 2017). However, Zhang *et al.* prepared a core-shell structured nanomaterial composed of Fe_3O_4 NPs and their coating with 2,3-dialdehyde nanocrystalline cellulose (DA-NCC). Fe_3O_4@DA-NCC core-shell structured materials were further attached to 4-aminophenyl boronic acid (PBA) to obtain Fe_3O_4@DANCC-PBA. This core-shell system showed good affinity adsorption of glycoproteins through the active sites (aldehyde groups) in forming a complex with glycol-sites in glycoproteins. In this case, the preconcentration characteristics of the core-shell system through PBA adsorption could be pH-triggered with disassembling the complex structures. Moreover, this complex system exhibited a high efficiency towards affinity adsorption and purification of glycoproteins (Zhang et al., 2020)

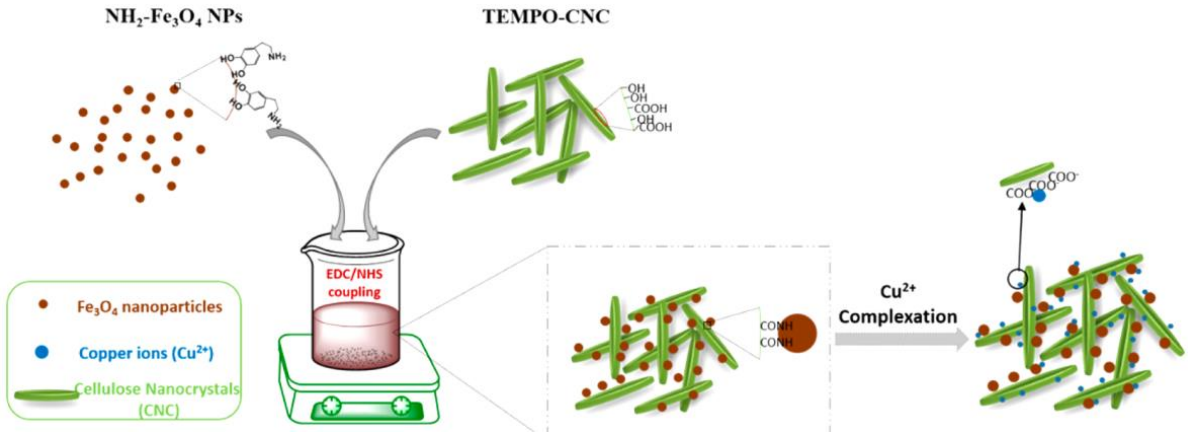

Figure 3. Schematic presentation of the preparation of Cu(II)-complexed Fe_3O_4@CNCs hybrids. Reproduced with permission from [Guo et al., 2017]. Copyright 2017 American Chemical Society

Amyloid-like aggregation of proteins is a general characteristic of their polypeptide chains, which are majorly responsible for different pathological situations and diseases. This aggregation transforms soluble proteins to insoluble fibrils and deposits in specific body tissues, accounting for different diseases (Matiiv et al., 2020). To overcome this aggregation, organic-inorganic hybrid nanocomposite systems were prepared by Singla *et al*. through *in-situ* synthesis of Fe_3O_4 NPs (~6.5-7.0 nm)@CNCs (that were extracted from the plant leaves of *Syzygium cumini* (SC) and *Pinus roxburghii* (PR) needles) to analyse their effect on inhibition and dissociation of human serum albumin (HSA). The results from short-fibre-based SC nanocomposite systems exhibited better inhibition and dissociation of HSA aggregates. Native poly (acrylamide) gel electrophoresis concluded reported dissociation of higher protein aggregates in the presence of prepared nanocomposite system. Notably, the dissociated proteins maintained their biological activity by retaining a high amount of α-helix. Further, this developed nanocomposite system reduced aggregation-induced cytotoxicity in-vitro by intracellular reactive oxygen species (ROS) scavenging and preserving the Ca^{2+} ion-channel.

Moreover, this nanocomposite system provided concurrent sites for hydrophilic and hydrophobic interactions and a higher surface area for Fe_3O_4@CNCs and protein interactions that eventually disfavors the nucleation pace fibrillation for protein aggregates (Singla et al., 2019). Facile and cost-effective protein isolation and purification method marks the beginning of many experiments related to the understanding of protein structures and their biologic activity. MNC have the ability to efficiently and effectively isolate proteins and the abundance of cellulose in nature makes it a cost-effective material for protein separation.

2.6 Cancer treatment

Cancer has been flagged as the second leading cause of global deaths. Early detection and effective cancer treatment are still the focus of research worldwide (Nagai & Kim, 2017). A wide range of materials have been under investigation in order to achieve the

goal of cancer treatment and early detection. In this regard, Torkashvand *et al*. developed a composite system as dual positive and negative (T1-T2) contrast agent based on ultra-small superparamagnetic Fe_3O_4 NPs for magnetic resonance imaging (MRI). The study reported the synthesis of Fe_3O_4 NPs by thermal decomposition process and then loaded onto CNCs-poly (citric acid) (Fe_3O_4/CNCs-PCA) platform. The obtained composite exhibited high saturation magnetisation (52.2 emu/g), ultra-small hydrodynamic size, hydrophilicity, water dispersibility, and colloidal stability. Also, Fe_3O_4/CNCs-PCA showed remarkable biocompatibility, non-significant cytotoxicity *in-vitro* (upto 200 µg/mL Fe) and substantial cellular uptake with regard to HeLa cells. Furthermore, Fe_3O_4/CNCs-PCA exhibited excellent contrast improvement on both T1 and T2-weighted MR images (high values of r1: 13.8 $mM^{-1}s^{-1}$ and r2: 96.2 $mM^{-1}s^{-1}$) relaxivity as compared to commercial and clinical agents) (Torkashvand & Sarlak, 2019)**.** Compared to conventional chemotherapy, nanotechnology combined with stimuli-responsive and activated agents have shown a great interest as cancer therapeutics. Therefore, Zhang developed a targeted drug delivery system to improve tumour growth inhibition by targeting cancer under a static magnetic field and laser irradiation. In this study, Fe_3O_4 NPs were used as the core coated with hydrogels of loaded both doxorubicin (DOX) and hematoporphyrin monomethyl ether (HMME) and then grafted with folic acid onto the surface of the composite system to establish a laser-responsive Fe_3O_4 NPs (L-Fe_3O4). Further, these L-Fe_3O_4 NPs were loaded into BNC membrane. The results exhibited 80.38% tumor growth inhibition after 14^{th} day of the treatment. Moreover, laser-activable and magnetic-targeting L-Fe_3O_4 NPs exert a synergistic effect on breast cancer inhibition and may provide a solution for the cancer treatment challenges, specifically limited penetration depth and oxygen-deficient microenvironments (Zhang et al., 2019).

2.7 Miscellaneous

Nanomaterials, especially anti-microbial nanoparticles, have attained great attraction due to increased demand in the community healthcare systems (e.g., water purification, infectious and chronic wounds) (Sonawane et al., 2018). Among various anti-microbial agents, silver nanoparticles (AgNPs) exhibited remarkable efficacy towards various bacteria, fungi, and viruses (Kim et al., 2007). On consideration this efficacy, Fe_3O_4 NPs were *in-situ* precipitated inside the BNC matrix and then coated with self-polymerised polydopamine (PDA) adherent layer. Further, it was soaked in silver nitrate solution and the PDA surface effectively reduced it to form AgNPs within the Fe_3O_4/BNC nanocomposite matrix. As-prepared AgNPs-Fe_3O_4/BNC exhibited high anti-microbial property against *Escherichia coli* and *Bacillus subtilis*. Also, this nanocomposite showed sterilising ability for LB culture medium by showing no significant contamination in a freshly prepared medium for 4 h (Sureshkumar et al., 2010)**.** The work could have implication in the food industry as a packaging material. Further improvement could be achieved in this field by studying the time dependent study on the anti-microbial effect of the designed system.

The life activities of humans revolves around enzymes. Enzymes are natural catalysts that speeds up many biochemical and chemical reactions (Homaei et al., 2013). Free enzymes are less robust and prone to environmental changes compared to immobilised enzymes. This marks the importance of enzyme immobilisation. Enzyme immobilisation and its efficient stability by using a suitable carrier is a desirable approach. In this regard, papain (PA) was immobilised favorably onto magnetic nanocrystalline cellulose (PA@Fe3O4/NCC) to prepare a nano-biocatalyst as potential carrier for enzyme immobilisation through co-precipitation/crosslinking method (Fig. 4). This nanocomposite system showed remarkable stability than that of Fe_3O_4/NCC and exhibited highly loading of PA (333 mg/g) and enzyme activity recovery (more than 80%). Here, PA@Fe_3O_4/NCC demonstrated significantly improved solvent tolerance as well as pH and thermal stability higher than the respective free counterpart. This composite system exhibited enhanced enzyme-substrate affinity for efficient biosynthesis of N-(benzyloxycarbonyl)-alanyl-glutamine dipeptide in deep eutectic solvent (choline chloride: urea (1:2)) with a high yield around 71.5% and recycled easily from the green reaction medium by using magnetic forces. Moreover, PA@Fe_3O_4/NCC showed higher biocatalytic efficiency and lower activation energy (Cao et al., 2015).

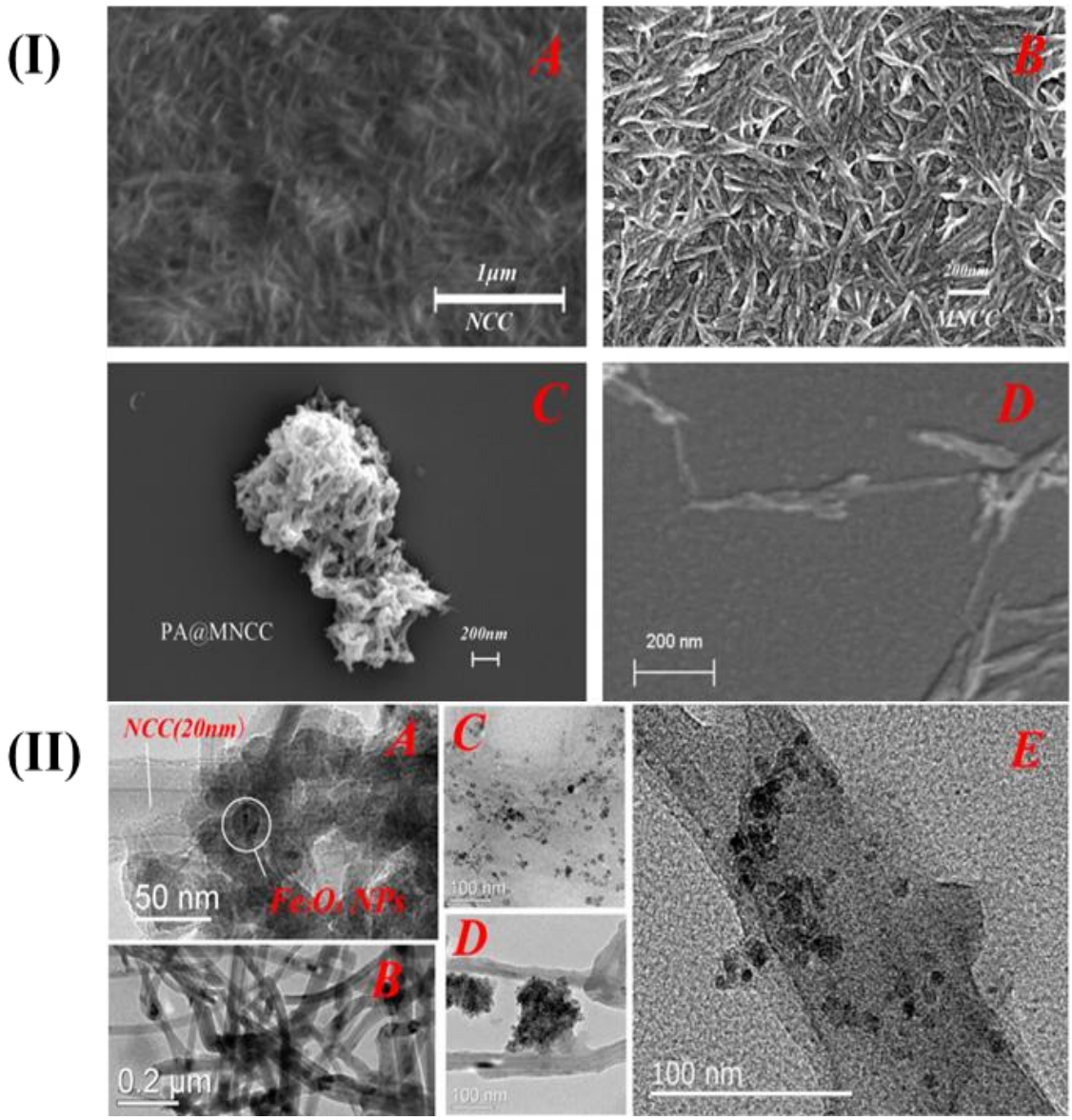

Figure 4. (I) SEM images of NCC (A), Fe_3O_4/NCC (B, D), and PA@Fe_3O_4/NCC (C). (II) TEM images of Fe_3O_4/NCC (A, B), Fe_3O_4 (C), a comparative co-precipitation method with epichlorohydrin crosslinker (D), and PA@Fe_3O_4/NCC (E). Reproduced with permission from [Cao et al., 2015]. Copyright 2015 American Chemical Society

Further, in this advancement, Drozd *et al*. developed a BNC bead spheres-based immobilisation carrier through amination and inlaid functionalisation with superparamagnetic molecules for Lecitase® Ultra (LU). In this study, BNC bead spheres were biosynthesised by using *Komagataeibacter xylinus* and subjected to further modifications. The results exhibited 70% as maximum yield of LU immobilisation and this process did not affect the optimum pH and LU, and enzyme KM value remarkably. This immobilised LU showed temperature stability profile as similar to its native form. Further, the immobilised enzyme maintained over 70% of its elementary activity after using through 8 cycles and showed good storage stability (80% of its initial activity) after 4 weeks (4ºC) (Drozd et al., 2019).

Magnetic nanocellulose (MNC) can offer significant features with utility in a wide range of applications. The field of MNC is fascinating and have shown its potential in biomedical applications, drug delivery, wastewater treatment, protein separation, tissue engineering. MNC are being reviewed for many industrial-based applications with the capability of scale-up. Table 1 summarises the utility of MNC in various fields

Hybrid	**Other components**	**Synthesis method**	**Application**	**Remark**	**Ref.**
Fe_3O_4@CNCs	Poly citric acid	Ex-situ synthesis/polymerization/ultrasonication/solvent-casting	Contrast agent for Magnetic resonance imaging	negligible in vitro cytotoxicity and considerable cellular uptake, High contrast enhancement in MRI	(Torkashvand & Sarlak, 2019)
Fe_3O_4@BNC	Poly ethylene glycol	In-situ co-precipitation	Tissue engineering	High viability, low ROS production	(Pastrana et al., 2016)
Fe_3O_4@BNC	Poly ethylene glycol	In-situ co-precipitation	Neuro-endovascular reconstruction	Enhanced cell proliferation and recovery	(Echeverry-Rendon et al., 2017)
Fe_3O_4@BNC	NA	In-situ co-precipitation	Neuro-endovascular reconstruction	High elastic property, Adequate mechanical resposne	(Pavón et al., 2019)
Fe_3O_4@BNC	Poly ethylene glycol	In-situ co-precipitation	Tissue engineering	Adequate Young's modulus for blood vessels	(Arias et al., 2016)
Fe_3O_4@BNC	DEX	In-situ co-precipitation	Tissue engineering	Young's Modulus in the range of 200–380 KPa, ability to capture and improve cell retention	(Arias et al., 2018)
Fe_3O_4@BNC	Hydroxyapatite (HAp)	Ultrasonic-served co-precipitation	Bone tissue engineering	Uniform distribution of Fe_3O_4 and Hap NPs in BNC matrix, Enhanced porosity (81.1%) and mechanical properties (9.87 MPa and 1.85 GPa)	(Torgbo & Sukyai, 2019)
Fe_3O_4@BNC	Pematoporphyrin monomethyl ether (HMME), Folate acid	In-situ co-precipitation	Breast cancer treatment	Targeted drug delivery	(Zhang et al., 2019)
$CoFe_2O_4$@CNCs	NA	In-situ co-precipitation	Magnetic fluid hyperthermia, drug delivery	Responsive to low strength magnetic fields, easily separated from the medium	(Nypelö et al., 2014)
Fe_3O_4@CNFs	Alginate	In-situ co-precipitation	Drug delivery	Improved physical and mechanical properties, increased swelling behavior decreasing the drug release rate	(Supramaniam et al., 2018)
Fe_3O_4@CNCs	NA	In-situ co-precipitation	Drug delivery	Sustained drug release, antifungal acticity	(Tade et al., 2018)
Fe_3O_4@BNC	Ethylenediamine and benzil	In-situ co-precipitation	Cancer treatment	Narrow size distribution, stronger anti-microbial and cytotoxic activities	(Chaabane et al., 2020)
Co@CNC	β-cyclodextrin	Chemical precipitation	Tumor-targeted gene delivery	88.2% of the gene was transfected at high dose of DNA	(Anirudhan & Rejeena, 2014)
Fe_3O_4@BNC	Polyethylene glycol	Agitation culture	Wound healing	Uniformly dispersed Fe_3O_4 NPs, Enhanced cellular proliferation	(Galateanu et al., 2015)
Fe_3O_4@BNC	NA	In-situ co-precipitation	Wound healing	Excellent wound healing efficiency after 48 hours, Antibacterial activity	(Moniri et al., 2018)
Fe_3O_4@CNCs	Poly methacrylic acid Vinyl sulfonic acid	In-situ co-precipitation	Immunoglobulins (IgG) separation and recovery	Selective separation of IgG from mixture of proteins, Enhanced recovery rate	(Anirudhan & Rejeena, 2013)
Fe_3O_4@CNCs	Cu (II) ions	Agitation	Protein separation	Lysozyme was separated from matrices having egg white	(Guo et al., 2017)
Fe_3O_4@DA-CNCs	4-aminophenylboronic acid	Chemical crosslinking	Adsorption and purification of glycoproteins	Affinity towards the adsorption of glycoproteins, Superior magnetic response, adsorption capacity, recovery, and reproducibility	(Zhang et al., 2020)
Fe_3O_4@CNCs	Human serum albumin	In-situ co-precipitation	Neurodegenerative disorders	Inhibition of protein aggregation	(Singla et al., 2019)
Fe_3O_4@BNC	Silver NPs (AgNPs)	In-situ co-precipitation	Antibacterial	Easy recovery of AgNPs, ability to sterilise LB culture medium	(Sureshkumar et al., 2010)
Fe_3O_4@CNCs	Papain	In-situ co-precipitation	Nanobiocatalyst	High papain loading (333 mg/g) and recovery (≥80%)	(Cao et al., 2015)

Fe_3O_4@BNC	Polyethyleneimine	In-situ co-precipitation	Enzyme immobilisation	Easy separation, efficient immobilisation	(Drozd et al., 2019)

Table 1. Application of magnetic nanocellulose-based functional materials for biomedical applications

Conclusions

Nanocellulose, with its unique structure and properties, offers a compelling platform for diverse applications. The presence of abundance hydroxyl group aids in functionalisation of nanocellulose that further enhances the applicability of this interesting biomaterial. With the amalgamation of magnetic nanomaterials, the range of its applicability is further augmented. Magnetic nano cellulose (MNC) have been widely used for biomedical applications. The importance of MNC has been proved in fields like protein separation and enzyme immobilisation that plays a significant role in the normal life activities.

Furthermore, there are high chances that in the near future we will see the applicability of MNC in other fields like friction layers for triboelectric nanogenerator (TENG), energy production, hydrogen splitting etc. MNC could also play a massive role in the development of self-powered implantable or wearable electronics. Many opportunities are still awaited to be explored for the use of MNC and take advantage of significant characteristics.

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