CELLULOSE-BASED COMPOSITES AND THEIR BIOMEDICAL APPLICATIONS

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Biopolymers have gained significant attention from researchers belonging to diverse fields, due to their unique physicochemical properties, renewability, biocompatibility and biodegradability, rendering them suitable for a wide variety of applications. Within its class of materials, cellulose has been the most widely exploited one. The present review aims to critically appraise the reported biomedical applications of cellulose and cellulose-based composite materials. The fabrication methods of the composites are discussed in brief and subsequently, the biomedical applications, including tissue engineering, wound healing, drug delivery *etc*., are reviewed.

Keywords: cellulose, composite material, drug delivery, biomedical application, tissue engineering, wound healing

INTRODUCTION

The past decade has witnessed remarkable biomedical applications of materials derived from natural resources, such as cellulose, starch, alginic acid, chitosan, collagen fibre, elastin, gelatin, *etc*.[1-6] Amongst these resources, cellulose is probably the most abundant organic compound produced in the biosphere. A variety of living organisms are responsible for its biosynthesis, yielding about 7.5×10^{10} metric tons *per annum*.[7] This fascinating biopolymer has interesting physico-chemical properties, renewability, biocompatibility and biodegradability, rendering it suitable for a variety of applications. Recently, nanocelluloses have attracted a tremendous level of research attention, as evident from the increasing number of scientific contributions and industrial investments in diverse fields.[8-10] The family of nanocelluloses consists of cellulose nanocrystals, cellulose nanofibrils, amorphous nanocellulose, cellulose nanoyarn and bacterial nanocellulose. In this review, we focus on polymer composites of cellulosic materials and their biomedical applications. The performance of polymeric composite systems reinforced by natural fibres like cellulose are highly dependent on the chemical composition, structure, and physical and mechanical properties of the dispersed phase. It is apparent that, since the cellulose content varies from plant to plant, and even within different parts of the same plant, the mechanical properties of these fibres greatly vary with varied cellulose content.

FABRICATION METHODS OF CELLULOSE COMPOSITES

Cellulose composites are fabricated using various manufacturing methods, such as compression moulding, injection moulding, resin transfer moulding, and vacuum bagging. The processing factors affecting the quality of composites include temperature, pressure, and moulding time. It is often necessary to preheat the natural fibres to minimize the moisture content before further processing. However, cellulose degrades at a higher temperature, adversely affecting the mechanical properties of the composites. Also, improper fibre dispersion in the matrix may cause agglomeration, decreasing the tensile strength. The selection of the appropriate process technology depends greatly on the desired product geometry, expected performance, economy and the ease of manufacture. The various commonly adopted methods for fabrication of cellulose composite materials are depicted in Figure 1.

Hand lamination

In this method, the resin is applied using rollers to the fibres placed in a mould.

Vacuum bags are often used to remove the excess air and the exerted atmospheric pressure aids to compact the part.[11] This primitive method carries the advantages of being simple, with low cost of tooling, and flexibility of design. On the other hand, the time-consuming production procedure and its minimal automation potential are the major limitations of this fabrication method.

Resin transfer

In this method, the fibres are placed inside a mould consisting of two solid parts and a tube supplies the liquid resin, which is injected at low pressure through the mould, impregnating the fibres.[12] The mould is opened and the product is collected after curing carried out at or above the room temperature. This technique has the advantage of rapid manufacturing of large, complex, and high-performance parts. Diverse types of low viscosity resins, *e.g.* epoxy, polyester, phenolic, and acrylic, can be used in this method.[13]

Compression moulding

Compression moulding is another widely used method for the fabrication of composites. It involves a semi-finished composite sheet or a sheet moulding compound (SMC), which is later moulded into the final parts by compression.[14] The fabrication of the SMC consists in rolling a film of resin on which fibres are added. Another resin film is then added and later compressed in a composite sheet. Finally, the reinforced sheet is processed in a press to provide the desired shape. This method of composite manufacturing has numerous advantages, including relatively large production ability, high part reproducibility and short cycle times. The major concern in compression moulding is that the pressure needs to be always optimized in order to prevent damage of the fibres or structure.[15]

Injection moulding

Injection moulding is considered the ideal method for composite manufacturing, allowing to achieve complex shapes and fine details. The products have good surface finish, with precise dimensional accuracy, obtainable at high production rate and low labour cost.[16] In this method, the resin granules and fibres are mixed in a heated barrel and conveyed to the mould cavity by a spindle.[17]

Pultrusion

In this continuous composite manufacturing method, the impregnated fibres are pulled through a die, which is shaped according to the desired cross-section of the product.[18] This process offers the possibility to build thin-wall structures and a wide variety of cross-sectional shapes. Another advantage is that it allows the possibility for a high degree of automation.[19]

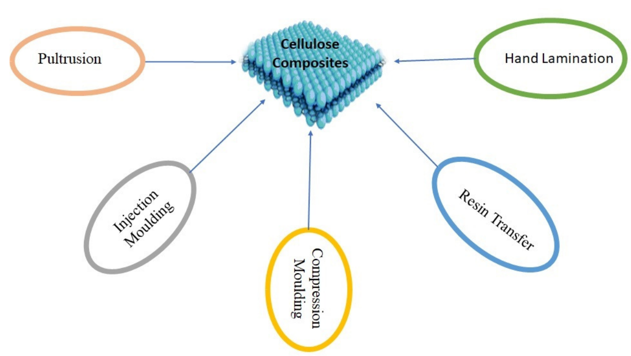

Figure 1: Methods of fabrication of cellulose composite materials

SURFACE FUNCTIONALIZATION

A major obstacle in using cellulose nanofibers and cellulose nanocrystals as mechanical reinforcing fillers in composite manufacturing lies in their poor dispersibility in non-polar organic solvents and poor interfacial interaction with the polymer matrix. This has triggered much research to improve the compatibility of these nanomaterials with polymers. The objectives of subjecting the cellulose fibre to pretreatments are to chemically modify its surface, limit the moisture absorption process, and increase its surface roughness. The various pretreatment techniques for surface modification of natural fibres include silylation, carboxylation, esterification, benzoylation, graft copolymerization, and bacterial cellulose treatment. The following section briefly highlights the surface treatment approaches for cellulose fibres (Fig. 2).

Chemical surface modification

The degree of interfacial cross-linking is usually improved through silane coupling, rendering a perfect bonding at the interface.[20] Owing to the availability of more reaction sites for the silane reaction, the efficiency of the silane treatment is high for alkaline treated fibres. Therefore, the usual practice is to subject the fibres to pretreatment with sodium hydroxide for about half an hour before its cross-linking with silane.[21] The hydrolyzable alkoxy group leads to the formation of silanols in the presence of moisture, which further reacts with the hydroxyl group of the fibre, forming stable covalent bonds to the cell wall.[22]

Carboxylic acid groups can be coupled to the surface of cellulose fibres through TEMPO (2,2, 6,6-tetramethylpiperidine-1-oxyl) treatment in alkaline media, using sodium hypochlorite and sodium bromide as primary oxidant and co-oxidant, respectively.[23,24]

Peroxide treatment of cellulose fibre has also gained the attention of researchers, owing to easy processability and improvement in mechanical properties.[25,26] Organic peroxides tend to decompose to free radicals, which further react with the hydrogen group of the matrix and cellulose fibres. Usually, fibres are treated with 6% benzoyl peroxide in acetone solution for about 30 min after alkali pretreatment.

In the benzoylation treatment, benzoyl chloride is most often used in fibre pretreatment and the inclusion of the benzoyl group in the fibre is responsible for the decreased hydrophilic nature of the treated fibre.[27,28] Similarly, esterification of hydroxyl groups on the surface of the cellulose fibres can be induced by reaction with fatty acids, esters, anhydride and acid chloride.[29,30]

Polymer grafting

Graft copolymerization imparts required properties to the cellulose fibres, so as to meet the requirements for specialized applications. Different binary vinyl monomers and their mixtures have been graft copolymerized onto cellulosic materials for modifying the properties of numerous polymer backbones.[31] The creation of an active site on the pre-existing polymeric backbone is the common feature of most methods for the synthesis of graft copolymers. The active site may be either a free radical or a chemical group, which may get involved in an ionic polymerization or in a condensation process.[32] Polymerization of an appropriate monomer onto this activated backbone polymer leads to the formation of a graft copolymer. [33,34]

Bacterial cellulose modification

The coating of bacterial cellulose onto cellulose fibres provides new means of controlling the interaction between fibres and polymer matrices. Coating of fibres with bacterial cellulose does not only facilitate good distribution of bacterial cellulose within the matrix, but also results in an improved interfacial adhesion between the fibres and the matrix.[35] This enhances the interaction between the fibres and the polymer matrix through mechanical interlocking.[35]

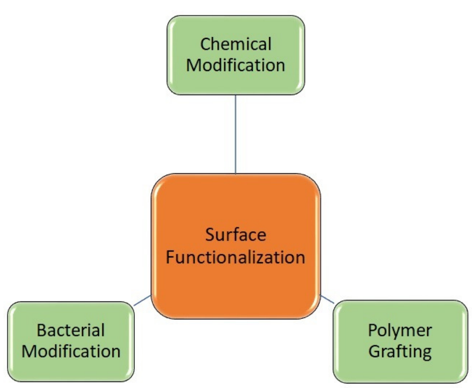

Figure 2: Surface functionalization approaches

BIOMEDICAL APPLICATIONS OF CELLULOSE-BASED COMPOSITES

Cellulose-based composites have received special attention as suitable and inexpensive alternatives for a wide range of medical applications, including scaffolds for tissue engineering, wound healing and healthcare systems. The following subsection will give a detailed overview of recent developments using cellulose-based composites for biomedical applications.

Cell culture, tissue engineering and wound healing

Owing to the properties of biocompatibility and mechanical properties identical to natural tissues, cellulose-based composites can provide a stimulating micro-environment to encourage cell attachment and proliferation. Amongst available cellulose types, bacterial cellulose seems to be the most prevalent choice for the medium of cell culture, probably due to its low cytotoxicity and high porosity.

It has been reported that bacterial cellulose (BC)/gelatin hydrogels were successfully synthesized to be examined as scaffolds for cancer cells *in vitro* culture, simulating the tumor microenvironment.[36] The properties and ability of the hydrogels to support normal growth of cancer cells were evaluated. In particular, the human breast cancer cell line (MDA-MD-231) was seeded into the BC/gelatin scaffolds to investigate their potential in 3D cell *in vitro* culture. Various analysis techniques, such as MTT proliferation assay, scanning electron microscopy, hematoxylin and eosin staining and immunofluorescence, were used to determine cell proliferation, morphology, adhesion, infiltration, and receptor expression. The *in vitro* MDA-MD-231 cell culture results demonstrated that cells cultured on the BC/gelatin scaffolds had significant adhesion, proliferation, in-growth and differentiation. More importantly, MDA-MD-231 cells cultured on the BC/gelatin scaffolds retained triple-negative receptor expression, demonstrating that the BC/gelatin scaffolds could be used as ideal *in vitro* culture scaffolds for tumor cells.

In another interesting research, a cellulose-nanofibers/polyethylene glycol diacrylate (CNFs/PEGDA) mixture was prepared and then used to fabricate a 3D CNFs/PEGDA hydrogel scaffold by stereolithography (SLA).[37] It was found that the CNFs in the composite scaffolds played a significant role, providing structural shape integrity, porous structure and mechanical strength. In addition, the NIH3T3 cells tightly adhered onto the CNFs/PEGDA materials and spread on the scaffolds, with good differentiation and viability.

Cellulose nanocrystals have been widely deployed in cell culture media, with promising cellular uptake and excellent proliferation, without any significant cytotoxicity to various cell line models.[38-40] In the field of neural tissue engineering, it was demonstrated for the first time that three-dimensional (3D) bacterial nanocellulose (BNC) scaffolds could be successfully used for culture of SH-SY5Y neuroblastoma cells – the cells adhered, proliferated and also differentiated to mature neurons, as indicated by functional action potentials detected by electrophysiological recordings.[41] Also, aqueous suspensions of CNF at optimal levels were used to form hydrogels, which offered a conducive environment, with required mechanical support, for tissue culture applications. The CNF hydrogels found to promote cellular differentiation of the human hepatic cell lines, and induced spheroid formation.[42] Scaffolds composed of natural polymers, such as pectin and carboxymethyl cellulose (CMC), with CNF, were found suitable for culture of NIH3T3 fibroblast.[43]

Wound healing is another application where cellulose biocomposites have been exploited by the researchers across the globe. The antimicrobial capacity and wound healing of bacterial cellulose-zinc oxide nanocomposites was tested against common burn pathogens.[44] Bacterial cellulose-zinc oxide nanocomposites exhibited 90%, 87.4%, 94.3% and 90.9% activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Citrobacter freundii*, respectively. Animals treated with the developed bacterial cellulose-zinc oxide nanocomposites showed significant (66%) healing activity. The histological analysis revealed fine tissue regeneration in the group treated with the composites.

Wang *et al*. designed a novel composite prepared from natural bacterial cellulose (BC), polyethylene glycol (PEG) and polyhexamethylene biguanidine (PHMB), which exhibited strong and sustained antibacterial effect.[45] *In vivo* tests further demonstrated that the composite could efficiently promote skin wound healing and regeneration in a rat model.

In an attempt to fabricate an efficient antimicrobial agent in the form of dressing to be used in the treatment of chronic wounds, a composite hydrogel, comprising bacterial cellulose (BC) and dehydrogenative polymer of coniferyl alcohol (DHP), BC-DHP, was developed by Zmejkoski *et al*.[46] The composite showed bactericidal effects against selected pathogenic bacteria, including clinically isolated ones. High-performance liquid chromatography coupled with mass-spectrometry showed that BC-DHP releases DHP oligomers, which are proposed to be antimicrobially active DHP fractions.

In another study, silver nanoparticle impregnated cellulose composites has shown a good zone of inhibition against *Staphylococcus aureus* and *Escherichia coli*, along with wound healing activity.[47]

Substitutes/medical biomaterials

The acceptable physico-mechanical properties and good biocompatibility of cellulose composites have boosted research and development targeting cellulose-based substitute/medical biomaterials, such as for the replacement of blood vessels (vascular graft), soft tissue, and nucleus pulposus. The results obtained so far in using nanocellulose in blood vessel replacement are quite promising in preclinical studies.[48]

Coronary bypass graft surgery is performed to supply blood to the heart tissue, with a suitable blood vessel replacement. Bacterial nanocellulose composites, which are tuned to possess good mechanical strength and blood compatibility, are used as material for artificial tubes used as potential replacement of small (<4 mm) or large (>6 mm) size vascular grafts. In a ground-breaking research reported from Germany, bacterial cellulose based materials were used as artificial vascular substitute. They have described a clinical product named BActerial SYnthesized Cellulose (BASYC®), with high mechanical strength in wet state, enormous water retention property and low roughness of inner tube surface. It is reported that BASYC® has been successfully used as artificial blood vessel in rats and pigs for microsurgery.[49]

Recently, Brown *et al*. reported the synthesis of cellulose biocomposites for the potential application of small-diameter replacement vascular graft. Cellulose nanocrystal was covalently grafted onto a fibrin matrix to provide reinforcement in terms of strength and elasticity to the composites.[50]

The specific demand for cellulose based biocomposite materials for soft tissue replacement is due to their improved lifespan, biocompatibility, durability, and low degree of calcification. In the human body, the main function of the tendon is to transfer the force of the muscle contraction to the bones, whereas ligaments stabilise the joints, preventing abnormal movements. Using a double network method, BC/polyacrylamide (PMm) gels can be synthesized by combining BC gel as the first network, and PMm as the second network in the presence of a crosslinker. The BC/PMm gels presented high elongation and high tensile fracture stress (40 ± 10 MPa), which was similar to the tensile fracture stress of ligaments (38 ± 10 MPa), and could be potentially used as ligament replacement.[51] Cellulose nanofibre/collagen composites for potential ligament or tendon replacement were also proposed by Mathew *et al*.[52] The reported composites exhibited mechanical properties and stress relaxation behaviour comparable to those of natural ligaments and tendons.

It is reported that about 80% of the world population suffers from back pain, and in the majority of cases, this is a direct consequence of disc degenerative processes, in particular, nucleus pulposus degeneration. Nucleus pulposus (NP) is a gelatinous core inside two vertebral bodies for intervertebral disks, which is important to provide flexibility and dissipate the stress acting on the spine. A crosslinked, carboxymethylcellulose-methylcellulose dual-polymer hydrogel was recently formulated as an injectable NP replacement that gelled *in situ* and restored disc height and compressive biomechanical properties.[53] Injectable suspensions of viscous chitosan (1.7-3.3% (w/w)), filled with nanofibrillated cellulose, were proposed for visco-supplementation of the intervertebral disc nucleus pulposus tissue. The achievement of formulations that can gel *in situ* at the disc injection site constitutes a minimally invasive approach to restore damaged/degenerated discs.[54]

Drug delivery

Cellulose is known to have a long history of use in the pharmaceutical industry. It is blended with pharmaceutical excipients and used to develop drug-loaded tablets, which form dense matrices and are suitable for the oral administration of drugs. Polysaccharides, in general, are widely favoured biomaterials for controlled release dosage forms, while using a hydrophilic polymer matrix is one of the preferred approaches in formulating extended release dosage forms.[55-59] Crystalline nanocellulose offers several potential advantages as a drug delivery excipient. Along with other types of cellulose, nanocellulose is used to develop advanced pelleting systems, allowing to control the rate of tablet disintegration and drug release by microparticle inclusion, excipient layering or tablet coating.[60] The very large surface area and negative charge of crystalline nanocellulose suggest that large amounts of drugs might be bound to the surface of this material, with the potential for high payloads and optimal control of dosing.

Recently, Yan *et al.* reported the use of bacterial cellulose nanocrystals as stabilizers in pickering emulsions for the delivery of alfacalcidol using alginate beads.[61] Cellulose nanofibre aerogels were also successfully deployed for gastroretentive delivery of bendamustine hydrochloride with a 3.25-fold increase in oral bioavailability.[62] A ciprofloxacin (CIP)-MMT composite was fabricated using carboxymethylated nanocellulose (CMCNF) and the nanocellulose was responsible for controlling the erosion of the matrix, influencing drug release.[63] A constant antibacterial activity for 12 days was displayed by the composite system.

A nanocomposite hydrogel based on cellulose nanocrystal (CNC) and chitosan (CS) was fabricated and applied as a carrier for the controlled delivery of theophylline.[64] CNC was firstly periodate-oxidized to obtain dialdehyde nanocellulose (DACNC). Then, chitosan was crosslinked using DACNC as both the matrix and crosslinker in different weight ratios, to fabricate CNC/CS composites. As the swelling ratio of the drug-loaded hydrogels differed as a function of pH, the cumulative drug release percentage of the composite hydrogel reached approximately 85% and 23% in gastric (pH 1.5) and intestinal (pH 7.4) fluids, respectively.

Recently, pH- and magnetism dual-responsive Fe_3O_4@C/carboxymethyl cellulose (CMC)/chitosan composite microbeads have been developed for controlled release of diclofenac sodium (DS).[65] The drug entrapment efficiency into the composite microbeads reached up to $70.8 \pm 0.65\%$ at optimal levels of processing factors. The beads showed a higher swelling index in alkaline medium, providing opportunities for excellent pH-sensitive drug release profiles. Yet, in another work, pH-sensitive ZnO/carboxymethyl cellulose/chitosan bio-nanocomposite beads were effectively deployed for colon-specific release of 5-fluorouracil.[66]

In another research study, a sodium carboxymethylcellulose/chitosan composite sponge was used as a delivery device for a few hydrophobic model drugs, namely gentamicin, ibuprofen and roxithromycin.[67] The CMC/chitosan ratio and the pH value significantly affected the appearance of the blending solution and the microstructure of the final product, as well as the sponge's degradation behavior, drug-loading capacity and the antibacterial activity.

CONCLUDING REMARKS

The very concept of green chemistry has evolved simultaneously in the academia, research, business and regulatory communities as an initiative for pollution prevention. Some chemicals in common use are suspected of causing human cancer and other adverse human and environmental health outcomes. Green chemistry revolves around the sound principles of designing chemicals, chemical processes and commercial products so as to avoid the creation of toxic compounds and waste. Increasing environmental awareness and ecological concerns have renewed the research interest in natural fibre-based materials. The concept of composites made from cellulose-based materials appears to be an alternative route to achieve green polymer composites. A sizable volume of research pertaining to cellulose-based composites is in progress across the globe, aiming at a greener tomorrow.

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