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Novel carboxymethyl cellulose based nanocomposite: A promising biomaterial for biomedical applications

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ABSTRACT

The promising potential of biomaterials for biomedical applications has spurred conducting intensive studies in this field. Cellulose derivatives are biocompatible polymers with favorable physical and mechanical features. The distinctive properties of cellulose derivatives are gaining significant attention due to their potential for biomedical applications, including tissue engineering, wound dressing, and drug delivery. Carboxymethyl cellulose (CMC), the first and major cellulose derivative has been a promising cellulose-based compound since its development in 20th century. Water solubility, nontoxicity, biocompatibility, chemical stability, biodegradability with no side effects are among the unique attributes that have retained CMC's position as an attractive option for commercial applications, including the biomedical field. In this study, CMC properties and their potential for biomedical applications are discussed. Different methods to produce CMC hydrogels are reviewed. Extensive literature review has been added in terms of synthesis, and applications in biomedical fields. Various authors have demonstrated strong anti-bacterial, and anti-tumor application by elaborating different formulation strategies. This review highlights applications of CMC-based nanocomposites in tissue engineering, wound dressing, and drug delivery.

1. Introduction

Biopolymeric carbohydrates possess unique properties of natural polymers and enormous potential in biomedical applications[1]. Cellulose is a ubiquitous biopolymeric carbohydrate among diverse polysaccharides owing to its natural abundance. Plants and wood are the primary sources of cellulose [2]. Also, organisms like bacteria produce cellulose with interesting properties applicable for developing antibacterial dressings [3]. Cellulose is a linear and natural polymer made of glucose repeating units ($(C_6H_{10}O_5)_n$)[4]. The hierarchical structure of cellulose-based materials provides a wide range of dimensions spanning from nanoscale to macroscale [5]. Cellulose-based materials possess numerous remarkable properties, including excellent physical and mechanical properties, functionality, and strength. They are good candidates for biomedical applications due to their hierarchical structure, low price, biodegradability, and biocompatibility [6]. Despite the desirable features of cellulose, several other properties impede its use in the biomedical field. Poor microbiological resistance, sensitivity to moisture, and water insolubility are some notable drawbacks attributed to cellulose [7]. Cellulose poor solubility and high crystallinity is ascribed to inter and intramolecular hydrogen bonds, electrostatic, and hydrophobic interactions leading to multiple hydroxyl groups on the cellulose backbone within fibrils [8]. Nevertheless, chemical modification of cellulose can be performed by replacing its hydroxyl groups with other

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functional groups, including acids, oxides, and chlorides, to overcome undesirable properties and provide favorable features to pave the way toward applying cellulose-based materials in biomedicine [9]. In this direction, different chemical modifications have been proposed to fabricate cellulose derivatives applicable in the biomedical field. Cellulose ethers (i.e., Methyl cellulose [10], Carboxymethyl cellulose [11], Ethyl cellulose [12], and hydroxyethyl cellulose [13]) and Cellulose esters (i.e., Cellulose acetate [14] and Cellulose nitrate [15]) are among common cellulose derivatives.

Cellulose ethers can be produced by partial or total etherification of cellulose hydroxyl groups. Various reagents can be employed for cellulose etherification, such as epoxides, carboxylic acids, and halogenoalkanes[16]. The water solubility of cellulose ethers is determined by the chemical structure of the chemically modified functional groups. Also, the degree and pattern of these replacement functional groups affect cellulose ether water solubility and thermo-gelling property [9, 17]. While many cellulose ether compounds have been fabricated since the 1900 s, only a few have become prevalent in the market. Suitable rheological properties, inherent non-toxicity, and unique mechanical features have made carboxymethyl cellulose (CMC), methyl cellulose, and hydroxyethyl cellulose the most widely used cellulose ethers in the biomedical products industry [9-17].

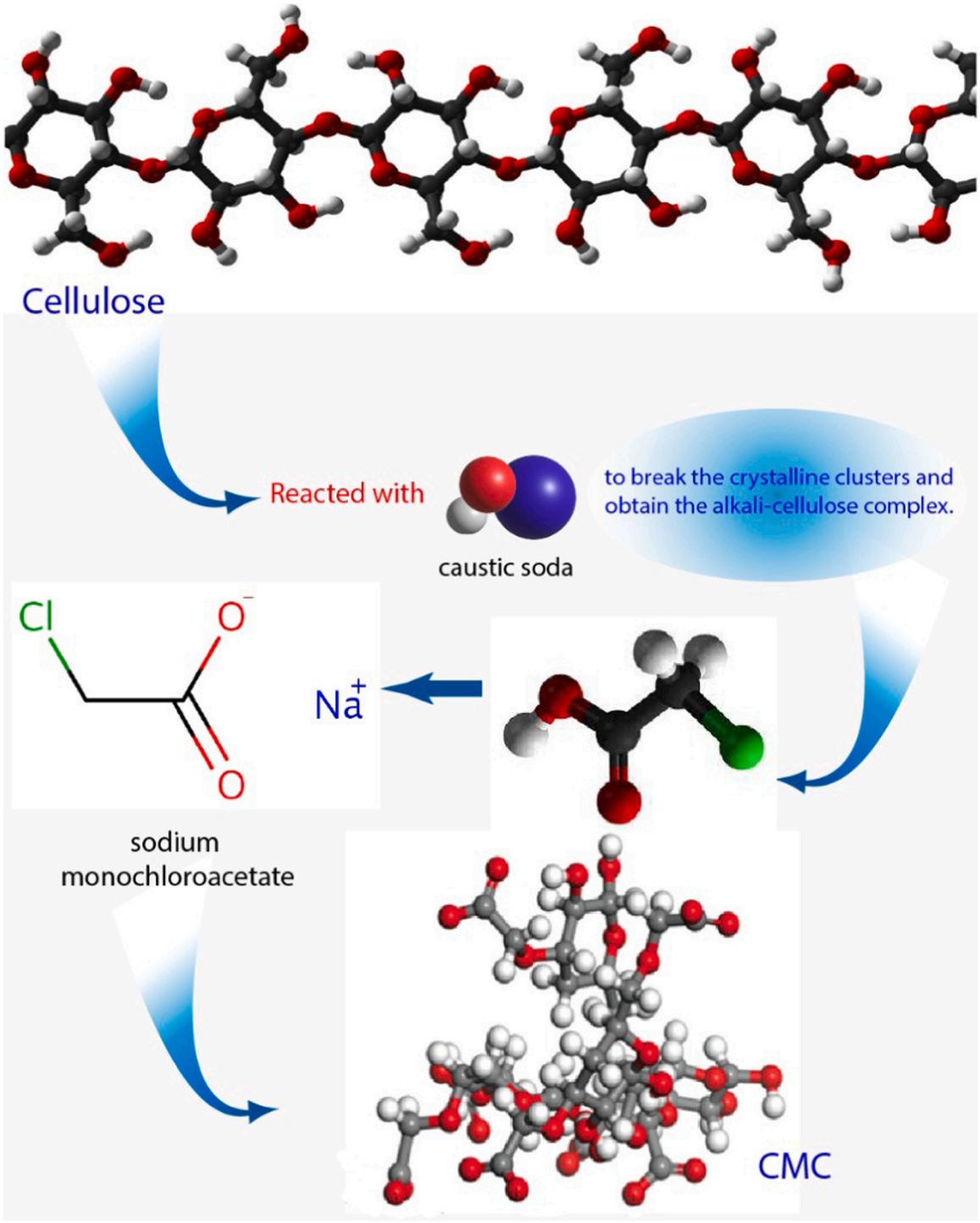

Fig. 1. Cellulose reaction with monochloroacetic acid to replace hydroxyl groups in carbon numbers 2, 3, and 6 of glucose residues with carboxymethyl groups.

CMC is the first and major derivative of cellulose. This water-soluble cellulose-based compound emerged in the 1920 s and is expected to continue its dominant position in the global market for the foreseeable future [18]. This cellulose-derived compound is produced by cellulose reaction with monochloroacetic acid which result in replacing hydroxyl groups in carbon numbers 2, 3, and 6 of glucose residues with carboxymethyl groups, with slightly more prominent replacement at carbon number 2 [19,20]. The schematic of producing CMC from cellulose is shown in Fig. 1.

CMC is a natural base material that due to its particular chemical structure has a great film-forming capability either physically with hydrogen bonds or chemically and by using some chemical crosslinkers. CMC has an amorph structure, which has introduced this biopolymer as an applicable material for being used in diverse hydrogels, however, its mechanical strength should be fortified to enhance its application efficacy [21–25].

Several desirable attributes make CMC an outstanding cellulose-based compound. Preparation with simple synthesis methods and inexpensive materials, as well as being the first cellulose-based compound approved by the United States Food and Drug Administration (FDA) pave the way toward its commercial application [26]. Besides, water solubility, nontoxicity, biocompatibility, chemical stability, biodegradability with no side effects on human tissue make CMC an appropriate candidate for commercial applications, including biomedical field[27]. As stated previously, the properties of CMC as a cellulose derivative are determined by the pattern, degree, and type of chemically modified functional groups replaced. In particular, the degree of substitution is an element for characterization of various CMC grades. For biomedical application, the favorable substitution degree should be between 0.6 and 1.25 [28].

CMC has been increasingly used in biomedical applications, such as tissue engineering, drug delivery, and wound dressing. Distinctive features, like ability to control rheological properties, viscosity, pH-sensitivity, bioadhesiveness, physical crosslinking, and film forming make CMC an excellent candidate for the aforementioned biomedical applications [28,29].

In addition to the suitable substitution degree of CMC, there are other features making CMC a preferable candidate among other cellulose ethers. The higher degree of polymerization of CMC contributes to its perfect film-forming ability [29]. Commercially available CMC has a molecular weight of 700 K, corresponding to a degree of polymerization of 3 K. Oral thin films were prepared by using CMC to deliver probiotics. The developed thin films preserved probiotics viable during 150 days [29]. Moreover, the polyanionic nature of CMC can be employed for preparing polyelectrolyte multilayers. This multilayers can be used for drug delivery applications such as embedding microparticles loaded with ibuprofen[30]. Although some polyanionic polymers have shown bioadhesive capability, anionic CMC adheres more strongly to biological surfaces than other cellulose derivatives. Due to this, CMC is a preferable option for transdermal and transmucosal drug delivery. In addition, CMC is superior to be used in ophthalmic applications due to high molecular weight, rheological properties, and aqueous solubility [31]. Commercial CMC products for ophthalmic applications have been developed, capable of binding to corneal epithelial cells for corneal wound healing. CMC's high viscosity increases the release period of drugs on the eye [32].

One of the common usages of CMC as a biomaterial is in the field of tissue engineering [32,33]. Developing biocompatible scaffolds with biomaterials capable of enhancing cell attachment, growth, and differentiation is a primary objective in tissue engineering [32,33]. The major setback for the use of cellulose as a scaffold is its low hydrophilicity, leading to poor attachment of cells and consequently cell death. In contrast, various studies have shown CMC scaffolds can enhance cell attachment and stimulate cell migration [33–35]. Moreover, CMC scaffolds enhance stem cell differentiation, such as enhanced osteoinductivity in bone tissue engineering [36–38].

Developing 3D vascularized tissue constructs for regenerative medicine and disease modeling is a novel approach toward functional tissue constructs and recapitulating 3D microenvironment for pathophysiological study [39,40]. The bioprinting method, cell and bioink type are among the crucial elements in 3D bioprinting[41]. Bioinks are made of a mixture of polymers, either natural or synthetic, and cells. Shear-thinning, stimuli-sensitivity, sol-gel transition, enhancing cell proliferation, and differentiation are among the requirements for suitable bioinks. Recently, CMC has emerged as a promising bioink as they provide the required properties [42–44].

In addition, CMC's outstanding features provide unparalleled prospects for its application in drug delivery systems. CMC is ionic strength and pH-responsive because of carboxyl groups protonation and polyelectrolyte nature [18,45]. Another remarkable attribute of CMC is its compatibility for mixing with other polymers through crosslinking. This feature makes CMC capable of absorbing immense amount of water and express swelling property, which is crucial for hydrogels and drug delivery [46]. Moreover, CMC can be used as the second network in preparing double network hydrogels and crosslinked with metal ions to produce pH-sensitive drug delivery platforms [47]. As hydrogel employment in biomedical applications has grown, the importance of biopolymers such as CMC has been fortified. This study provided the most important CMC characteristics such as pH-sensitivity, hydrophilicity, biocompatibility, bioadhesive properties, and gel-forming capability, which introduced CMC as an applicable biopolymer for employed in diverse biomedical applications. Furthermore, two broad categories of chemical and physical crosslinking techniques have been discussed and their advantages were provided that can be applied efficiently to fabricate the desired hydrogel in purposeful biomedical applications [45-48].

CMC has been used in clinical trials for a wide range of applications, including wound healing, dry eye syndrome, cancer treatment and gastrointestinal disorders. One of the earliest clinical trials involving CMC was conducted in the 1950 s, where it was used to study its effect in reducing constipation [48]. Later on, in 1979, Levine et al. reported stabilization of polyriboinosinic-polyribocytidylic acid with poly L-Lysine and CMC to promote consistent induction of high levels of serum interferon toward studies on its effect in human viral infections [49]. Since then, CMC has been studied extensively for its ability to improve the texture, viscosity, and stability of food, pharmaceuticals, and cosmetics. After that, CMC began to be studied as a topical wound healing agent. Clinical trials have investigated the use of CMC-based dressings for the treatment of chronic wounds, burn wounds, and diabetic foot ulcers [50–52]. CMC dressings have been found to be effective in promoting wound healing by maintaining a moist environment and preventing infection [50-52].

CMC research is a hot topic for researchers and according to the data of web of science (WOS), almost 9–10 publications per annum are consistent in previous five years as shown in Fig. 2.

2. CMC characteristics

2.1. Hydrophilicity

CMC and other cellulose derivatives have two major distinctions, originating from anionic carboxymethyl groups (i.e., -CH_2-COOH) present in CMC that take the place of the hydrogen atoms from some hydroxyl groups in the pristine cellulose structure [53,54]. First, water absorption and hydrogen binding are influenced by the hydrophilic moieties (CH_2COO^-) [53,54]. Second, the heterogeneous replacement of the CH_2COO^- molecules in both the substituted location and the extent of substitution enhances the intricacy of hydrogen bonding. After drying at 50 °C for 24 h in the vacuum oven, thermogravimetric measurements showed that CMC still retained water molecules, consistent with its hydrophilic nature [53]. Hydrogen bonding of water molecules with polymer chains (hydrophilic OH and COO units) is produced due to

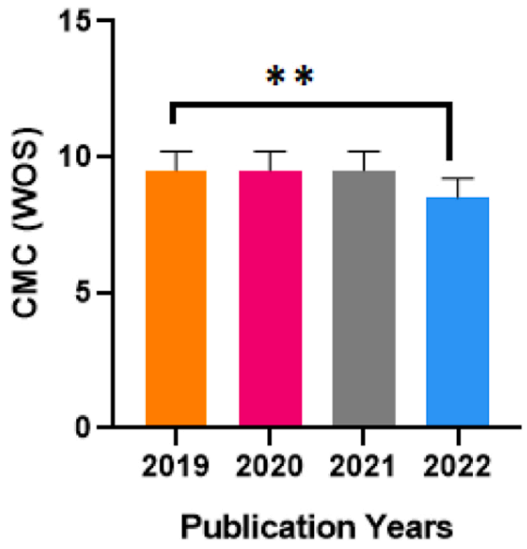

Fig. 2. Relation between swelling and deswelling of CMC and pH.

the availability of water in the system [54].

2.2. Bioadhesive

It has been discovered that CMC, as a polyanionic polymer, exhibits bioadhesive characteristics, meaning it adheres to biological surfaces better than the majority of nonionic cellulose compounds [53-55]. Hence, CMC is considered as a promising platform for cutaneous and transmucosal administration [53-55]. In a study, CMC tablets were developed for oral administration of sotalol HCL as a water-soluble medication [53-55]. The objectives of the study were to fabricate a platform capable of controlled release of the model drug with suitable bioadhesion and floating in acid condition of stomach [53-55]. The results of the in vitro experiments showed that CMC tablets controlled the drug release over 14 h and developed a suitable adherence to rabbit stomach and small intestine tissue[55]. In another study, it was shown that polymers carrying acetylsalicylic acid coated with CMC were more effective in attaching to the mucosal surface than unaltered ones[56]. In vivo tests showed an increase in metformin HCl's antidiabetic efficacy using mucoadhesive CMC microcapsules throughout diabetic albino rats [57]. Bioadhesive CMC matrices have been used for ciprofloxacin stability in the gastrointestinal tract (GIT) due to their water-soluble nature [58]. CMC tablets have been developed for the oral mucosal distribution of weakly water-soluble medications[59–61]such as pindolol[62]and glipizide [63]as well as water-soluble pharmaceuticals like metronidazole [64], miconazole nitrate [65], lignocaine HCl [66], and triamcinolone acetonide[67]. Losartan potassium [68], ketorolac tromethamine [69], and diltiazem hydrochloride [70]may be delivered through buccal mucoadhesive CMC biofilms. Additionally, atenolol's mucoadhesive buccal patches were developed for topical drug distribution in the oral space[71]. FDA allows for buccal preparations containing up to 10.95 mg CMC, ophthalmic preparations containing up to 0.5% CMC, and oral preparations containing 242 mg CMC[72].

2.3. Non-toxicity

Serving as the structural building blocks of biological organisms, carbohydrates have enormous promises in medication delivery. Biopolymeric carriers have several attractive features, including reduced cytotoxicity and enhanced pharmacokinetic properties. In this direction, several drug delivery platforms have been coupled with CMC biopolymers to concurrently reduce cytotoxicity, improve targeted delivery, and enhance therapeutic efficiency [58-72].

Javanbakht et al. [73] crosslinked CMC with copper acetate to produce CMC hydrogels. These hydrogels were loaded with graphene quantum dots to prepare a hydrogel nanocomposite for the oral delivery of Naproxen. The fabricated delivery platform is pH-responsive owing to CMC nature and using copper acetate as a novel CMC crosslinker. Moreover, the cytotoxicity assay showed that the prepared platform is a safe carrier with no significant toxicity on human epithelial cell line (Caco-2) [73]. In another research, a nanohybrid from metal organic framework (MOF) was developed to load Ibuprofen (IBU) [74]. The IBU-loaded nanohybrid was then coated with pH-sensitive CMC. Coating the nanocomposite hydrogel with CMC provided controlled and targeted release of the model drug. Besides, the prepared platform had low toxicity on Caco-2 cells [74]. The pH-sensitive property of CMC was also employed in another study for targeted delivery and prolonged release of Doxorubicin (DOX) toward apoptosis induction in K562 cells as blood cancer cells. Incorporation of graphene quantum dots in CMC hydrogel increased the loading of DOX in the fabricated platform. Moreover, the blank platform without the model drug showed no toxicity on K562 cell line [75]. The pH-responsive attribute of CMC for drug delivery with no cytotoxicity has been shown in other studies [76].

Based on the mentioned studies and other recent studies, CMC has been employed in diverse works on various normal cell lines. Outcomes indicated that CMC is a biocompatible natural base biopolymer that can be applied safely in biomedical applications [77–79].

2.4. Gel-forming

CMC is one of the most important cellulose-derived compounds as a superabsorbent polymer [80,81]. Significant volumes of physiological fluids or water may be absorbed and discharged at a regulated dose by hydrophilic CMC networks created as polymer hydrogels in three dimensions [80,81].

Gamma irradiation [82]or chloromethylene iodide [81]may be used to crosslink the polymer using polyvalent carboxylic acids like citric acid [83]. The physical or chemical crosslinking of homopolymers and copolymers may create networks that are insoluble in water [84]. As an example, superabsorbent polymers have been developed by combining CMC with different synthetic and organic polymers such as polyvinyl alcohol, chitosan (CS), alginate, starch, and polyvinylpyrrolidone [28, 80,84–87]. Nevertheless, the constants of dispersion and solvent front speeds increase by increasing CMC concentration as a hydrophilic compound in the polymer matrix, resulting in an increased swelling rate [88]. Moreover, combining the gel-forming property of CMC and nanoparticles offer considerable benefits, including improved therapeutic effect and reduced toxicity [73–75,89].

2.5. pH-sensitivity

CMC hydrogel exhibits pH-sensitive property as mentioned before [90]. This feature is due to the carboxyl groups present in the anionic polyelectrolyte CMC hydrogel, making CMC-based hydrogels a desirable carrier [90]. The swelling behavior is one of the major concerns in hydrogels applications [90]. The swelling rate is influenced by a wide range of parameters, including pH, structure, polymeric matrix crosslinking, temperature, and ionic power [90]. Negatively charged molecules in CMC hydrogels have carboxylic units attached to them [90]. When the pH of an anionic hydrogel is higher than its pKa, the ionized composition increases the electrostatic repulsive force between chains, resulting in an expansion of the platform's dimensions. Hydrogels are ideal in these situations because they can receive a high volume of water while maintaining a very weak arrangement [91]. The ionization of CMC attached groups (COO^-) and the creation of a significant osmotic occurrence cause the swelling rate of hydrogel to rise when the pH of the solution is higher than the polymeric pKa [92]. The deionization of carboxylate units in CMC hydrogel causes contraction in the polymeric matrix when the pH of the solution is lower than the polymeric pKa [73,

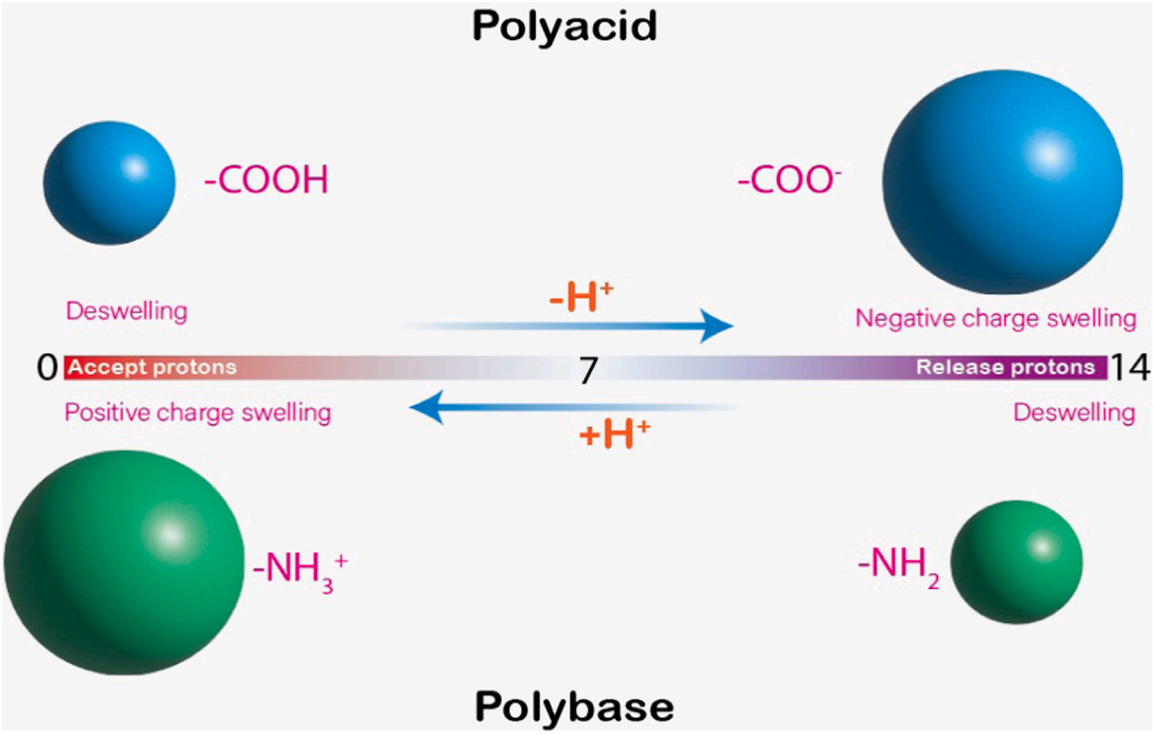

Fig. 3. : Effect of pH and pKa on the swelling rate of hydrogel.

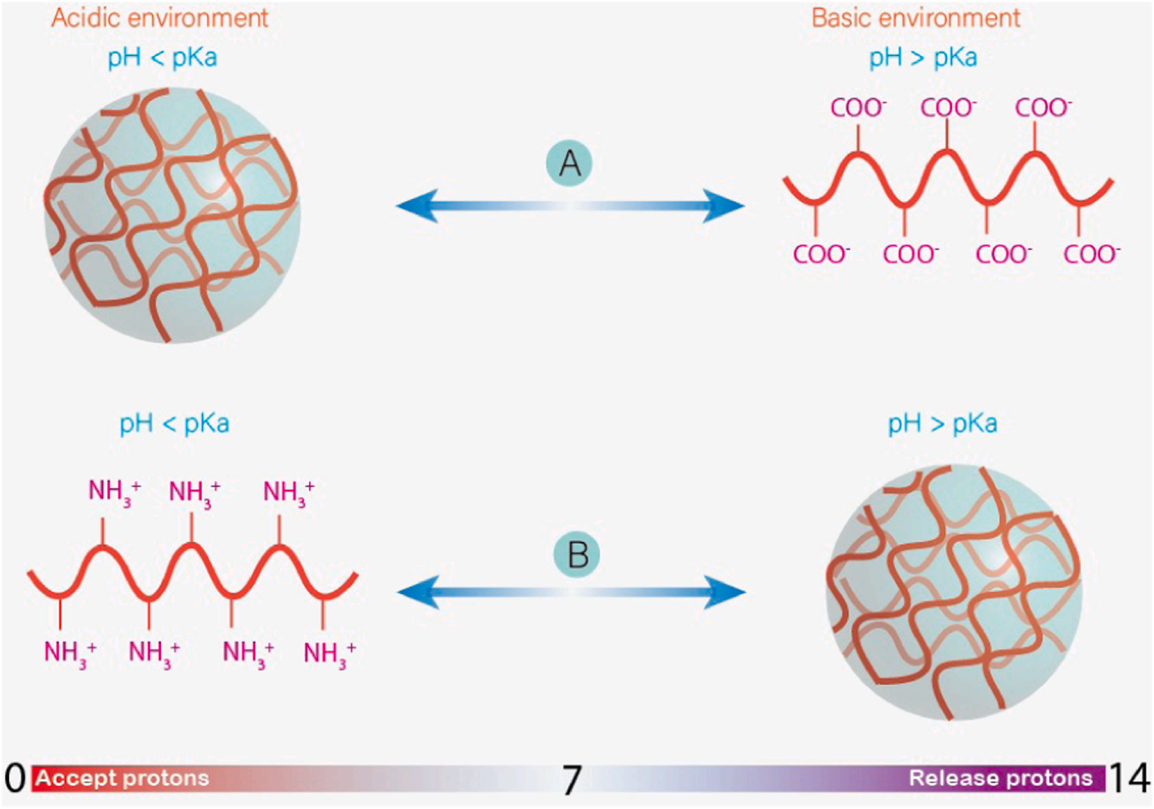

Fig. 4. Schematic representation of double-layer hydrogels' formation (APS = ammonium persulfate, BIS = *N*,*N*-methylenedibis-propionamide, DMAA = *N*,*N*-dimethylacrylamide, AA = acrylamide, and TEMED = tetra-methylethylenediamine.
Adapted from reference [103] under the terms and conditions of the Creative Commons Attribution (CC BY) license.

74]. Figs. 3 and 4 describe these changes in response to pH.Nanostructures including copper combinations [93], silver nanomaterials [89], Fe_3O_4[94], calcium carbonate [95], ZnS[96], cellulose nanocrystal [97], graphene quantum dot [73], and metal-organic frameworks [74] may be used to improve CMC pH-sensitivity qualities. CMS characteristics are summarized in Table 1.

3. Synthesis of Cellulose hydrogels

3.1. Physical crosslinking

Physical crosslinking has proven to be an intriguing approach for developing hydrogels [104,105]. This crosslinking strategy has several advantages compared to chemical crosslinking, including a lack of unreacted chemical compounds in the fabricated hydrogel which leads to the safety of physically crosslinked hydrogels for biomedical applications [104,105]. Besides, since physically-crosslinked hydrogels are fabricated by reversible intermolecular interactions, they have stimuli-sensitive and self-healing characteristics, which are favorable properties for delivery of cells and medications in drug delivery and tissue engineering applications. Physical crosslinking is accomplished in a variety of ways [104,105]. This method can provide some CMC-based hydrogels, which are more biocompatible due to the lack of chemical crosslinkers and this can be assumed as the major benefit of employing physical crosslinking to fabricate hydrogels [104,105]. Chemical crosslinkers can be toxic or make some highly toxic radicals in diverse conditions such as exposing to the UV assays that finally can be led to a hydrogel with high cytotoxicity [105,106].

3.1.1. Freeze-thawing method

This approach is used whenever massive solvents or lower molecular solutes solidify upon chilling, lowering the polymeric chain space, raises the polymeric content, and drives the polymeric chain to coordinate and connect into a hydrogel's connecting network arrangement [107,108]. Hydrogen bonds and covalent interactions often hold the connected network together when using this approach. Hyaluronic acid (HA), carboxymethylatedcurdlan (CMc), β-glucan, locust bean gum, and combinations of amylopectin and amylose have all been successfully frozen and thawed using this approach [107,108]. Nevertheless, pH, freezing temperature, freezing duration, and the length or cycle of freeze-thawing are several factors affecting the extent of gelation [107, 108].

Furthermore, the development of hydrogels using the freeze-thaw approach increases the characteristics of polymer gels without an impact on their biocompatibility, biodegradability, or non-toxicity, among other things [107,108]. The freeze-thawing approach, is a helpful strategy to manufacture gels owing to the deleterious impact of the chemicals used for covalent crosslinking during chemical crosslinking, demonstrating the association of hydrogen bonds throughout the procedure [107,108]. The freeze-thawing method used by Guan et al. [109] to create hydrogel from hemicellulose improved thermal durability, compressive potency, and crystallinity. This method contributed to hydrogel preparation with increased rigidity, a more durable characteristic, and a high level of crystallization. It has been shown by Butylina et al. [110] that the compressive properties (Compressive modulus and stress) of hydrogels increased by the inclusion of poly (vinyl alcohol) (PVA) in cellulose nanocrystal (CNC) using the freeze-thawing process. Mechanical characteristics of PVA hydrogels were enhanced through increasing the freeze-thaw cycles.

Throughout the freeze-thaw periods when physical crosslinking takes place, stretching commences in PVA hydrogels and prefers to be in the orientation of expansion. Using a similar approach, Zhang et al. [111] have come up with the significant power of hydrogels induced by intra- and intermolecular hydrogen bonding in PVA hydrogels. In addition, it has been claimed that this approach in ceramics areas may increase the durability of the ceramic structure. It is also worth mentioning that the major advantages of employing freeze-thawing method can enhance the rheological characteristics such asviscosity, texture, and bioadhesive properties [112,113]. These improved features would increase the capability of the synthesized nanocomposites for being employed in diverse biomedical applications.

Table 1
Key features of the CMC characteristics.

CMC characteristics	Key features	References
Hydrophilicity	CMC hydrophilicity is retained even after enduring harsh environmental conditions owing to strong hydrogen bonding	[98]
Bioadhesion	Promising platform for cutaneous and transmucosal administration owing to bio-adhesion to the cutaneous and transmucosal administration	[99]
Non-toxicity	CMC biopolymers reduce cytotoxicity owing to natural origin	[100]
pH - sensitivity	CMC hydrogel exhibits pH-sensitive owing to the carboxyl groups present in the anionic polyelectrolyte CMC.	[101]
Gel formation	Gelling capability results in an increased swelling rate and mucoadhesion, promoting adequate dosing and patient compliance	[102]

3.1.2. Photoinitiator method

This method has received popularity because of its ability to produce quick in-situ gel. There is a risk of tissue injury in living organisms if UV radiation has too much energy. However, a blue-light mediated crosslinking technique may resolve the issue [114]. A covalent bond might be formed in the hydrogel matrix using light photochemical crosslinking based on ruthenium (Ru) [114]. Fibrinogen, keratin, and gelatin hydrogels have also been made using the Ru-based technique. By employing Ru-based photochemical crosslinking, Lu et al. [114] demonstrated that cellulose hydrogel could be effectively manufactured.

Also, photo-crosslinking confers to hydrogel a high degree of tissue adhesiveness, hemostatic capability, and antimicrobial activity for medicinal applications [115]. For therapeutic purposes, hydrogels scaffolds were produced by Qi et al. using photo-crosslinking technique [115]. Biomedical photo-crosslinkable chitosan compounds motivated by biological processes have been synthesized by Zhao et al. [116]. Biomimetic hydrogels featuring different mechanical and swelling characteristics were created using photo-crosslinking. It is discovered that the optical-crosslinking method has various benefits over other crosslinking techniques, including moderate reaction settings, little byproduct generation, and control over crosslinking [116]. Through the use of a photo-crosslinkable technology, Qi et al. investigated the potential of sericin hydrogel during cartilage healing [115]. Hydrogels with photo-crosslinking were discovered to be injectable and less invasive when UV light was used to activate the crosslinking of the hydrogels in water. Using the photo-crosslinking approach, they developed non-toxic crosslinked chemicals that improved hydrogel compatibility and allowed direct live cell attachment [117]. Photo-crosslinking of glycidyl methacrylate in the presence of a photoinitiator in biological environment is achieved by Yuan et al. [117]. They discovered that the photo-crosslinking approach produced a better thermogel of glycidyl methacrylate compared to other techniques. Mechanical strength, durability, and biodegradation may all be controlled using the photo-crosslinking process. CMC-methacrylate gels and CMC-methacrylate/ polyethylene glycol dimethacrylate (PEG-DM) copolymer gels were made using the photo-crosslinking approach by Reeves et al. [118]. It was found that the rise in CMC-methacrylate amount results in an increase of enzymatic degradation rate, swelling, and model protein dispersion. Using cationic photoinitiators and UV light, Lin et al. carried out the photoinduced *grafting* of glycidyl pendant groups using cycloaliphatic diepoxides to create curative coating of

CMC- glycidylmethacyclate (GMA)[119]. Because of the increase in the photoinitiator concentration, the fabricated curable coating provided improved hardness. Besides, the increased concentration of the photoinitiator was shown to be the cause of decreased flexibility. The pretreatment of CMC was done using hydrogen peroxide and sulfuric acid prior to the photografting of acrylic acid (AA) into CMC to form CMC peroxides [118,119]. The rationale behind this decision was the fact that peroxides are activated for AA photografting. The photografting of CMC with grafting percent higher than 150% can be achieved by photoirradiation for 10 min at 30 °C[120]. Using sodium benzoate as photoinitiator, Villarruel et al. [121]photo-crosslinked polyvinyl alcohol and CMC. They also concluded microbial growth inhibition as a result of the sodium benzoate incorporation and subsequent exposure to UV light.

3.1.3. Radiation induction method

Hydrogels may be made with less harm to the ecosystem by using the radiation-induced crosslinking technique [122]. There are many benefits to this approach, including the fact that it can be performed without the need to any catalysts or reagents, it is an efficient and quick procedure to manufacture homogeneous hydrogel in a single process, and it can be regulated by altering the amount of radiation and dosage rate. In a prior investigation, it was discovered that employing gamma radiation to produce a methyl hydroxyethyl cellulose hydrogel incorporating poly (ethylene glycol) (PEG) was effective [122]. Aside from that, gamma radiation-induced graft polymerization may be occurred. Graft polymerization radiation may be regulated to provide the desired qualities. As a result, by employing certain monomers, this approach allows for the creation of a tailor-made grafted sequence. Gamma rays were used by Singh and Bala to make polysaccharide gel [123]. Applying ^{60}Co gamma-ray irradiation, the hydrogel was manufactured in their work with a constant radiation dosage. Hydrogels exhibit swelling, structural, and compositional changes as a consequence of radiation exposure, as shown by this study. Using radiation-induced methods, Saiki et al. [124] demonstrate that CMC may be employed for hydrogel formation. OH radicals formed during water radiolysis were discovered to be responsible for the radiation crosslinking of CMC. In the aqueous solution, nevertheless, they discovered that CMC radicals might be generated by reacting with the OH radical. The use of CMC to make radiation crosslinked biocompatible hydrogel-based hemostatic compounds for therapeutic purposes has also been investigated. High-mechanical strength, thermal sensitivity, and stable hydrogels can be achieved by gamma radiation in this research [125]. Using CMC with varying replacement percentages, radiation induction on polysaccharides was also begun. The approach was then frequently utilized to make hydrogels from different kinds of polysaccharides. Owing to the disinfection of products, the polysaccharide radiation-induced approach may be used. The benefit of polysaccharide polymer gels compared to synthetic gels is the starting point for the biodegradation of their substrate and product [126]. An initiator substance or high-energy irradiation may be used to start the free-radical synthesis of radiation-induced crosslink gel for agricultural purposes. For certain polymeric compounds, gamma radiation has been suggested as a possible radiation induction method. Using this method, the hydrogels with increased water absorbance and capacity may also be synthesized[127].

3.2. Chemical crosslinking

The linkages between the polymer and the crosslinking substance are generally the emphasis of chemical crosslinking in hydrogels [128]. The mechanical strength of the hydrogel is influenced by a certain functional group in the crosslinking compound [128]. Severe situations, such as lower pH, higher temperature, and the use of methanol as a suppressant, may cause polymers containing hydroxyl units to crosslink with glutaraldehyde [128]. Several chemicals, such as 1,6-hexamethylene diisocyanate and divinyl sulfone, may be used to crosslink polysaccharides to make hydrogels [128]. A particular polymer or functional group must be used in conjunction with these chemicals to guarantee crosslinking in the matrix, which is necessary for the synthesis of hydrogels [128]. Although the chemically crosslinking procedure with employing chemical crosslinkers can lead to higher cytotoxicity in some certain conditions, the fabricated hydrogel by this technique has an appropriate mechanical strength with high durability and swollen capability [112]. These features can be assumed as the principal advantages for employing chemical crosslinked hydrogels in various biomedical applications [112].

3.2.1. Citric acid (CA)

Citric acid (CA) has long been employed in crosslinking applications due to its hydrophilic nature and being inexpensive and harmless [129, 130]. Most hydrogel preparations may use this natural organic compound, which has three –OH groups and hence the ability to create a matrix [129,130]. To increase aqueous expansion and thermal durability, CA has been shown to create hydrogen bonds. Additionally, it aids in balancing hydrophilicity and contains an extra binding site and hydrogen bonding capacity [129,130]. CA, commonly referred to as a food additive, is a chemical compound utilized in food contact materials, water softening, anticoagulant, antiviral organ, and sanitizing items [131]. For a hydrogel matrix to crosslink firmly, CA also increases its tensile strength, thermal durability, and membrane characteristics [132]. With all its impacts on improving characteristics, CA has become a well-established crosslinking reagent for the production of cellulose hydrogels. According to the Food and Drug Administration (FDA), CA is a natural substance that can be used as a crosslinking compound and for human ingestion. At ambient temperature, researchers have found that CA is the simplest crosslinker to use during the formation of hydrogels [129-132].

3.2.2. Epichlorohydrin (ECH)

In most cellulose, starch, and biopolymers, ECH is often a crosslinker to strengthen the bonds between molecules [133]. Because of its low molecular weight and insoluble nature in polar solvents, the ECH employed in hydrogel formation yields a clear, transparent mixture that may be used to produce solvents and surfactants[133]. The gelation of polymers is confirmed by the ECH-OH reaction in most polysaccharides. Improved dispersion of pore size, chemical durability, mechanical strength, and adsorption/desorption potential may all be achieved using ECH [134].

The inclusion of ECH as a crosslinker increases the hydrogel's pore size and amount, resulting in an improvement in the hydrogel network's water-carrying ability [133-135]. Chitosan hydrogels prepared with ECH, on the other hand, have a higher tendency for metal absorption because ECH suppresses chitosan breakdown during metal absorption in acidic settings. As a result, ECH causes phase isolation and the creation of a heterogeneous matrix, hence boosting the water absorption potential of the hydrogel [135]. Because of the various levels of crosslinking compounds in the mixture, phase isolation develops. Higher ECH content results in increased water dissipation across the hydrogel matrix, leading to increased water absorption efficiency. Owing to the crosslinking chemical bonding, a larger quantity of crosslinker results in an increased water absorption potential [133-135].

3.2.3. Glutaraldehyde

Because of its simplicity of processing, low cost, strong reaction, higher solubility in aqueous solutions, lesser toxic effects, and significant crosslinking ability, glutaraldehyde is commonly used as a crosslinking compound [136]. The hydroxyl group in glutaraldehyde crosslinking may be very valuable in the construction of functional polymeric compounds derived from proteins, amino polysaccharides, and synthetic polymers [137,138]. As a ligand modification, glutaraldehyde may also be employed to eliminate metals from the solution. Glutaraldehyde is utilized in conjunction with chitosan as a crosslinking compound to improve the efficiency of ligands in order to eliminate

metal ions and boost the water absorption of the film [139]. Glutaraldehyde has also been investigated for use in the administration of ophthalmic drugs. Carboxymethyl chitosan hydrogels have been made using this chemical crosslinking reagent [136-139]. The use of glutaraldehyde as a crosslinking reagent contributed to forming a hydrogel that has a distinctive variety of characteristics. Biocompatibility, inflation, pH sensitivity, and viscosity of hydrogel are all enhanced following gelation [136-139]. Table 1 demonstrates the reported formulations, methods, and application of the aforementioned cellulose-based nanocomposites.

3.3. Cellulose based nanoemulsions

Nanoemulsions are typically composed of a dispersed phase (oil) and a continuous phase (water), having droplet size in nm [140]. CMC is hydrophilic polymer, being commonly used in the food and pharmaceutical industries as a thickener, stabilizer, and emulsifier [140]. In nanoemulsions, CMC can also be used as a stabilizer for preventing the oil droplets from coalescence [140]. The production of CMC-based nanoemulsion requires the use of high-energy methods such as sonication, homogenization, or micro-fluidization, or breaking down the oil droplets into smaller sizes and disperse them into the continuous phase [140]. CMC is added to the system either before or after the formation of the nanoemulsion droplets, and its concentration affects the stability and properties of the resulting nanoemulsion [140]. CMC-based nanoemulsions have several potential applications, including as delivery systems for drugs, nutraceuticals, and cosmetics [140]. They can also be used in the food industry as emulsifiers and stabilizers, and in the agricultural industry as pesticide carriers [140].

Various researches have been conducted to evaluate the use of CMC based cellulose in synthesis as well as separation of the both oil and water phases of nanoemulsions. As nanoemulsions are highly stable in solutions form and separation of oil and water can be done via cellulose based microfiltration for the waste water management. [140] In this work, Meng-Xin Hu and co-workers developed a cellulose microfiltration membrane with capability of acting as hydrophilic and hydrophobic agents using a thermal induced phase separation (TIPS) [140]. High coagulation temperature was induced for rapid phase separation and it enables the membrane having larger pore size [140]. By increasing the coagulation temperature up to 50 °C, the water flux capability of the cellulose membrane increased up to maximum level [140]. Capability of being both hydrophilic and lipophilic behaviors lead to the cellulose microfiltration membrane to display high efficiency in phase separation including the food and waste water nanoemulsions with very small size [140]. Results concluded that the cellulose microfiltration membranes can be used for oil/water nanoemulsions separation in natural way [140].

In another research, Roya Moghimi and co-workers developed edible films containing essential oils in the form of nanoemulsions as a natural anti-bacterial agent for food preservation [141]. Prepared HPMC were characterized for essential oil loading, surface morphology, and mechanical strength [141]. The morphology showed uniform distribution of nanoemulsions into the edible films with increased mechanical strength. Increased anti-bacterial action was observed as zone of inhibition was around 47 mm, indicating itself as an ideal candidate for food packaging[141].

4. Applications of CMC based Nanocomposite

The chemical structure of CMC can be varied, based on its carboxyl group abundance [142]. As a result, CMC can be used in so-called “grafting onto” techniques. CMC derivatives, acquired with the aid of grafting of small molecules and polymers can be engineered as assembled architectures (e.g., conjugates, nanoparticles, hydrogels) [142]. They are especially appropriate to improve drug transport structures or scaffolds for tissue engineering. CMC has attracted significant medical interest due to its improved water solubility and extensive variety of feasible chemical reaction [142]. For instance, in the fields of green nanocomposites for diverse applications, the CMC and its derivatives containing nanocomposites were broadly applied. Besides, because of its features such as particular superficial characteristics, suitable structural consistency and firmness, good immiscibility with water, high viscosity, accessibility and ampleness of natural substances, low-cost synthesis procedure, and also many contrasting elements[143]. It is also worth mentioning that there are some CMC-based smart composites including hydrogels with a great swollen ability, stable nanogels, and scaffolds for tissue engineering[144]. In respect of CMC-based scaffolds for tissue engineering applications, they are representing a good biodegradability due to the CMC’s inherent biodegradability, whether they were fabricated by electrospinning technique or 3D print method [145]. These CMC-based composites were proven in diverse studies that tend to be biocompatible and stable with stimuli-sensitive properties [145]. However, in most cases the mechanical strength of these composites can be modified to be employed more efficiently in biomedical purposes.

It’s far now broadly utilized in numerous fields, for instance, food industry, and agriculture[146], enzyme immobilization [103], wound healing [147], drug delivery [148], tissue engineering [149], dye effluent remediation [150], and energy-saving [151].

4.1. Tissue engineering

Tissue engineering (TE) is a swiftly progressing discipline that looks for restoring, substituting, or reviving tissues or organs by interpreting essential chemistry, physics, and biomedical sciences into sensible and impressive substances, gadgets, and medical techniques[152]. Currently, carboxymethyl cellulose-based substances are getting attention within the 3D bioprinting procedure, as an extraordinary technology applied in tissue engineering. In this procedure, tissue platforms are remanufactured through the layer accumulation of the suitable biomaterial by utilizing a digitally managed 3D printing machine[153].

Kanimozhi et al. [154] developed a hybrid porous scaffold made from chitosan, polyvinyl alcohol (PVA), and CMC using a freeze-drying and salt-leaching technique. The researchers used a combination of chitosan, PVA, and CMC because these materials have been shown to have good biocompatibility, mechanical properties, and porosity, which are important for tissue engineering applications. They also used a freeze-drying and salt-leaching technique to create a porous scaffold with a biomimetic structure that mimics the natural structure of bone tissue [154].

To evaluate the properties of the scaffold, the researchers conducted a series of experiments, including mechanical testing, SEM imaging, and in vitro biocompatibility studies using L929 fibroblast cells [154]. In conclusion, this study demonstrates the development of a biomimetic hybrid porous scaffold made from chitosan, PVA, and CMC using a freeze-drying and salt-leaching technique [154]. The scaffold was found to have good mechanical properties and biocompatibility and showed promise for use in bone tissue engineering applications [154]. The research has implications for the development of new strategies for tissue engineering and regenerative medicine [154].

Moreover, Janarthanan et al. [155] fabricated CMC and glycol chitosan (GC) nanocomposite as a capable 3D-bioprinting ink by employing a simple procedure, biocompatible in situ-gelling Schiff’s base reaction. The results showed that the well interactions with negative zeta potential between CMC and glycol chitosan resulted in a nanostructured with a balanced network, appropriate for drug and tissue engineering application [155].

Sathish et al. [156]developed a tri composite bioink using gelatin, CMC, and alginate, and evaluated its suitability for both direct and indirect 3D printing. The results showed that the tri composite bioink had good printability and mechanical properties, as well as biocompatibility with MG-63 cells. The SEM images revealed that the printed scaffolds had a porous structure, which is important for nutrient and oxygen

transport and cell growth. In addition, the scaffolds showed good compressive strength, which is important for load-bearing applications. The bioink was found to be suitable for both direct and indirect 3D printing and showed good mechanical properties, biocompatibility, and in vivo performance [156].

In another study, Zulkifli et al. [157] crafted nanostructured CMC-polyvinyl alcohol by employing the ultrafine fiber production approach. In this work, an examination of the cell-platform interactivity was accomplished through cultivating stromal cells on the ultrafine fibers to evaluate the expansion in size, quantity, and morphologies of the cells. The results showed a higher cell multiplication and attachment for the provided nanocomposite of CMC/PVA/AgNPs. Many studies have shown the practicability of using CMC-based materials for TE and bone revival purposes [157]. In another study, Qi and his colleagues [158] investigated the potential of calcium phosphate-loaded CMC non-woven sheets in bone revival in an upper section of rat skull and in vitro bone-forming cell transformation of mesenchymal stem cells (MSCs) with the aid of employing a spun-bond CMC leaf (laden with $Ca_3(PO_4)_2$) [158].

Tang et al.[159] explored the potential synergistic effects of CMC and low-intensity pulsed ultrasound (LIPUS) on bone tissue engineering. The researchers hypothesized that the combination of CMC and LIPUS would enhance the proliferation and differentiation of osteoblasts, leading to better bone regeneration [159]. They conducted a series of in vitro experiments using MC3T3-E1 cells. They compared the effects of CMC, LIPUS, and CMC combined with LIPUS on the proliferation and differentiation of the cells [159]. The results showed that the combination of CMC and LIPUS had a synergistic effect on the proliferation and differentiation of osteoblasts [159]. The cells grown on the CMC-LIPUS group exhibited higher expression levels of genes associated with bone formation and mineralization, as well as higher alkaline phosphatase (ALP) activity, which is a marker of osteoblast differentiation.In conclusion, this study suggests that the combination of CMC and LIPUS has a synergistic effect on bone tissue engineering, promoting the proliferation and differentiation of osteoblasts and enhancing bone regeneration [159].

In another study, Namkaew et al. [160]suggested a PVA-primarily based platform component for assisting cartilage developments in post-operative situations. The inclusion of carboxymethyl cellulose with this porous platform fiber improved the structural and bulging features, making it more appropriate for this application. Moreover, Sharmila et al. [161] suggested herb-primarily based ultrafine fibers elicited from *Spinaciaoleracea* therapeutic vegetation with carboxymethyl cellulose and artificial alginate (Alginate-carboxymethyl cellulose-sulfur oxide) for bone TE applications. The nanofibers (ultrafine fibers) demonstrated remarkable cell viability and outstanding bio-adjustability discovered through in vitro assessments carried out on osteogenic sarcoma cancer cells. Lately, Priya et al.[34]pronounced a bio-adjustable carboxymethyl cellulose platform substance connected to citric acid as a promising approach towards the bone TE programs; however, most of the platform nanofibers were mentioned in the essay primarily composed of carboxymethyl cellulose and were not fabricated with a novel technique or new substances to give them some diverse characteristics. The synthesis of novel bio-composites with stepped forward biophysical characteristics in a more systematic approach may assist to increase this area within the future [34].

4.2. Wound dressing

CMC is extensively used to enhance the properties and effectiveness of diverse wound dressing and wound recuperation materials in numerous clinical packages due to their outstanding binding potential to the inner frame cells [162]. CMC's nontoxicity, biocompatibility with mucous membrane, swelling capacity, water binding affinity, and low immunogenicity has attracted its application for developing wound dressings. Several wound dressings have been fabricated for the release of therapeutics like Diclofenac or growth factors delivery [33].

CMC-based hydrogels have received a lot of interest because of their great functionality for retaining the moisture around the wound region that hastens the cell growth, allowing the operation of enzymes and diverse hormones and generally improves the cell proliferation considerably [163]. Bayindir et al. [164] provided a co-polymeric nanocomposite of chitosan-carboxymethyl cellulose loaded with α-tocopherol (a type of vitamin E) and suggested its tremendous wound recuperation without stimulating any cytotoxicity or dangerous side effects. The cell multiplication evaluation demonstrated the synthesized hydrogel's viability by employing the MTT assay technique. In another study, Joorabloo et al. [165] fabricated a zinc oxide/polyvinyl alcohol/CMC-based nanocomposite fabric for wound dressing through a freeze-thawing technique. The hydrocolloids indicated remarkable bioavailability, biodegradability, and good physical characteristics with manageable steam transfer rate and level of swelling that ameliorated wound recuperation.

Recently, Koneru et al. [166] manufactured a sodium-CMC-hydroxypropyl methylcellulose nanocomposite with promising applications in drug transport and wound treating aids. The elicitation of Citrus paradisi seeds has been included in the hydrocolloid structure which enhanced the antimicrobial properties. The results of the SEM and TEM assessments showed that the Citrus paradisi seed extracts' glycerides were blended with the sodium-carboxymethyl cellulose of the structural grid and formed micelles responsible for antimicrobial interactions. Many studies have demonstrated the practicability and capability of CMC-primarily based hydrocolloids for wound remedial applications [167–169]. Substantial issues in synthesizing the best wound dressing substances are reaching appropriate pore sizes of the substances for the same platform of the wound places, acquiring awesome physical characteristics, suitable steam transference, and adjustability with the wounded tissue position through a simplistic devising approach [167-169]. In a recent study, Li et al. [169] introduced a double-sheet wound bandage fabric made up of polyvinyl alcohol/CMC/poly-(ethylene glycol) that demonstrated relatively better opposition to microbial spread with accompanying a remarkable physical structure compared to the sole-layered hydrocolloids [169]. They also produced the fabric by employing a simplistic procedure of freeze-thawing technique (an easy part of the detachment process) without including any types of immoderate inorganic components that would similarly result in venomous impressions on wound skins or the epidermis after bandage [169]. Non-poisonous hydrocolloid becomes validated by assessing the poisonous examinations primarily based on the L929-fibroblast cell, which can be employed in the progression of brand-new anti-cancer treatments. Moreover, the porous structure and pore dimension of the hydrocolloids have been verified to be compatible and can be customized by altering the factor proportion and concentration of the polyvinyl alcohol within the hydrocolloid [169].

During the same year, Jantrawut et al. [170] developed an LM pectin/gelatin/carboxymethyl cellulose-based double-sheet hydrocolloid emulsion that still demonstrated excessive fluid absorption functionality and water reservation potential with a significant consistency. Moreover, properly managed drug delivery of the hydrocolloid films loaded with povidone-iodine verified its capabilities as an optional tool for transporting sterilizer compounds to the wet wound locations to speed up the recuperation process without any types of afterward microbial contaminations [170].In a most current study, Sharma et al. [171]synthesized a photosensitizer which was implanted in a Na-alginate/pectin/carboxymethyl cellulose double-sheet emulsion for germicidal photosensitive-based remedy of contaminated wound areas [171].

The aforementioned procedure is employed to deal with wounds, which have been contaminated via multi-resistant organisms. The vitally important section of the entire technique is transporting photosensitizing substances at a suitable amount into the contaminated surface. This problem was easily resolved with the aid of the fabricated

double-layer films in the present work [170-172].

Farshi et al.[172] focused on the design, preparation, and characterization of a silk fibroin (SF)/CMC wound dressing for skin tissue regeneration applications. They sought to develop a wound dressing with good mechanical properties, biocompatibility, and the ability to promote skin tissue regeneration [172]. The researchers prepared the SF/CMC wound dressing using a combination of SF and CMC, which are both known for their biocompatibility and biodegradability [172]. They also added glycerol as a plasticizer to improve the flexibility of the dressing [172]. The wound dressing was then characterized using various techniques, including SEM imaging, mechanical testing, and in vitro biocompatibility studies [172].The results showed that the SF/CMC wound dressing had a porous structure with interconnected pores, which could promote cell proliferation and tissue regeneration [172]. The dressing also had good mechanical properties, including tensile strength and elongation at break, indicating that it could withstand mechanical stresses during the healing process [172].

The in vitro biocompatibility studies showed that the SF/CMC wound dressing was non-toxic to human dermal fibroblasts, indicating that it could be safely used for skin tissue regeneration applications. The dressing also promoted cell proliferation and migration, which are important for tissue regeneration [172].

Another study focused on the development of 3D printed CMC scaffolds for autologous growth factors delivery in wound healing [173]. The researchers aimed to develop a scaffold that could be used to deliver growth factors to the wound site, which would promote tissue regeneration and wound healing [173]. The CMC scaffolds were prepared using a 3D printing technique, and they were loaded with growth factors such as platelet-rich plasma (PRP) [173]. The results showed that the 3D printed CMC scaffolds had a porous structure with interconnected pores, which could facilitate cell migration and tissue regeneration. The scaffolds also had good mechanical properties, including compressive strength and elasticity, which could prevent the scaffold from collapsing under mechanical stress [173].

Change et al. [174] developed a new type of carboxymethyl cellulose self-healing hydrogel (CMCSH) as a biodegradable and injectable material for diabetic wound healing.The hydrogel was formed by formed by N, O-carboxymethyl chitosan-heparin (CMCS-Hep) and carboxymethyl cellulose-aldehyde (CMC-A) [174]. To create the material, CMCS was modified with Hep to synthesize CMCS-Hep, and CMC-A was synthesized through the periodate oxidation method [174]. The study utilized a dual-drug delivery system, with superoxide dismutase (SOD) and recombinant human epidermal growth factor (rhEGF) being encapsulated in the CMCSH to moderate the microenvironment of the diabetic wound bed and promote wound healing [174]. The results showed that the CMCSH had positive effects on diabetic wound healing by improving drug availability, promoting cell migration and proliferation, reducing DNA damage, shortening the inflammatory period, and accelerating the deposition of collagen fibers and the formation of blood vessels [174].

4.3. Drug delivery

CMC-based materials are also extensively used for drug delivery. Many researchers have suggested the transport of effective medical composites via CMC-based bioactive compounds. For instance, Du et al. developed a double polymeric hydrogel nanocomposite based on CM-chitosan and oxidized CMC laden with two peptides capsules, BSA, and thermazene[175]. Afterward, the drug was loaded into a prepared hydrocolloid nanocomposite through Schiff-base response and then the pH-responsive drug transport complex of the hydrogels with a remarkable antimicrobial activity has been fabricated [175]. Moreover, cellulose-based nanocomposites are renowned as bioadjustable aid for cellular association, improvement, and growth. Although, these kinds of cell operations (adherence, growth, and many others) are rather easy while nanocomposite platforms are changed with diverse anionic (negative superficial charge) or cationic (positive superficial charge) types in place of the tidy-cellulose providers [175]. Recently, Ramezani et al. [176]fabricated a multi-operational and hydrophilic carboxymethylated nanocomposite derived from cellulose (common thickness and length of 1700 ± 80 micrometers) by employing the positively charged resin of diethylamonioethyl cellulose with the simultaneous presence of anionic and cationic moieties. The carboxymethyl cellulose-diethylaminoethyl cellulose nanocomposites indicated an excessive function assisting for cell adherence, stabilization, and growth. Cheng et al. [177]synthesized a core-shell-dependent (double-layer) micro-compacted composite for cells or diverse healing applications through the traditional deviating microfluidic gadget and electrostatic dispersing. The sodium alginate was prepared and employed as the exterior (shell) stream inside the apparatus shape, while the sodium CMC was employed as the interior (centric) stream for the overall transport of medication or cell subculture [177].

Kandalam et al. [178]utilized sodium CMC as a capable device for therapeutically active nanocomposites incorporating stem cells from the apical papilla and brain-acquired neurotrophic elements. The most broadly used gelatin-based tough capsule package for oral drug delivery has been substituted for a CMC-based bionanocomposite. In 2020, Hamdan et al. [179]advanced a bionanocomposite-based tough composite consisting of carboxymethyl cellulose, carrageenan, and cellulose crystals. In another study, Rao et al. [180]demonstrated amino corporations into graphene oxide (GO) to configure energetic fumed graphene and combine it with CMC to produce GO-CMC complex as a drug conveyor matrix. The anti-cancer drug DOX was loaded into GO-CMC via π-π band interconnection and bipolar-bipolar affinities to shape GO-CMC/DOX drug loading device and their outcomes denoted that GO-CMC represented a negligible amount of toxicity and appropriate bioavailability. In 2020, Rakhshaei et al. [181]reported the component of graphene quantum dots as a unique and secure conjoining element for CMC to make biodegradable and bio adjustable composite. The production was changed into employing a convenient technique for devising the CMC/GQDs mixture. As a result, they showed that the organized CMC/GQDs were biocompatibility and had a pH-responsive behavior. This proposed that the prepared nanocomposite hydrogel can be used as a pH-induced targeted drug transport device. Moreover, Nezami et al. [148] developed some novel and multi-stimuli sensitive beads, which have been fabricated primarily based on CMC epychlorhydrine- chitosan (CMC-ECH-CTS) with a diverse CMC/CTS ratio equal to 1:1, 1:2, and a pair of:1 (S1–S3) to survey the focused transport and the prompted launch of the model drugs. The results indicated an enhanced drug delivery and better-targeted transportation of DOX as well as less cytotoxicity in comparison with the free drug (DOX) [148].

In another study, Hu et al. [182] fabricated a double layer hydrogel with polysaccharides inner core and synthetic polymer out-layer for potential applications in sustained drug delivery. Physical crosslinking method was used to form polysaccharide inner core containing sodium alginate (SA) and CMC [182]. Out-layer introduced by chemical crosslinking functions as a barrier in the way of drug release from inner core, leading to the sustained and controllable drug release [182]. The proposed method for the formation of double-layer hydrogels is presented in Fig. 5.

In more recent studies, graphene oxide was functionalized with CMC by chemically bonding the graphene oxide with the CMC hydrogel, then adding silk fibroin and Fe_3O_4 nanoparticles [183]. The use of silk fibroin enhanced the biocompatibility and biodegradability of the final nanobiocomposite as observed by non-toxic impact on healthy HEK293T cells and effective toxicity on BT549 cells. Also, the developed platform had potential for use in hyperthermia[183].

In another study toward developing a promising option for delivering drugs in a minimally invasive manner, a microneedle patch that could deliver diclofenac sodium salt through the skin using sodium CMC was created [184]. Conducted tests on human skin and a skin simulant showed that the patches were able to deliver the drug to the desired depth and dissolve quickly without leaving any residue. The

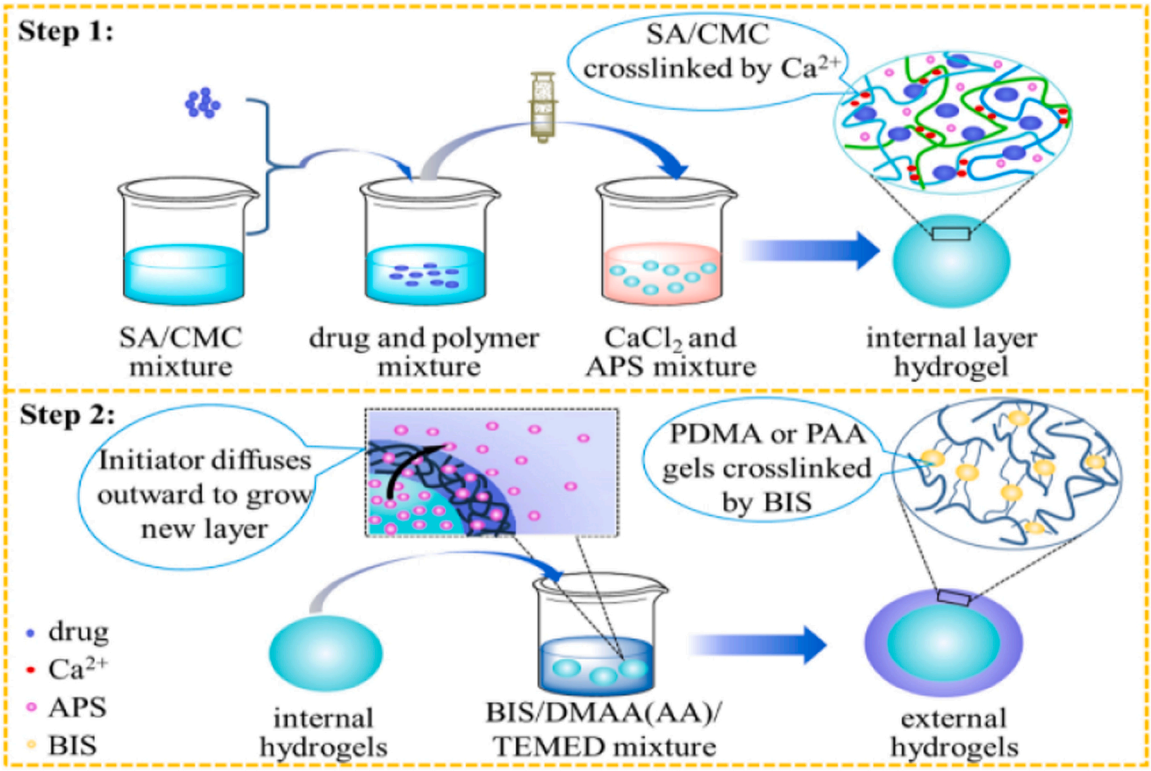

Fig. 5. : Schematic representation of double-layer hydrogels' formation (APS = ammonium persulfate, BIS = N,N-methylenedibis-propionamide, DMAA = N,N-dimethylacrylamide, AA = acrylamide, and TEMED = tetra-methylethylenediamine.
Adapted from reference [103] under the terms and conditions of the Creative Commons Attribution (CC BY) license.

bio-polymeric patches were also found to be non-toxic to human skin cells [184].

A pH-sensitive hydrogel network made of sodium CMC and pectin was developed for the controlled release of the anticancer drug cytarabine [185]. The hydrogels were synthesized using an aqueous free radical polymerization technique and were characterized for their texture, morphology, drug loading efficiency, structural properties, and drug release profile [185]. The results showed efficient encapsulation of cytarabine into the prepared network, with a sustained release response for all formulations [185]. The hydrogel system was found to be safe, biocompatible, and non-irritant, and pharmacokinetic estimation showed a remarkable increase in the plasma half-life and area under the curve (AUC) of cytarabine [185].

Yang et al. developed zein-CMC nanoparticles for the co-delivery of quercetin and resveratrol [186]. The results showed that the nanoparticles had a mean particle size of approximately 200 nm and a negative zeta potential [186]. The release studies indicated sustained release of both antioxidants from the nanoparticles, which could be attributed to the electrostatic interaction between the zein and CMC [186]. Simultaneously encapsulating quercetin and resveratrol within composite nanoparticles enhanced their antioxidant activities [186]. The study indicates that composite nanoparticles possess good physical and chemical stability, which can make them promising co-delivery systems for bioactive components. Such nanoparticles may have potential for personalized nutrition applications that require the oral delivery of combinations of bioactive compounds [186].

In another study, researchers developed a sustained release delivery system for curcumin by chemically transforming CMC with curcumin in ester form [187]. They synthesized and characterized the curcumin-CMC ester and found it to be stable in simulated gastric and intestinal fluids. Upon simulation in liver homogenate, curcumin was released from the ester in a consistent amount for five hours [187]. The release of curcumin was highest at pH 8.0 in the presence of liver enzymes, indicating that the modified CMC support can be used not only for the delivery of curcumin in the liver but also as a prodrug system that releases free curcumin in the presence of liver esterases [187].

Verma et al. developed a sustainable hydrogel for colon-specific delivery of the antibiotic gentamicin [188]. The hydrogel was created using CMC and showed promising results in vitro for its ability to release gentamicin specifically in the colon region [188]. The study found that the hydrogel was able to sustain the release of gentamicin [188]. They tested the hydrogel in simulated conditions that mimic the pH and enzymes found in the stomach and intestine. They found that the hydrogel was able to withstand the acidic conditions in the stomach release the drug in intestine, where the pH is higher, and the enzymes are able to break down the hydrogel and release the drug [188].

4.4. *Anti-bacterial properties*

Studies have shown that CMC can inhibit the growth of certain bacteria, including Escherichia coli, Staphylococcus aureus, and Pseudomonas aeruginosa [189]. The antibacterial action of CMC is thought to be due to its ability to bind to bacterial cells and disrupt their membrane integrity. CMC can also interfere with bacterial adhesion and biofilm formation, which can reduce bacterial colonization and infection [189]. In addition to its direct antibacterial effects, CMC can also enhance the activity of some antibiotics [189]. Studies have shown that the combination of CMC with antibiotics such as penicillin and ampicillin can increase their antibacterial activity against some bacterial strains [189]. Overall, while CMC is not a strong antibacterial agent on its own, it has some antibacterial properties that make it useful in certain applications [189]. Its ability to inhibit bacterial growth and enhance the activity of antibiotics make it a potential candidate for use in wound dressings, medical implants, and other biomedical applications where bacterial infection is a concern [189]. However, further research is needed to better understand the antibacterial mechanism of CMC and

optimize its antibacterial activity[189].

Nafees and co-workers synthesized CMC loaded Ag NPs and tested their anti-bacterial action on the strains of Klebsiellaoxytoca, E. coli, and S. aureus [190]. Additionally, a bactericidal activity was validated via utilization of the fluoroquinolones (anti-biotic) drug through implication of the agar-well diffusion method [190]. In this method, 100 μL of bacterial strains were transported to the plates containing nutrient agar, followed by distribution via streaking and incubation at 37 ± 2 °C for 24 h [190]. Afterwards, around 20 μL of the tested CMC/Ag-NPs was added to the wells, followed by the refrigeration for 1 h and overnight incubation at 37 ± 2 °C [190]. Vernier caliper was used to measure the clear zones of inhibition and disc diameter (mm) after the incubation period [190]. The in vitro anti-bacterial activity of naturally synthesized CMS/Ag-NPs was done through agar well diffusion method. Minimal inhibitory concentrations (MICs) against tested organisms were determined using the micro-broth dilution method [190]. Minimum bactericidal concentration (MBC) was calculated after the no colony appearance Antibacterial activity was evaluated via MIC index (MBC/MIC). Results concluded strong bactericidal and bacteriostatic action of CMC/Ag-NPs [190].

Moustafa M.G. Fouda developed CMC loaded gold nanoparticles (CMC-Au NPs) and determined its anti-bacterial activity against *E. coli* and *P. aeruginosa, S. aureus* and *B. subtilis* by disc diffusion method. Results concluded that CMC-Au NPs showed stronger bactericidal effects with extensive antibacterial activity and maximum zone of inhibition [191].

4.5. Anti-tumor applications

CMC can be functionalized with targeting ligands such as antibodies, peptides, or small molecules, which can selectively bind to tumor cells and enhance the accumulation of CMC in the tumor site [192]. Once at the tumor site, CMC can be used as a carrier for delivering anticancer drugs or imaging agents. One approach to using CMC for tumor targeting is through the use of nanoparticles. CMC nanoparticles have been shown to have favorable properties such as good biocompatibility, biodegradability, and low toxicity [192]. By attaching targeting ligands to the surface of CMC nanoparticles, they can be directed towards specific cancer cells and accumulate in the tumor site. Once inside the tumor, the nanoparticles can release their payload, which can be an anticancer drug or an imaging agent [192]. Another approach is to use CMC hydrogels, which can be injected directly into the tumor site [192,193]. CMC hydrogels can form a stable network that can trap anticancer drugs and release them slowly over time, providing sustained drug delivery to the tumor site [192,193]. The hydrogel can also create a barrier that prevents the drug from spreading to healthy tissues [192,193]. While CMC-based tumor targeting is still in the early stages of research, it shows promise as a potential therapeutic strategy for cancer treatment [192,193]. CMC has several advantages including its biocompatibility, biodegradability, and ability to be functionalized with targeting ligands [193]. However, further studies are needed to optimize the design of CMC-based systems for efficient and targeted drug delivery to tumors. Zhang and co-workers developed CMC based hydrogel having anti-tumor capabilities of PTT and PDT. Sodium periodate (NaIO4) was also added to promote the formation of gelling network CMC based hydrogel can produce cytotoxic ROS and targeted tumor killing [193]. In another research, pH sensitive microspheres were developed by polyacrylamide sodium and CMC mixing for colon targeted drug delivery by Vijay kumar and co-workers [194]. Authors modified the CMC with PAA to promote the drug release in the intestine and targeted killing of colon tumor cells. Similarly, Sangsuriyonk et al. showed that CMC was also a potential candidate for anti-cancer drug delivery by developing matrix hydrogels having different concentrations of citric acid as the cross-linker. Zhao et al. developed bismuth functionalized nano-hydrogels synthesized by UV irradiation, having good features of PTT and PTD. Moreover, CMC addition induces the synergistic effects of doxorubicin by producing strong anti-cancer action [195].

5. Conclusion

Nowadays, with the advent of cutting-edge technologies in the field of biomedical sciences, employment of the most appropriate raw materials is vitally important to optimize the treatmentefficacy. In this regard, CMC as a natural based biopolymer has some remarkable characteristics including biodegradability, biocompatibility, stimuli-sensitivity, and hydrophilicitywith special bioadhesive properties that have introduced CMC as a potential biopolymer for employing in various biomedical applications.It is also worth mentioning that CMC-based nanocomposites can be synthesized more conveniently than other biopolymeric carbohydrates with higher cost-efficiency. Furthermore, due to the great film-forming capability of CMC, the CMC-based nanocomposites either synthesized by physical crosslinking methods or chemical ones have been employed effectively for biomedical purposes. In addition to the suitable substitution degree of CMC, there are other features making CMC a preferable candidate among other cellulose ethers. The higher degree of polymerization of CMC contributes to its perfect film-forming ability.

Moreover, the polyanionic nature of CMC can be employed for preparing polyelectrolyte multilayers. Although some polyanionic polymers have shown bioadhesive capability, anionic CMC adheres more strongly to biological surfaces than other cellulose derivatives. Due to this, CMC is a preferable option for transdermal and transmucosal drug delivery. In addition, CMC is superior to be used in ophthalmic applications due to high molecular weight, rheological properties, and aqueous solubility. This specific characteristic of CMC represents a bright future outlook for modifying CMC with other materials to enhance its mechanical strength, which can be assumed as its major bottleneckand fabricate the CMC-based nanocomposites for applying more efficiently in biomedical applications.

More importantly, the long history of its application in clinical trials for a wide range of applications, including wound healing, dry eye syndrome, cancer treatment and gastrointestinal disorders demonstrates its promising potential for future biomedical applications compared to other comparable carbohydrates. For instance, carboxymethyl cellulose (CMC) has been used in clinical trials for a wide range of applications, including wound healing, dry eye syndrome, cancer treatment and gastrointestinal disorders. In wound healing clinical trials, CMC dressings have been found to be effective in promoting wound healing by maintaining a moist environment and preventing infection.

Ethical approval

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Authors' contributions

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Data Availability

No data was used for the research described in the article.

References

[1] E. Rahmani, et al., Preparation of a pH-responsive chitosan-montmorillonite-nitrogen-doped carbon quantum dots nanocarrier for attenuating doxorubicin limitations in cancer therapy, Eng. Life Sci. 22 (10) (2022) 634–649, https://doi.org/10.1002/elsc.202200016.

[2] R.J. Moon, et al., Cellulose nanomaterials review: structure, properties and nanocomposites, Chem. Soc. Rev. 40 (7) (2011) 3941–3994, https://doi.org/10.1039/C0CS00108B.

[3] S. Malmir, et al., Antibacterial properties of a bacterial cellulose CQD-TiO2 nanocomposite, Carbohydr. Polym. 234 (2020), 115835, https://doi.org/10.1016/j.carbpol.2020.115835.

[4] A.D. French, Glucose, not cellobiose, is the repeating unit of cellulose and why that is important, Cellulose 24 (11) (2017) 4605–4609, https://doi.org/10.1007/s10570-017-1450-3.

[5] F. Ansari, et al., Hierarchical wood cellulose fiber/epoxy biocomposites–materials design of fiber porosity and nanostructure, Compos. Part A: Appl. Sci. Manuf. 74 (2015) 60–68, https://doi.org/10.1016/j.compositesa.2015.03.024.

[6] L.C. Fidale, T. Heinze, O.A.El Seoud, Perichromism: a powerful tool for probing the properties of cellulose and its derivatives, Carbohydr. Polym. 93 (1) (2013) 129–134, https://doi.org/10.1016/j.carbpol.2012.06.061.

[7] C. Dumitriu, et al., Production and characterization of cellulose acetate–titanium dioxide nanotubes membrane fraxiparinized through polydopamine for clinical applications, Carbohydr. Polym. 181 (2018) 215–223, https://doi.org/10.1016/j.carbpol.2017.10.082.

[8] B. Lindman, et al., The relevance of structural features of cellulose and its interactions to dissolution, regeneration, gelation and plasticization phenomena, Phys. Chem. Chem. Phys. 19 (35) (2017) 23704–23718, https://doi.org/10.1039/C7CP02409F.

[9] H. Seddiqi, et al., Cellulose and its derivatives: towards biomedical applications, Cellulose 28 (4) (2021) 1893–1931, https://doi.org/10.1007/s10570-020-03674-w.

[10] R.G. Viera, et al., Synthesis and characterization of methylcellulose from sugar cane bagasse cellulose, Carbohydr. Polym. 67 (2) (2007) 182–189, https://doi.org/10.1016/j.carbpol.2006.05.007.

[11] N.S. Capanema, et al., Superabsorbent crosslinked carboxymethyl cellulose-PEG hydrogels for potential wound dressing applications, Int. J. Biol. Macromol. 106 (2018) 1218–1234, https://doi.org/10.1016/j.ijbiomac.2017.08.124.

[12] M. Davidovich-Pinhas, S. Barbut, A. Marangoni, The gelation of oil using ethyl cellulose, Carbohydr. Polym. 117 (2015) 869–878, https://doi.org/10.1016/j.carbpol.2014.10.035.

[13] W. Wang, et al., Influence of substitution on the rheological properties and gelation of hydroxyethyl cellulose solution in NaOH–water solvent, Carbohydr. Polym. 124 (2015) 85–89, https://doi.org/10.1016/j.carbpol.2015.01.065.

[14] M.R. Kulterer, et al., Nanoprecipitation of cellulose acetate using solvent/nonsolvent mixtures as dispersive media, Colloids Surf. A: Physicochem. Eng. Asp. 375 (1–3) (2011) 23–29, https://doi.org/10.1016/j.colsurfa.2010.11.029.

[15] S. Sun, et al., Microstructural effects on permeability of Nitrocellulose membranes for biomedical applications, J. Membr. Sci. 595 (2020), 117502, https://doi.org/10.1016/j.memsci.2019.117502.

[16] S. Kamel, et al., Pharmaceutical significance of cellulose: a review, Express Polym. Lett. 2 (11) (2008) 758–778, https://doi.org/10.3144/expresspolymlett.2008.90.

[17] T. Sanz, L. Laguna, A. Salvador, Biscuit dough structural changes during heating: influence of shortening and cellulose ether emulsions, LWT-Food Sci. Technol. 62 (2) (2015) 962–969, https://doi.org/10.1016/j.lwt.2015.02.036.

[18] A. Zennifer, et al., Key advances of carboxymethyl cellulose in tissue engineering & 3D bioprinting applications, Carbohydr. Polym. 256 (2021), 117561, https://doi.org/10.1016/j.carbpol.2020.117561.

[19] T. Heinze, K. Pfeiffer, Studies on the synthesis and characterization of carboxymethylcellulose, Die Angew. Makromol. Chem. 266 (1) (1999) 37–45, https://doi.org/10.1002/(SICI)1522-9505(19990501)266:1%3C37::AID-APMC37%3E3.0.CO;2-Z.

[20] L. Xiquan, Q. Tingzhu, Q. Shaoqui, Kinetics of the carboxymethylation of cellulose in the isopropyl alcohol system, Acta Polym. 41 (4) (1990) 220–222, https://doi.org/10.1002/actp.1990.010410406.

[21] L. Upadhyaya, et al., In situ grafted nanostructured ZnO/carboxymethyl cellulose nanocomposites for efficient delivery of curcumin to cancer, J. Polym. Res. 21 (9) (2014) 1–9.

[22] L. Upadhyaya, et al., Biomedical applications of carboxymethyl chitosans, Carbohydr. Polym. 91 (1) (2013) 452–466.

[23] L. Upadhyaya, et al., The implications of recent advances in carboxymethyl chitosan based targeted drug delivery and tissue engineering applications, J. Control. Release 186 (2014) 54–87.

[24] B. Diwakar, et al., Carboxymethyl Cellouse stabilized cobalt sulfide nanoparticles: preparation, characterization and application, J. Clust. Sci. (2022) 1–11.

[25] J. Kumar, J. Singh, V. Reddy, Carboxymethyl cellulose stabilized lead sulfide nanocrystals: Synthesis, characterization and catalytic applications, Colloids Surf. A: Physicochem. Eng. Asp. 620 (2021), 126572.

[26] Marques-Marinho, F.D. and C.D. Vianna-Soares, Cellulose and its derivatives use in the pharmaceutical compounding practice, in Cellulose-Medical, Pharmaceutical and Electronic Applications. 2013 https://doi.org/10.5772/56637, IntechOpen.

[27] P.K. Sahoo, D.K. Jena, Synthesis and study of mechanical and fire retardant properties of (carboxymethyl cellulose-g-polyacrylonitrile)/montmorillonite biodegradable nanocomposite, J. Polym. Res. 25 (12) (2018) 1–10, https://doi.org/10.1007/s10965-018-1659-3.

[28] B.Y. Swamy, Y.-S. Yun, In vitro release of metformin from iron (III) cross-linked alginate–carboxymethyl cellulose hydrogel beads, Int. J. Biol. Macromol. 77 (2015) 114–119, https://doi.org/10.1016/j.ijbiomac.2015.03.019.

[29] S. Saha, et al., Novel probiotic dissolvable carboxymethyl cellulose films as oral health biotherapeutics: in vitro preparation and characterization, Expert Opin. Drug Deliv. 10 (11) (2013) 1471–1482.

[30] X. Qiu, et al., Studies on the drug release properties of polysaccharide multilayers encapsulated ibuprofen microparticles, Langmuir 17 (17) (2001) 5375–5380.

[31] H.C. Arca, et al., Pharmaceutical applications of cellulose ethers and cellulose ether esters, Biomacromolecules 19 (7) (2018) 2351–2376.

[32] J.G. Vehige, et al., Cytoprotective properties of carboxymethyl cellulose (CMC) when used prior to wearing contact lenses treated with cationic disinfecting agents, Eye Contact lens 29 (3) (2003) 177–180.

[33] L. Diaz-Gomez, et al., 3D printed carboxymethyl cellulose scaffolds for autologous growth factors delivery in wound healing, Carbohydr. Polym. 278 (2022), 118924, https://doi.org/10.1016/j.carbpol.2021.118924.

[34] G. Priya, et al., In vitro and in vivo evaluation of carboxymethyl cellulose scaffolds for bone tissue engineering applications, ACS Omega 6 (2) (2021) 1246–1253, https://doi.org/10.1021%2Facsomega.0c04551.

[35] A. Shapourzadeh, et al., Enhanced adipose mesenchymal stem cells proliferation by carboxymethyl-chitosan functionalized polycaprolactone nanofiber, Iran. Biomed. J. 24 (4) (2020) 236, https://doi.org/10.29252%2Fibj.24.4.236.

[36] B. Singh, et al., Carboxymethyl cellulose enables silk fibroin nanofibrous scaffold with enhanced biomimetic potential for bone tissue engineering application, Carbohydr. Polym. 151 (2016) 335–347, https://doi.org/10.1016/j.carbpol.2016.05.088.

[37] G. Teti, et al., In vitro osteogenic and odontogenic differentiation of human dental pulp stem cells seeded on carboxymethyl cellulose-hydroxyapatite hybrid hydrogel, Front. Physiol. 6 (2015) 297, https://doi.org/10.3389/fphys.2015.00297.

[38] Z. Yu, et al., Enhanced bioactivity and osteoinductivity of carboxymethyl chitosan/nanohydroxyapatite/graphene oxide nanocomposites, RSC Adv. 8 (32) (2018) 17860–17877, https://doi.org/10.1039/C8RA00383A.

[39] W. Aljohani, et al., Bioprinting and its applications in tissue engineering and regenerative medicine, Int. J. Biol. Macromol. 107 (2018) 261–275, https://doi.org/10.1016/j.ijbiomac.2017.08.171.

[40] D.G. Hwang, Y.-m Choi, J. Jang, 3D bioprinting-based vascularized tissue models mimicking tissue-specific architecture and pathophysiology for in vitro studies, Front. Bioeng. Biotechnol. (2021) 426, https://doi.org/10.3389/fbioe.2021.685507.

[41] G. Saini, et al., Applications of 3D bioprinting in tissue engineering and regenerative medicine, J. Clin. Med. 10 (21) (2021) 4966, https://doi.org/10.3390/jcm10214966.

[42] A. García-Lizarribar, et al., Composite biomaterials as long-lasting scaffolds for 3D bioprinting of highly aligned muscle tissue, Macromol. Biosci. 18 (10) (2018), 1800167, https://doi.org/10.1002/mabi.201800167.

[43] A. Habib, et al., 3D printability of alginate-carboxymethyl cellulose hydrogel, Materials 11 (3) (2018) 454, https://doi.org/10.3390/ma11030454.

[44] S. Ji, et al., Novel bioinks from UV-responsive norbornene-functionalized carboxymethyl cellulose macromers, Bioprinting 18 (2020), e00083, https://doi.org/10.1016/j.bprint.2020.e00083.

[45] S. Kalliola, et al., The pH sensitive properties of carboxymethyl chitosan nanoparticles cross-linked with calcium ions, Colloids Surf. B: Biointerfaces 153 (2017) 229–236, https://doi.org/10.1016/j.colsurfb.2017.02.025.

[46] P. Colombo, et al., Analysis of the swelling and release mechanisms from drug delivery systems with emphasis on drug solubility and water transport, J. Control. Release 39 (2–3) (1996) 231–237, https://doi.org/10.1016/0168-3659(95)00158-1.

[47] M. Rasoulzadeh, H. Namazi, Carboxymethyl cellulose/graphene oxide bio-nanocomposite hydrogel beads as anticancer drug carrier agent, Carbohydr. Polym. 168 (2017) 320–326, https://doi.org/10.1016/j.carbpol.2017.03.014.

[48] M.M. Marks, Cellulose esters in the treatment of constipation, Am. J. Dig. Dis. 16 (6) (1949) 215–217.

[49] A.S. Levine, et al., Initial clinical trials in cancer patients of polyriboinosinic-polyribocytidylic acid stabilized with poly-L-lysine, in carboxymethylcellulose [poly (ICLC)], a highly effective interferon inducer, Cancer Res. 39 (5) (1979) 1645–1650.

[50] D. Bowers, R.B. Raybon, C.R. Wheeless Jr, Hyaluronic acid–carboxymethylcellulose film and perianastomotic adhesions in previously irradiated rats, Am. J. Obstet. Gynecol. 181 (6) (1999) 1335–1338.

[51] J.K. Song, et al., Efficacy of carboxymethylcellulose and hyaluronate in dry eye disease: a systematic review and meta-analysis, Korean J. Fam. Med. 38 (1) (2017) 2.

[52] M. Labetoulle, et al., Osmoprotectants, carboxymethylcellulose and hyaluronic acid multi-ingredient eye drop: a randomised controlled trial in moderate to severe dry eye, Eye 31 (10) (2017) 1409–1416.

[53] W. Li, B. Sun, P. Wu, Study on hydrogen bonds of carboxymethyl cellulose sodium film with two-dimensional correlation infrared spectroscopy, Carbohydr. Polym. 78 (3) (2009) 454–461, https://doi.org/10.1016/j.carbpol.2009.05.002.

[54] M.P. Adinugraha, D.W. Marseno, Synthesis and characterization of sodium carboxymethylcellulose from cavendish banana pseudo stem (Musa cavendishii LAMBERT), Carbohydr. Polym. 62 (2) (2005) 164–169, https://doi.org/10.1016/j.carbpol.2005.07.019.

[55] M.R. Jiménez-Castellanos, H. Zia, C.T. Rhodes, Design and testing in vitro of a bioadhesive and floating drug delivery system for oral application, Int. J. Pharm. 105 (1) (1994) 65–70, https://doi.org/10.1016/0378-5173(94)90236-4.
[56] K.R. Rao, P. Buri, A novel in situ method to test polymers and coated microparticles for bioadhesion, Int. J. Pharm. 52 (3) (1989) 265–270, https://doi.org/10.1016/0378-5173(89)90229-9.
[57] S. Javanbakht, A. Shaabani, Carboxymethyl cellulose-based oral delivery systems, Int. J. Biol. Macromol. 133 (2019) 21–29, https://doi.org/10.1016/j.ijbiomac.2019.04.079.
[58] J. Varshosaz, N. Tavakoli, F. Roozbahani, Formulation and in vitro characterization of ciprofloxacin floating and bioadhesive extended-release tablets, Drug Deliv. 13 (4) (2006) 277–285, https://doi.org/10.1080/10717540500395106.
[59] N.A. Nafee, et al., Mucoadhesive buccal patches of miconazole nitrate: in vitro/in vivo performance and effect of ageing, Int. J. Pharm. 264 (1–2) (2003) 1–14, https://doi.org/10.1016/S0378-5173(03)00371-5.
[60] Y. Sudhakar, K. Kuotsu, A. Bandyopadhyay, Buccal bioadhesive drug delivery—a promising option for orally less efficient drugs, J. Control. Release 114 (1) (2006) 15–40, https://doi.org/10.1016/j.jconrel.2006.04.012.
[61] J. Varshosaz, Z. Dehghan, Development and characterization of buccoadhesive nifedipine tablets, Eur. J. Pharm. Biopharm. 54 (2) (2002) 135–141, https://doi.org/10.1016/S0939-6411(02)00078-4.
[62] B. Dortunç, L. Özer, N. Uyanik, Development and in vitro evaluation of a buccoadhesive pindolol tablet formulation, Drug Dev. Ind. Pharm. 24 (3) (1998) 281–288, https://doi.org/10.3109/03639049809085621.
[63] M. Semalty, A. Semalty, G. Kumar, Formulation and characterization of mucoadhesive buccal films of glipizide, Indian J. Pharm. Sci. 70 (1) (2008) 43, https://doi.org/10.4103%2F0250-474X.40330.
[64] L. Perioli, et al., Novel mucoadhesive buccal formulation containing metronidazole for the treatment of periodontal disease, J. Control. Release 95 (3) (2004) 521–533, https://doi.org/10.1016/j.jconrel.2003.12.018.
[65] F.A. Mohammed, H. Khedr, Preparation and in vitro/in vivo evaluation of the buccal bioadhesive properties of slow-release tablets containing miconazole nitrate, Drug Dev. Ind. Pharm. 29 (3) (2003) 321–337, https://doi.org/10.1081/DDC-120018206.
[66] N. Parviez, A. Ahuja, R. Khar, Development and evaluation of muco-adhesive buccal tablets of lignocaine hydrochloride, Indian J. Pharm. Sci. 64 (6) (2002) 563.
[67] J. Ali, R. Khar, A. Ahuja, Formulation and characterisation of a buccoadhesive erodible tablet for the treatment of oral lesions, Die Pharm. 53 (5) (1998) 329–334.
[68] M. Koland, N.R. Charyulu, Design and in vivo evaluation of buccoadhesive hydrophilic polymer matrix films of losartan potassium, INDIAN J. Pharm. Educ. Res. 50 (2) (2016) S115–S124, https://doi.org/10.5530/ijper.50.2.26.
[69] F. Alanazi, et al., Formulation and physicochemical characterisation of buccoadhesive films containing ketorolac, J. Drug Deliv. Sci. Technol. 17 (3) (2007) 183–192, https://doi.org/10.1016/S1773-2247(07)50034-1.
[70] M.I. Mohamed, M. Haider, M.A.M. Ali, Buccal mucoadhesive films containing antihypertensive drug: In vitro/in vivo evaluation, J. Chem. Pharm. Res 3 (6) (2011) 665–686.
[71] N. Verma, et al., Evaluation of a mucoadhesive buccal patch for delivery of atenolol: in vitro screening of bioadhesion, J. Pure Appl. Microbiol 1 (115) (2007) 8.
[72] H.C. Arca, et al., Pharmaceutical applications of cellulose ethers and cellulose ether esters, Biomacromolecules 19 (7) (2018) 2351–2376, https://doi.org/10.1021/acs.biomac.8b00517.
[73] S. Javanbakht, et al., Cu-crosslinked carboxymethylcellulose/naproxen/graphene quantum dot nanocomposite hydrogel beads for naproxen oral delivery, Carbohydr. Polym. 195 (2018) 453–459, https://doi.org/10.1016/j.carbpol.2018.04.103.
[74] S. Javanbakht, et al., Carboxymethylcellulose capsulated Cu-based metal-organic framework-drug nanohybrid as a pH-sensitive nanocomposite for ibuprofen oral delivery, Int. J. Biol. Macromol. 119 (2018) 588–596, https://doi.org/10.1016/j.ijbiomac.2018.07.181.
[75] S. Javanbakht, H. Namazi, Doxorubicin loaded carboxymethyl cellulose/graphene quantum dot nanocomposite hydrogel films as a potential anticancer drug delivery system, Mater. Sci. Eng.: C. 87 (2018) 50–59, https://doi.org/10.1016/j.msec.2018.02.010.
[76] S. Javanbakht, A. Shaabani, Encapsulation of graphene quantum dot-crosslinked chitosan by carboxymethylcellulose hydrogel beads as a pH-responsive bio-nanocomposite for the oral delivery agent, Int. J. Biol. Macromol. 123 (2019) 389–397, https://doi.org/10.1016/j.ijbiomac.2018.11.118.
[77] J. Shen, et al., Light emitting CMC-CHO based self-healing hydrogel with injectability for in vivo wound repairing applications, Carbohydr. Polym. 281 (2022), 119052.
[78] Q. Meng, et al., Synthesis and characterization of curcumin-loaded pH/reduction dual-responsive folic acid modified carboxymethyl cellulose-based microcapsules for targeted drug delivery, J. Ind. Eng. Chem. 105 (2022) 251–258.
[79] I. Ali, et al., Reduction-responsive and bioorthogonal carboxymethyl cellulose based soft hydrogels cross-linked via IEDDA click chemistry for cancer therapy application, Int. J. Biol. Macromol. 219 (2022) 109–120.
[80] Y. Bao, J. Ma, N. Li, Synthesis and swelling behaviors of sodium carboxymethyl cellulose-g-poly (AA-co-AM-co-AMPS)/MMT superabsorbent hydrogel, Carbohydr. Polym. 84 (1) (2011) 76–82, https://doi.org/10.1016/j.carbpol.2010.10.061.
[81] R. Barbucci, A. Magnani, M. Consumi, Swelling behavior of carboxymethylcellulose hydrogels in relation to cross-linking, pH, and charge density, Macromolecules 33 (20) (2000) 7475–7480, https://doi.org/10.1021/ma0007029.
[82] P. Liu, et al., Radiation crosslinking of CMC-Na at low dose and its application as substitute for hydrogel, Radiat. Phys. Chem. 72 (5) (2005) 635–638, https://doi.org/10.1016/j.radphyschem.2004.03.090.
[83] C. Demitri, et al., Novel superabsorbent cellulose-based hydrogels crosslinked with citric acid, J. Appl. Polym. Sci. 110 (4) (2008) 2453–2460, https://doi.org/10.1002/app.28660.
[84] K.M. El Salmawi, Application of polyvinyl alcohol (PVA)/carboxymethyl cellulose (CMC) hydrogel produced by conventional crosslinking or by freezing and thawing, J. Macromol. Sci., Part A: Pure Appl. Chem. 44 (6) (2007) 619–624, https://doi.org/10.1080/10601320701285045.
[85] N. Dhar, S.P. Akhlaghi, K.C. Tam, Biodegradable and biocompatible polyampholyte microgels derived from chitosan, carboxymethyl cellulose and modified methyl cellulose, Carbohydr. Polym. 87 (1) (2012) 101–109, https://doi.org/10.1016/j.carbpol.2011.07.022.
[86] T. Fekete, et al., Synthesis of carboxymethylcellulose/starch superabsorbent hydrogels by gamma-irradiation, Chem. Cent. J. 11 (1) (2017) 1–10, https://doi.org/10.1186/s13065-017-0273-5.
[87] N. Roy, et al., Biodegradation of PVP–CMC hydrogel film: a useful food packaging material, Carbohydr. Polym. 89 (2) (2012) 346–353, https://doi.org/10.1016/j.carbpol.2012.03.008.
[88] A.P. Rokhade, et al., Semi-interpenetrating polymer network microspheres of gelatin and sodium carboxymethyl cellulose for controlled release of ketorolac tromethamine, Carbohydr. Polym. 65 (3) (2006) 243–252, https://doi.org/10.1016/j.carbpol.2006.01.013.
[89] A. Hebeish, et al., Development of CMC hydrogels loaded with silver nano-particles for medical applications, Carbohydr. Polym. 92 (1) (2013) 407–413, https://doi.org/10.1016/j.carbpol.2012.08.094.
[90] Y. Qiu, K. Park, Environment-sensitive hydrogels for drug delivery, Adv. Drug Deliv. Rev. 53 (3) (2001) 321–339, https://doi.org/10.1016/S0169-409X(01)00203-4.
[91] F. Ullah, et al., Classification, processing and application of hydrogels: a review, Mater. Sci. Eng.: C. 57 (2015) 414–433, https://doi.org/10.1016/j.msec.2015.07.053.
[92] N. Das, Preparation methods and properties of hydrogel: a review, Int. J. Pharm. Pharm. Sci. 5 (3) (2013) 112–117.
[93] M. Yadollahi, et al., Synthesis and characterization of antibacterial carboxymethylcellulose/CuO bio-nanocomposite hydrogels, Int. J. Biol. Macromol. 73 (2015) 109–114, https://doi.org/10.1016/j.ijbiomac.2014.10.063.
[94] P.R. Chang, et al., Polysaccharides as stabilizers for the synthesis of magnetic nanoparticles, Carbohydr. Polym. 83 (2) (2011) 640–644, https://doi.org/10.1016/j.carbpol.2010.08.027.
[95] J. Shen, et al., Carboxymethyl cellulose/alum modified precipitated calcium carbonate fillers: preparation and their use in papermaking, Carbohydr. Polym. 81 (3) (2010) 545–553, https://doi.org/10.1016/j.carbpol.2010.03.012.
[96] J. Luna-Martínez, et al., Synthesis and optical characterization of ZnS–sodium carboxymethyl cellulose nanocomposite films, Carbohydr. Polym. 84 (1) (2011) 566–570, https://doi.org/10.1016/j.carbpol.2010.12.021.
[97] Y. Choi, J. Simonsen, Cellulose nanocrystal-filled carboxymethyl cellulose nanocomposites, J. Nanosci. Nanotechnol. 6 (3) (2006) 633–639, https://doi.org/10.1166/jnn.2006.132.
[98] M.E. Alemán-Domínguez, et al., Tunability of polycaprolactone hydrophilicity by carboxymethyl cellulose loading, J. Appl. Polym. Sci. 135 (14) (2018) 46134.
[99] A. Di Michele, et al., Bioadhesive patches based on carboxymethyl cellulose/polyvinylpyrrolidone/bentonite composites and Soluplus® for skin administration of poorly soluble molecules, Appl. Clay Sci. 216 (2022), 106377.
[100] M.R. Zare, et al., Dissolvable carboxymethyl cellulose/polyvinylpyrrolidone microneedle arrays for transdermal delivery of Amphotericin B to treat cutaneous leishmaniasis, Int. J. Biol. Macromol. 182 (2021) 1310–1321.
[101] J. Tan, et al., Controllable aggregation and reversible pH sensitivity of AuNPs regulated by carboxymethyl cellulose, Langmuir 26 (3) (2010) 2093–2098.
[102] W. Zhang, et al., Synthesis and applications of carboxymethyl cellulose hydrogels, Gels 8 (9) (2022) 529.
[103] V. Azizi, et al., Immobilization of α-amylase on modified magnetic zeolite (MAZE) coated with carboxymethyl cellulose (CMC) composite and its properties, LWT 144 (2021), 111214, https://doi.org/10.1016/j.lwt.2021.111214.
[104] H. Nasution, et al., Hydrogel and effects of crosslinking agent on cellulose-based hydrogels: a review, Gels 8 (9) (2022) 568.
[105] J. Yang, et al., Constructions and properties of physically cross-linked hydrogels based on natural polymers, Polym. Rev. (2022) 1–39.
[106] C. Chen, et al., Tannic acid: a crosslinker leading to versatile functional polymeric networks: a review, RSC Adv. 12 (13) (2022) 7689–7711.
[107] A. Timofejeva, M. D'Este, D. Loca, Calcium phosphate/polyvinyl alcohol composite hydrogels: a review on the freeze-thawing synthesis approach and applications in regenerative medicine, Eur. Polym. J. 95 (2017) 547–565, https://doi.org/10.1016/j.eurpolymj.2017.08.048.
[108] Y. Zhao, et al., Preparation, characterization and protein sorption of photo-crosslinked cell membrane-mimicking chitosan-based hydrogels, Carbohydr. Polym. 151 (2016) 237–244, https://doi.org/10.1016/j.carbpol.2016.05.067.
[109] Y. Guan, et al., High strength of hemicelluloses based hydrogels by freeze/thaw technique, Carbohydr. Polym. 101 (2014) 272–280, https://doi.org/10.1016/j.carbpol.2013.08.085.

[110] S. Butylina, S. Geng, K. Oksman, Properties of as-prepared and freeze-dried hydrogels made from poly (vinyl alcohol) and cellulose nanocrystals using freeze-thaw technique, Eur. Polym. J. 81 (2016) 386–396, https://doi.org/10.1016/j.eurpolymj.2016.06.028.
[111] X. Zhang, et al., Innovative application of PVA hydrogel for the forming of porous Si3N4 ceramics via freeze-thaw technique, Ceram. Int. 44 (11) (2018) 13409–13413, https://doi.org/10.1016/j.ceramint.2018.03.071.
[112] M.S. Pascuta, et al., Polysaccharide-based edible gels as functional ingredients: characterization, applicability, and human health benefits, Gels 8 (8) (2022) 524.
[113] A. Manzoor, et al., Recent insights into polysaccharide-based hydrogels and their potential applications in food sector: A review, Int. J. Biol. Macromol. 213 (2022) 987–1006.
[114] M. Lu, et al., Fabrication of photo-crosslinkable glycol chitosan hydrogel as a tissue adhesive, Carbohydr. Polym. 181 (2018) 668–674, https://doi.org/10.1016/j.carbpol.2017.11.097.
[115] C. Qi, et al., Photo-crosslinkable, injectable sericin hydrogel as 3D biomimetic extracellular matrix for minimally invasive repairing cartilage, Biomaterials 163 (2018) 89–104, https://doi.org/10.1016/j.biomaterials.2018.02.016.
[116] Y. Zhao, et al., Freeze-thaw induced gelation of alginates, Carbohydr. Polym. 148 (2016) 45–51, https://doi.org/10.1016/j.carbpol.2016.04.047.
[117] M. Yuan, et al., Thermosensitive and photocrosslinkable hydroxypropyl chitin-based hydrogels for biomedical applications, Carbohydr. Polym. 192 (2018) 10–18, https://doi.org/10.1016/j.carbpol.2018.03.031.
[118] R. Reeves, et al., Synthesis and characterization of carboxymethylcellulose-methacrylate hydrogel cell scaffolds, Polymers 2 (3) (2010) 252–264, https://doi.org/10.3390/polym2030252.
[119] O.H. Lin, et al., Grafting of sodium carboxymethylcellulose (CMC) with glycidyl methacrylate and development of UV curable coatings from CMC-g-GMA induced by cationic photoinitiators, Carbohydr. Polym. 59 (1) (2005) 57–69, https://doi.org/10.1016/j.carbpol.2004.08.027.
[120] S. Kuwabara, H. Kubo, Water-absorbing characteristics of acrylic acid-grafted carboxymethyl cellulose synthesized by photografting, J. Appl. Polym. Sci. 60 (11) (1996) 1965–1970, https://doi.org/10.1002/(SICI)1097-4628(19960613)60:11%3C1965::AID-APP20%3E3.0.CO;2-Z.
[121] S. Villarruel, et al., Changes induced by UV radiation in the presence of sodium benzoate in films formulated with polyvinyl alcohol and carboxymethyl cellulose, Mater. Sci. Eng.: C. 56 (2015) 545–554, https://doi.org/10.1016/j.msec.2015.07.003.
[122] M. González-Torres, et al., Biological activity of radiation-induced collagen–polyvinylpyrrolidone–PEG hydrogels, Mater. Lett. 214 (2018) 224–227, https://doi.org/10.1016/j.matlet.2017.12.006.
[123] B. Singh, R. Bala, Development of hydrogels by radiation induced polymerization for use in slow drug delivery, Radiat. Phys. Chem. 103 (2014) 178–187, https://doi.org/10.1016/j.radphyschem.2014.06.002.
[124] S. Saiki, et al., ESR study on radiation-induced radicals in carboxymethyl cellulose aqueous solution, Radiat. Phys. Chem. 80 (2) (2011) 149–152, https://doi.org/10.1016/j.radphyschem.2010.07.024.
[125] B.J.D. Barba, et al., Hemostatic granules and dressing prepared from formulations of carboxymethyl cellulose, kappa-carrageenan and polyethylene oxide crosslinked by gamma radiation, Radiat. Phys. Chem. 144 (2018) 180–188, https://doi.org/10.1016/j.radphyschem.2017.08.009.
[126] R.A. Wach, et al., Hydroxyl radical-induced crosslinking and radiation-initiated hydrogel formation in dilute aqueous solutions of carboxymethylcellulose, Carbohydr. Polym. 112 (2014) 412–415, https://doi.org/10.1016/j.carbpol.2014.06.007.
[127] A.M. Elbarbary, et al., Radiation induced crosslinking of polyacrylamide incorporated low molecular weights natural polymers for possible use in the agricultural applications, Carbohydr. Polym. 176 (2017) 19–28, https://doi.org/10.1016/j.carbpol.2017.08.050.
[128] W.E. Hennink, C.F. van Nostrum, Novel crosslinking methods to design hydrogels, Adv. Drug Deliv. Rev. 64 (2012) 223–236, https://doi.org/10.1016/j.addr.2012.09.009.
[129] D. Gyawali, et al., Citric acid-derived in situ crosslinkable biodegradable polymers for cell delivery, Biomaterials 31 (34) (2010) 9092–9105, https://doi.org/10.1016/j.biomaterials.2010.08.022.
[130] S.A. Stone, et al., In situ citric acid crosslinking of alginate/polyvinyl alcohol electrospun nanofibers, Mater. Lett. 112 (2013) 32–35, https://doi.org/10.1016/j.matlet.2013.08.100.
[131] C. Menzel, et al., Molecular structure of citric acid cross-linked starch films, Carbohydr. Polym. 96 (1) (2013) 270–276, https://doi.org/10.1016/j.carbpol.2013.03.044.
[132] V.S. Ghorpade, A.V. Yadav, R.J. Dias, Citric acid crosslinked cyclodextrin/hydroxypropylmethylcellulose hydrogel films for hydrophobic drug delivery, Int. J. Biol. Macromol. 93 (2016) 75–86, https://doi.org/10.1016/j.ijbiomac.2016.08.072.
[133] A.H. Jawad, M. Nawi, Oxidation of crosslinked chitosan-epichlorohydrine film and its application with TiO2 for phenol removal, Carbohydr. Polym. 90 (1) (2012) 87–94, https://doi.org/10.1016/j.carbpol.2012.04.066.
[134] O.S. Kittipongpatana, N. Kittipongpatana, Physicochemical, in vitro digestibility and functional properties of carboxymethyl rice starch cross-linked with epichlorohydrin, Food Chem. 141 (2) (2013) 1438–1444, https://doi.org/10.1016/j.foodchem.2013.04.030.
[135] Z.E. Meybodi, M. Imani, M. Atai, Kinetics of dextran crosslinking by epichlorohydrin: a rheometry and equilibrium swelling study, Carbohydr. Polym. 92 (2) (2013) 1792–1798, https://doi.org/10.1016/j.carbpol.2012.11.030.
[136] W. Wang, et al., Effect of vapor-phase glutaraldehyde crosslinking on electrospun starch fibers, Carbohydr. Polym. 140 (2016) 356–361, https://doi.org/10.1016/j.carbpol.2015.12.061.
[137] S. Nagireddi, V. Katiyar, R. Uppaluri, Pd (II) adsorption characteristics of glutaraldehyde cross-linked chitosan copolymer resin, Int. J. Biol. Macromol. 94 (2017) 72–84, https://doi.org/10.1016/j.ijbiomac.2016.09.088.
[138] Z. Tian, W. Liu, G. Li, The microstructure and stability of collagen hydrogel cross-linked by glutaraldehyde, Polym. Degrad. Stab. 130 (2016) 264–270, https://doi.org/10.1016/j.polymdegradstab.2016.06.015.
[139] N.M.A. Khairuddin, et al., Immobilization of bovine serum albumin on the chitosan/PVA film, Sains Malays. 47 (6) (2018) 1311–1318, https://doi.org/10.17576/jsm-2018-4706-28.
[140] M.-X. Hu, et al., Natural cellulose microfiltration membranes for oil/water nanoemulsions separation, Colloids Surf. A: Physicochem. Eng. Asp. 564 (2019) 142–151.
[141] R. Moghimi, A. Aliahmadi, H. Rafati, Antibacterial hydroxypropyl methyl cellulose edible films containing nanoemulsions of Thymus daenensis essential oil for food packaging, Carbohydr. Polym. 175 (2017) 241–248.
[142] A. Pettignano, A. Charlot, E. Fleury, Carboxyl-functionalized derivatives of carboxymethyl cellulose: towards advanced biomedical applications, Polym. Rev. 59 (3) (2019) 510–560, https://doi.org/10.1080/15583724.2019.1579226.
[143] M.S. Rahman, et al., Recent developments of carboxymethyl cellulose, Polymers 13 (8) (2021) 1345, https://doi.org/10.3390/polym13081345.
[144] C. Vasile, et al., New developments in medical applications of hybrid hydrogels containing natural, *Polym.* Mol. 25 (7) (2020) 1539.
[145] A. Zennifer, et al., Key advances of carboxymethyl cellulose in tissue engineering & 3D bioprinting applications, Carbohydr. Polym. 256 (2021), 117561.
[146] S. Dong, et al., Factors influencing the adhesive behavior of carboxymethyl cellulose-based hydrogel for food applications, Int. J. Biol. Macromol. 179 (2021) 398–406, https://doi.org/10.1016/j.ijbiomac.2021.03.027.
[147] V. Kanikireddy, et al., Carboxymethyl cellulose-based materials for infection control and wound healing: a review, Int. J. Biol. Macromol. 164 (2020) 963–975, https://doi.org/10.1016/j.ijbiomac.2020.07.160.
[148] S. Nezami, et al., pH-sensitive drug delivery systems based on CMC-ECH-CTS and CMC-ECH-CTS/Fe3O4 beads, Polym. Test. 97 (2021), 107144, https://doi.org/10.1016/j.polymertesting.2021.107144.
[149] V. Saxena, A. Hasan, L.M. Pandey, Antibacterial nano-biocomposite scaffolds of Chitosan, Carboxymethyl Cellulose and Zn & Fe integrated Hydroxyapatite (Chitosan-CMC-FZO@ HAp) for bone tissue engineering, Cellulose 28 (14) (2021) 9207–9226, https://doi.org/10.1007/s10570-021-04072-6.
[150] W. Wang, et al., Synthesis of carboxymethyl cellulose-chitosan-montmorillonite nanosheets composite hydrogel for dye effluent remediation, Int. J. Biol. Macromol. 165 (2020) 1–10, https://doi.org/10.1016/j.ijbiomac.2020.09.154.
[151] Y. Liu, et al., Molecularly engineered CMC-caged PNIPAM for broadband light management in energy-saving window, Carbohydr. Polym. 281 (2022), 119056, https://doi.org/10.1016/j.carbpol.2021.119056.
[152] J.L. Paternoster, J.J. Vranckx, State of the art of clinical applications of tissue engineering in 2021, Tissue Eng. Part B: Rev. 28 (3) (2022) 592–612, https://doi.org/10.1089/ten.teb.2021.0017.
[153] S. Mallakpour, M. Tukhani, C.M. Hussain, Recent advancements in 3D bioprinting technology of carboxymethyl cellulose-based hydrogels: Utilization in tissue engineering, Adv. Colloid Interface Sci. 292 (2021), 102415, https://doi.org/10.1016/j.cis.2021.102415.
[154] K. Kanimozhi, et al., Development of biomimetic hybrid porous scaffold of chitosan/polyvinyl alcohol/carboxymethyl cellulose by freeze-dried and salt leached technique, J. Nanosci. Nanotechnol. 18 (7) (2018) 4916–4922, https://doi.org/10.1166/jnn.2018.15306.
[155] G. Janarthanan, et al., 3D printable and injectable lactoferrin-loaded carboxymethyl cellulose-glycol chitosan hydrogels for tissue engineering applications, Mater. Sci. Eng.: C. 113 (2020), 111008, https://doi.org/10.1016/j.msec.2020.111008.
[156] P. Sathish, et al., Tricomposite gelatin-carboxymethylcellulose-alginate bioink for direct and indirect 3D printing of human knee meniscal scaffold, Int. J. Biol. Macromol. 195 (2022) 179–189.
[157] F.H. Zulkifli, N.A.M. Rani, F. Shahitha, Carboxymethyl cellulose nanofibres impregnated with silver nanoparticles for tissue engineering applications, Mater. Today.: Proc. 16 (2019) 1715–1721, https://doi.org/10.1016/j.matpr.2019.06.041.
[158] P. Qi, et al., Fabrication of calcium phosphate-loaded carboxymethyl cellulose non-woven sheets for bone regeneration, Carbohydr. Polym. 189 (2018) 322–330, https://doi.org/10.1016/j.carbpol.2018.02.050.
[159] L. Tang, et al., Study on synergistic effects of carboxymethyl cellulose and LIPUS for bone tissue engineering, Carbohydr. Polym. 286 (2022), 119278.
[160] J. Namkaew, et al., Carboxymethyl cellulose entrapped in a poly (vinyl) alcohol network: plant-based scaffolds for cartilage tissue engineering, Molecules 26 (3) (2021) 578, https://doi.org/10.3390/molecules26030578.
[161] G. Sharmila, et al., Fabrication and characterization of Spinacia oleracea extract incorporated alginate/carboxymethyl cellulose microporous scaffold for bone tissue engineering, Int. J. Biol. Macromol. 156 (2020) 430–437, https://doi.org/10.1016/j.ijbiomac.2020.04.059.
[162] M. Abdollahi, et al., Carboxymethyl cellulose-agar biocomposite film activated with summer savory essential oil as an antimicrobial agent, Int. J. Biol. Macromol. 126 (2019) 561–568, https://doi.org/10.1016/j.ijbiomac.2018.12.115.
[163] M.H. Malik, et al., Thyroxine-loaded chitosan/carboxymethyl cellulose/hydroxyapatite hydrogels enhance angiogenesis in in-ovo experiments, Int. J.

Biol. Macromol. 145 (2020) 1162–1170, https://doi.org/10.1016/j.ijbiomac.2019.10.043.
[164] M. Bayindir Bilgic, et al., In vitro evaluation of alpha-tocopherol loaded carboxymethylcellulose chitosan copolymers as wound dressing materials, Mater. Technol. 34 (7) (2019) 386–393, https://doi.org/10.1080/10667857.2019.1573944.
[165] A. Joorabloo, et al., Fabrication of heparinized nano ZnO/poly (vinylalcohol)/carboxymethyl cellulose bionanocomposite hydrogels using artificial neural network for wound dressing application, J. Ind. Eng. Chem. 70 (2019) 253–263, https://doi.org/10.1016/j.jiec.2018.10.022.
[166] A. Koneru, K. Dharmalingam, R. Anandalakshmi, Cellulose based nanocomposite hydrogel films consisting of sodium carboxymethylcellulose–grapefruit seed extract nanoparticles for potential wound healing applications, Int. J. Biol. Macromol. 148 (2020) 833–842, https://doi.org/10.1016/j.ijbiomac.2020.01.018.
[167] E.-E. Tudoroiu, et al., An overview of cellulose derivatives-based dressings for wound-healing management, Pharmaceuticals 14 (12) (2021) 1215, https://doi.org/10.3390/ph14121215.
[168] S. Javanbakht, et al., Carboxymethyl cellulose/tetracycline@ UiO-66 nanocomposite hydrogel films as a potential antibacterial wound dressing, Int. J. Biol. Macromol. 188 (2021) 811–819, https://doi.org/10.1016/j.ijbiomac.2021.08.061.
[169] Y. Li, et al., A bi-layer PVA/CMC/PEG hydrogel with gradually changing pore sizes for wound dressing, Macromol. Biosci. 19 (5) (2019), 1800424, https://doi.org/10.1002/mabi.201800424.
[170] P. Jantrawut, et al., Fabrication and characterization of low methoxyl pectin/gelatin/carboxymethyl cellulose absorbent hydrogel film for wound dressing applications, Materials 12 (10) (2019) 1628, https://doi.org/10.3390/ma12101628.
[171] M. Sharma, A. Dube, S.K. Majumder, Antibacterial photodynamic activity of photosensitizer-embedded alginate-pectin-carboxymethyl cellulose composite biopolymer films, Lasers Med. Sci. 36 (4) (2021) 763–772, https://doi.org/10.1007/s10103-020-03083-2.
[172] P. Farshi, et al., Design, preparation, and characterization of silk fibroin/carboxymethyl cellulose wound dressing for skin tissue regeneration applications, Polym. Eng. Sci. 62 (9) (2022) 2741–2749.
[173] L. Diaz-Gomez, et al., 3D printed carboxymethyl cellulose scaffolds for autologous growth factors delivery in wound healing, Carbohydr. Polym. 278 (2022), 118924.
[174] G. Chang, et al., Carboxymethyl chitosan and carboxymethyl cellulose based self-healing hydrogel for accelerating diabetic wound healing, Carbohydr. Polym. 292 (2022), 119687.
[175] S. Du, et al., Covalent chitosan-cellulose hydrogels via schiff-base reaction containing macromolecular microgels for pH-sensitive drug delivery and wound dressing, Macromol. Chem. Phys. 220 (23) (2019), 1900399, https://doi.org/10.1002/macp.201900399.
[176] R.R. Kalmer, et al., Fabrication and evaluation of carboxymethylated diethylaminoethyl cellulose microcarriers as support for cellular applications, Carbohydr. Polym. 226 (2019), 115284, https://doi.org/10.1016/j.carbpol.2019.115284.
[177] Y. Cheng, et al., Centrifugal microfluidics for ultra-rapid fabrication of versatile hydrogel microcarriers, Appl. Mater. Today 13 (2018) 116–125, https://doi.org/10.1016/j.apmt.2018.08.012.
[178] S. Kandalam, et al., Human dental stem cells of the apical papilla associated to BDNF-loaded pharmacologically active microcarriers (PAMs) enhance locomotor function after spinal cord injury, Int. J. Pharm. 587 (2020), 119685, https://doi.org/10.1016/j.ijpharm.2020.119685.
[179] M.A. Hamdan, et al., Characterization and property investigation of microcrystalline cellulose (MCC) and carboxymethyl cellulose (CMC) filler on the carrageenan-based biocomposite film, Mater. Today.: Proc. 42 (2021) 56–62, https://doi.org/10.1016/j.matpr.2020.09.304.
[180] Z. Rao, et al., Carboxymethyl cellulose modified graphene oxide as pH-sensitive drug delivery system, Int. J. Biol. Macromol. 107 (2018) 1184–1192.
[181] R. Rakhshaei, et al., Graphene quantum dot cross-linked carboxymethyl cellulose nanocomposite hydrogel for pH-sensitive oral anticancer drug delivery with potential bioimaging properties, Int. J. Biol. Macromol. 150 (2020) 1121–1129, https://doi.org/10.1016/j.ijbiomac.2019.10.118.
[182] Y. Hu, et al., A double-layer hydrogel based on alginate-carboxymethyl cellulose and synthetic polymer as sustained drug delivery system, Sci. Rep. 11 (1) (2021) 1–14, https://doi.org/10.1038/s41598-021-88503-1.
[183] M.G. Gorab, et al., Decoration of graphene oxide nanosheets with carboxymethylcellulose hydrogel, silk fibroin and magnetic nanoparticles for biomedical and hyperthermia applications, Nanoscale Adv. 5 (1) (2023) 153–159.
[184] A.C. Silva, et al., Dissolvable carboxymethylcellulose microneedles for noninvasive and rapid administration of diclofenac sodium, Macromol. Biosci. 23 (1) (2023), 2200323.
[185] N. Batool, et al., Development and evaluation of cellulose derivative and pectin based swellable ph responsive hydrogel network for controlled delivery of cytarabine, Gels 9 (1) (2023) 60.
[186] Z. Yang, et al., Fabrication of zein–carboxymethyl cellulose nanoparticles for co-delivery of quercetin and resveratrol, J. Food Eng. 341 (2023), 111322.
[187] N. Mor, N. Raghav, Design and development of carboxymethylcellulose ester of curcumin as sustained release delivery system in liver, Int. J. Biol. Macromol. (2023), 123296.
[188] A. Verma, et al., Carboxymethyl cellulose based sustainable hydrogel for colon-specific delivery of gentamicin, Int. J. Biol. Macromol. 228 (2023) 773–782.
[189] B. Darbasizadeh, et al., Crosslinked-polyvinyl alcohol-carboxymethyl cellulose/ZnO nanocomposite fibrous mats containing erythromycin (PVA-CMC/ZnO-EM): fabrication, characterization and in-vitro release and anti-bacterial properties, Int. J. Biol. Macromol. 141 (2019) 1137–1146.
[190] S. Ahmad, et al., Chromium-resistant Staphylococcus aureus alleviates chromium toxicity by developing synergistic relationships with zinc oxide nanoparticles in wheat, Ecotoxicol. Environ. Saf. 230 (2022), 113142.
[191] H. Moustafa, H.E. Nasr, A.M. Youssef, Development of antibacterial carboxymethyl cellulose/quaternized starch bionanocomposites based on cinnamon essential oil nanoemulsion for wound healing applications, Biomass Convers. Biorefinery (2022) 1–13.
[192] K. Zhang, et al., Cellulose based self-healing hydrogel through Boronic Ester connections for wound healing and antitumor applications, Int. J. Biol. Macromol. (2023), 123294.
[193] N. Stoyanova, et al., Antioxidant and antitumor activities of novel quercetin-loaded electrospun cellulose acetate/polyethylene glycol fibrous materials, Antioxidants 9 (3) (2020) 232.
[194] V. Kumar, J. Kang, R.J. Hohl, Improved dissolution and cytotoxicity of camptothecin incorporated into oxidized-cellulose microspheres prepared by spray drying, Pharm. Dev. Technol. 6 (3) (2001) 459–467.
[195] K. Sangsuriyonk, N. Paradee, A. Sirivat, Electrically controlled release of anticancer drug 5-fluorouracil from carboxymethyl cellulose hydrogels, Int. J. Biol. Macromol. 165 (2020) 865–873.