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Research Article

Recent Advancements in Biomedical Applications Of Carboxymethyl Cellulose

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ABSTRACT

Carboxymethyl Cellulose (CMC), a hydrophilic polymer derived from cellulose, has gained considerable attention in the biomedical sector due to its outstanding physicochemical properties and biocompatibility. Recent advancements have broadened its range of applications, particularly in wound care, drug delivery, and tissue engineering. In wound dressing, CMC's hydrogel-forming capability creates a moist healing environment, enhances exudate absorption, and improves antimicrobial effectiveness by incorporating nanoparticles. In drug delivery, CMC-based systems have shown potential for controlled release and targeted delivery of therapeutics, improving pharmacokinetics and patient adherence. Additionally, CMC's incorporation into 3D bioprinting has transformed tissue engineering by offering a versatile scaffold material that promotes cell growth and differentiation. This review explores the latest research and developments in CMC's biomedical applications, emphasizing its multifunctional role and its potential to revolutionize therapeutic strategies. The future outlook of CMC in biomedicine is discussed, with attention to its evolving applications and the challenges ahead in optimizing its clinical use.

Keywords: Carboxymethyl cellulose, wound dressing, drug delivery, bio-sensing, 3D bio-printing.

1. Introduction

Carboxymethyl cellulose (CMC) is a derivative of cellulose, the most abundant natural polymer on earth. It is synthesized through the carboxymethylation of cellulose, resulting in a water-soluble polysaccharide with a range of molecular weights and degrees of substitution [1]. These modifications endow CMC with unique physicochemical properties, such as high viscosity, excellent water retention, and film-forming abilities, which have made it a critical component in various industrial applications [2-4]. Over recent decades, CMC has gained significant attention in biomedical applications due to its remarkable physicochemical properties, such as high water solubility, biocompatibility and non-toxicity. These attributes have facilitated its integration into a wide range of medical and pharmaceutical products, positioning CMC as a critical component in the advancement of modern healthcare solutions [5-7]. **Figure 1.** Shows various biomedical applications of cmc. One of the most notable applications of CMC in the biomedical field is in wound dressing. The polymer's ability to form hydrogels allows it to maintain a moist environment conducive to healing, promote cellular migration, and absorb exudates effectively. These properties not only enhance the wound healing process but also reduce the risk of infection and improve patient comfort. Generally, wound healing process consists of four phases: Hemostasis, Inflammation, Proliferation, and Maturation. Hemostasis aims to stop bleeding immediately after injury. Inflammation focuses on destroying bacteria and preparing the wound bed. Proliferation involves filling and covering the wound with new tissue. Maturation entails the gradual regeneration of collagen fibers and strengthening of the tissue. Several factors influence wound healing, including moisture, infection, age, and body type. Kim *et al.* [8] developed a nonwoven calcium carboxymethyl cellulose/chitosan blend as a hemostatic agent. Similarly, Basu *et al.* [9] created carboxymethyl cellulose-based films for both normal and chronic wound healing. These films showed excellent hemolytic and cytocompatibility with fibroblast cells,

enhancing wound healing in both normal and diabetic rats by promoting wound closure and tissue regeneration. Wound dressing materials are essential for protecting wounds and accelerating healing.

In pharmaceutical formulations, CMC serves as an essential excipient. Its role as a thickener, binder, and stabilizer in drug formulations ensures the consistent delivery and efficacy of active pharmaceutical ingredients. Moreover, CMC is utilized in controlled-release drug delivery systems, where its gel-forming capability is exploited to modulate the release rate of drugs, thereby improving therapeutic outcomes. Recent advancements in drug delivery systems aim to provide effective medication concentrations to target areas, enhancing treatment outcomes. Key challenges include identifying efficient carriers such as polymeric particles, nanomaterials, microspheres, dendrimers, and liposomes [10, 11].

These carriers improve drug delivery, energy applications and water treatment. Notably, nanocarriers enhance the efficacy and distribution of poorly water-soluble medications, addressing many conventional drug therapy issues [12, 13]. Nanoparticle drug conjugates have shown clinical effectiveness. Recent studies highlight the synthesis of metal–organic framework (MOF) and carboxymethyl cellulose (CMC) nanocomposites [14,15]. MOFs, made of organic linkers and metal ions, can form composites with CMC due to its carboxylic and hydroxyl groups.

Beyond wound care and drug delivery, CMC is being explored in the emerging field of 3D bio-printing. Here, its biocompatibility and viscosity are leveraged to create scaffolds that support cell growth and tissue regeneration. This innovative use of CMC is paving the way for the development of custom-made implants and the potential for tissue engineering breakthroughs [16].

Tissue engineering, a branch of biomedical engineering, focuses on developing biomaterial scaffolds, integrating cells or stem cells, and utilizing biochemical signalling molecules for tissue regeneration, organoid culture, and therapeutic applications. Successful tissue engineering relies on seamlessly integrating components.

3D scaffolds, made from biocompatible, biodegradable polymers, mimic the ECM with matching mechanical strength. They must degrade safely in vitro or in vivo, supporting regeneration without toxic byproducts. Carboxymethyl cellulose (CMC) stands out for its ease of modification, flexibility, stability, and pH sensitivity, making it ideal for diverse applications like tissue engineering, 3D bioprinting, drug delivery, cosmetics, and cancer therapy. Conventional tissue engineering combines cells, scaffolds, and growth factors to promote tissue regeneration.

These approaches have successfully developed effective scaffolds for bone, skin, trachea, myocardium, liver, and esophagus [17, 18]. However, many current scaffolds inadequately replicate the intricate structures of native tissues [19].

Additionally, Cellulose is investigated as a smart material capable of actuation when exposed to electric voltage, initially reported by Kim *et al.* [20]. Coating cellulose with conductive polymers enhances its actuator performance [21],

while hybridizing it with carbon nanotubes improves force and actuation frequency [22]. Cellulose-based nanocomposites are explored for disposable sensors, biosensors, and energy devices [23], with metal oxide immobilization enhancing mechanical properties, chemical stability, photosensitivity and conductivity for bioelectronics [24]. Because of their porous nature and large surface area, cellulose and its derivatives allow analytes to be adsorbed and diffused quickly in biosensors [25].

Cellulose strips in paper-based biosensors offer cost-effective, portable detection platforms for biomarkers like α-amylase and various analytes such as hydrogen sulfate and DNA [26, 27]. They feature stimuli-responsive materials like dopamine for equipment-free, visual detection, and can be enhanced with nanomaterials such as gold or silver nanoparticles for ultra-sensitive detection [28]. These advancements are crucial for the early detection of diseases and for monitoring various biomarkers in clinical diagnostics.

Overall, the ongoing research and development in the biomedical applications of carboxymethyl cellulose highlight its significant impact on enhancing medical treatments and patient care. The multifaceted utility of CMC underscores its potential to drive further innovations in healthcare, making it an indispensable material in the pursuit of advanced medical technologies.

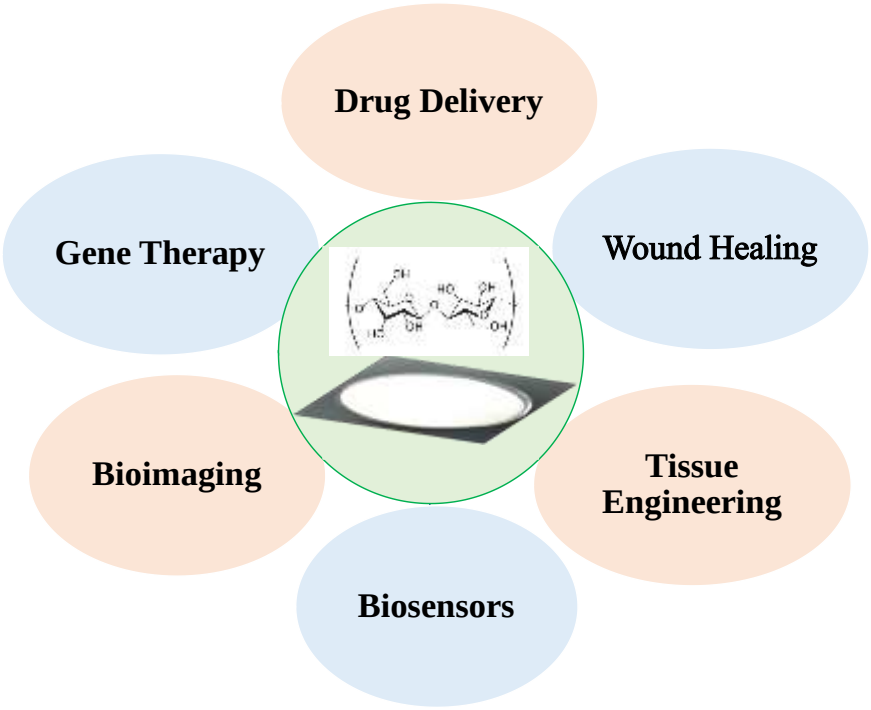

Figure 1. Various biomedical applications of cmc.

2. Applications Carboxymethyl cellulose (CMC)

2.1. Wound Dressing:

Carboxymethyl cellulose (CMC) is a versatile biomaterial widely employed in pharmaceuticals and biomedical fields. Its applications extend beyond wound dressing and drug delivery to include diverse uses in tissue engineering. Capanema *et al.* conducted a study on the synthesis and characterization of hydrogel membranes made from carboxymethyl cellulose (CMC) for wound dressing and skin repair. They created new CMC hydrogels with varying degrees of functionalization and crosslinked them with citric acid to adjust their properties. Additionally, they blended the CMC hydrogels with polyethylene glycol (PEG) to form CMC-based hybrids. The results showed that the hydrogels had high swelling capacities, influenced by the crosslinker concentration and PEG addition. Spectroscopic analyses revealed that the crosslinking mechanism involved a chemical reaction with CMC hydroxyl groups, and PEG contributed to the formation of a hybrid polymeric network. The hydrogels had different morphological features and surface nanomechanical properties depending on the degree of crosslinking. They also demonstrated cytocompatibility with human embryonic kidney cells [29]. The biocompatibility, ease of modification and sustainability of CMC make it an attractive choice for developing advanced biomedical materials that cater to both chronic and acute wound healing needs, ranging from diabetic ulcers to abrasions and burns. CMC (carboxymethyl cellulose) is the base for the extremely absorbent wound dressings Aqua Rite and Extra CMC. Because it is non-toxic and works with a variety of tissues, Pristine CMC promotes skin regeneration and wound healing [30]. Its application to chronic wounds such as diabetic foot ulcers is, however, not well supported by research. In order to minimize bacterial wound infections, Wong *et al.* created non-crosslinked CMC films [31]. However, these quickly deteriorate and need to be replaced on a regular basis. Through efficient distribution of growth factors and antibiotics, overall developments in CMC-based wound dressings aim to maximize healing. In the literature, various reports discuss antibacterial agents, including both organic and inorganic materials, for wound dressing applications [32]. Among these, metal nanoparticles have been extensively studied due to their beneficial physicochemical properties [33], demonstrating excellent antibacterial activity against human pathogens [34]. Combining metal nanoparticles with biopolymers can enhance the chemical and medicinal properties of the materials, improving their suitability for clinical applications.

In addition to blending well with water-soluble polymers like poly(ethylene glycol) and poly(vinyl alcohol), CMC binds well to ocular cells and is safe for use on mucous membranes, bones and skin. It is perfect for clinical applications because of its hydrophilicity and stable structure, particularly in wound dressings [35]. CMC/MCM-41 nanocomposite hydrogel films coated with antibiotics were created by Namazi *et al.* [30] as possible wound dressings. Similar to this, antibacterial cotton gauzes were created by Paladini *et al.* to stop wound infections [36]. For the purpose of delivering Propolis medication, Oliveira *et al.* developed PVA-NaCMC hydrogels, which demonstrated the antibacterial capabilities of Propolis as well as strong mechanical strength, high water absorption and flexibility [37]. The developed hydrogels exhibited favorable mechanical strength, significant water absorption capacity, flexibility, and remarkable antimicrobial properties derived

from Propolis. **Figure 2** illustrates the different types of wound dressing materials derived from CMC. Li and his coworkers used a straightforward, non-toxic phase separation/one-step thawing-freezing process to create porous, pH-sensitive PVA-CMC-PEG hydrogels [29]. By changing the PVA concentration, the pore size may be regulated. According to tests, the hydrogel encouraged wound healing and was non-toxic. The bi-layer hydrogel was excellent for clinical usage because to its good mechanical properties, low adhesion, bacterial resistance, and water vapor permeability. The fabrication of porous hybrid hydrogels was carried out by Arezou *et al.* by utilizing decellularized human placenta (dHplacenta) and silk fibroin. These hydrogels exhibited a consistent 3-D microstructure that featured an interconnected porous network. Notably, the hydrogels with a 30/70 dHplacenta/silk fibroin ratio displayed enhanced mechanical properties. Following the acquisition of adipose tissue through liposuction, adipose-derived stem cells (ADSCs) were successfully cultured on these hydrogels [38]. CMC-based films have gel-like qualities, dissolve easily in water, and are helpful for food packaging, wound treatment, and antibacterial applications. The process of making them involves dissolving polymers in water, mixing in additional components such as plasticizers, cross-linkers, and polymers and then drying the mixture on a dish at a particular temperature. Strong gas and lipid barrier qualities as well as exceptional mechanical strength were demonstrated by Tufan *et al.*'s synthesis and characterization of CMC films made from sunflower stalks [39]. The mechanical, barrier, and thermal characteristics of polymer matrix composites are also improved by the introduction of cellulose derivatives.

Various dressings are needed for wound healing depending on the kind and stage of the wound. For wounds that are heavily fluid-laden, high-absorptive dressings are excellent. Because of their flexibility, non-adherence, and absorbency, fibers, gauzes, and non-woven fabrics are recommended [40]. CMC hydrogel fibers with superior moisture absorption and CMC viscose non-woven fibers with good absorbency and vapor permeability were created by Liu *et al.* and are both perfect for low-cost wound dressings [41]. In order to create carboxymethyl cotton knitted fabrics for use as wound dressings, Zhao *et al.* used a variety of solvents, such as water, ethanol-water and isopropanol-water [42]. Platelet-rich plasma is now being used more frequently in wound healing because of its high platelet concentration, which speeds up tissue regeneration. To overcome the limited effectiveness of platelet-rich plasma due to its short biological activity, Yassin *et al.* developed lyophilization-based CMC platelet-rich plasma wafers.

Figure 2. Various types of cmc based wound dressing material.

These wafers improve the longevity of platelet-rich plasma and enhance its wound healing capabilities [43]. Chen and his coworkers have devised a technique for producing a long-lasting hemostatic sponge by utilizing hydrogen bond reinforcement and bubble expansion during the polymerization process. By combining carboxymethyl cellulose (CMC) with a hydrogen bonding N-acryloyl-2-glycine (ACG) monomer and an initiator, air bubbles are generated within the liquid mixture. Upon heating, rapid polymerization occurs, causing the bubbles to expand and become fixed within the structure, resulting in porous hydrogels. Through lyophilization, PACG/CMC sponges with high compressive strengths are created due to the hydrogen bonding interactions. These sponges possess adjustable liquid absorption capacities, as well as in vitro hemostatic properties, enhanced hemocompatibility, and cytocompatibility. In experiments with rat injury models, the PACG/CMC sponge demonstrates a significant reduction in bleeding time and blood loss compared to traditional gauze and gelatin sponges, indicating its potential as an effective hemostatic agent for emergency situations [44] In the last ten years, CMC has been utilized to modify nanoparticles, particularly in biomedical

uses. The carboxylate ions in CMC help nanoparticles stick to surfaces, creating targeted nanoparticles that are more efficient, long-lasting, and water-soluble [45].

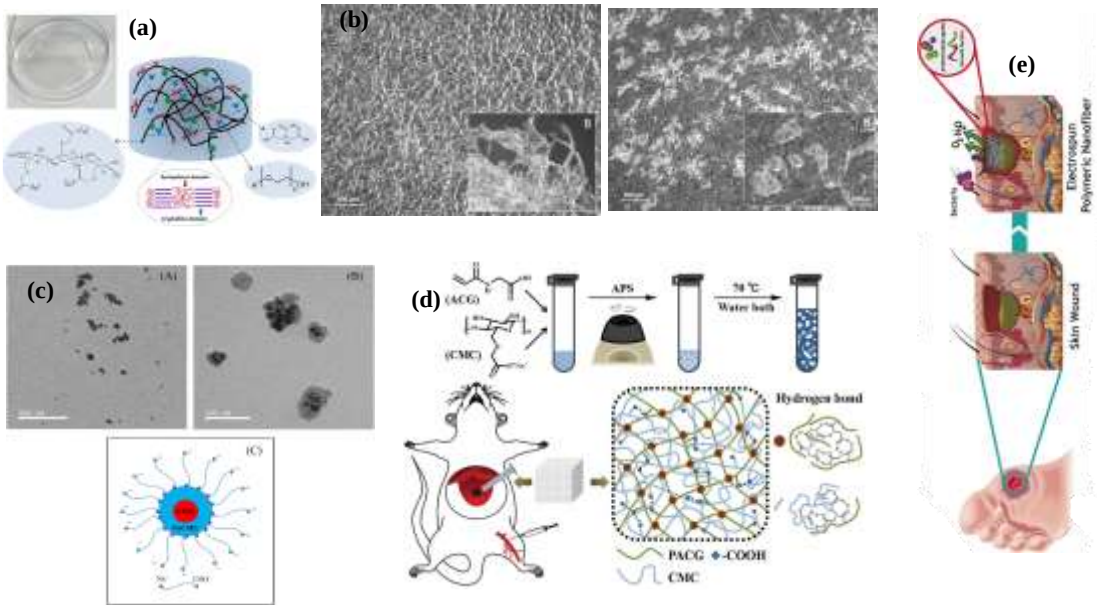

Figure 3. 1. Materials for wound dressings based on CMC (a) Hydrogels [29], (b) Film [32], (c) Nanoparticles [45], (d) Wafers [44] and (e) Fiber [40].

2.2. Pharmaceutical Industry:

CMC is crucial in the pharmaceutical industry, serving as a binder, disintegrant, viscosity modifier, and stabilizer. It regulates drug release, enhances tablet coating, and improves drug delivery in nasal sprays and inhalers. Its significance is evident in its essential role across multiple pharmaceutical applications. Sathasivam *et al.* showed that CMC beads made from sago biomass can control the release of red palm oil and its nutrients in intestinal fluid [46]. CMC also aids in managing gastric ulcers by protecting the stomach lining and assisting in the delivery of medicinal substances. Drug carriers securely bind medications for safe and efficient delivery to specific areas, commonly using CMC. CMC is especially beneficial for anti-cancer drugs like docetaxel (DTX). However, DTX formulations often contain Tween 80 to enhance solubility, which can raise the risk of severe allergic reactions and peripheral neuropathy symptoms like injuries, infections, and burning pain. Jiang *et al.* successfully resolved the challenges associated with utilizing Tween 80 alongside docetaxel (DTX) through the creation of a nanoparticle copolymer composed of Na-CMC-graft-histidine and D-α-Tocopheryl polyethylene glycol 1000 succinate [47]. This innovative nanocomposite efficiently tackles DTX's multidrug resistance by encapsulating the drug. CMC conjugates play a crucial role in oral insulin delivery by acting as a mucoadhesive polymer. This offers a more comfortable alternative to subcutaneous injections for diabetes patients. However, challenges such as overcoming absorption barriers and enzyme degradation hinder the feasibility of oral insulin administration. Marschu *et al.* proposed a new method using CMC to create a protective carrier for oral insulin administration [48]. They developed polymer-protease inhibitor conjugates, specifically CMC-Bowman Birk inhibitor and CMC-Elastatinal conjugates, to ensure effective delivery. Hamdan *et al.* introduced a biocomposite-based hard capsule made of CMC, carrageenan, and microcrystalline cellulose as an alternative to gelatin-based capsules [49]. In recent years, carboxymethyl cellulose (CMC) has been used as a thick polymer in ophthalmic drug delivery systems. CMC acted as a biocompatible emulsifier, creating a thick medium that slowed drug absorption and improved delivery through sustained-release properties. The TDDS is often used for drug delivery, but it has drawbacks. One challenge is the hindrance caused by the skin. To address this, Park *et al.* developed a dissolvable microneedle with enhanced skin permeability [50].

This study highlights the various roles of CMC in pharmaceutical applications, including binding, emulsifying, film-forming, and acting as carriers with unique properties such as pH sensitivity, thermosensitivity and multidrug resistance in different drug delivery systems. Recently Sujie *et al.* have successfully demonstrated the feasibility of creating aerogels using CMC and supercritical CO_2 drying. The team's objective is to investigate the potential of these aerogels as drug carriers, which possess unique characteristics compared to traditional freeze-dried materials. As CMC aerogels are a new concept, the initial focus is on examining the effects of CMC properties (such as molecular weight and DS) and processing parameters (such as polymer concentration, non-solvent type, and presence of Ca^{2+} ions) on aerogel density, specific surface area, and morphology. Following this, L-ascorbic acid 2-phosphate (Asc-2P) is employed as a model drug for release studies from CMC aerogels [51].

2.3. CMC in 3D bioprinting:

Recent global demand for organ and tissue regeneration has been met with advancements in 3D bioprinting technology using bioink containing live cells and biomaterials. Cellulose and its derivatives are ideal materials for 3D bio-printing due to their biocompatibility and strength. Habib *et al.* successfully developed alginate-carboxymethyl cellulose 3D bioprinting hydrogel for large-scale tissue scaffold production, showcasing their potential for 3D applications [52]. 3D printed porous scaffolds were successfully prepared by extrusion printing using a storable, ready-to-use CMC ink by Luis et al. [53]. Dispersions prepared with 15%w/v CMC and citric acid (20% with respect to CMC) showed adequate rheological properties for 3D printing without the need of additional components. Aizada *et al.* studied 3-D scaffolds with CMC hydrogel and Centella asiatica extract [54]. Gopinathan and Noh reviewed bioinks for 3D printing [55], while Sultan *et al.* reviewed nanocellulosic inks for biomedical applications [56]. Markstedt *et al.* used nanocellulose and alginate bioink to 3D bioprint human chondrocytes for cartilage tissue engineering [57]. Kageyama *et al.* analyzed gelatin-CMC hydrogels for creating perfusable vasculatures [58]. Ávila *et al.* studied 3D bioprinting of chondrocyte-laden nanocellulose hydrogels for auricular cartilage regeneration. Maver *et al.* developed wound dressing materials for drug delivery using alginate and CMC biopolymers [59]. The cytotoxicity of these films on human skin cells was highlighted as crucial prior to their application in wound dressing. Diclofenac sodium and lidocaine were combined in a CMC/PEO material using electrospinning to create a pain relief dressing. The 3D printed layer improved drug release, providing extended pain relief for up to 2 days. Some biomaterials have been made using 3D bioprinting, but they are static and cannot adapt to changes in the body.

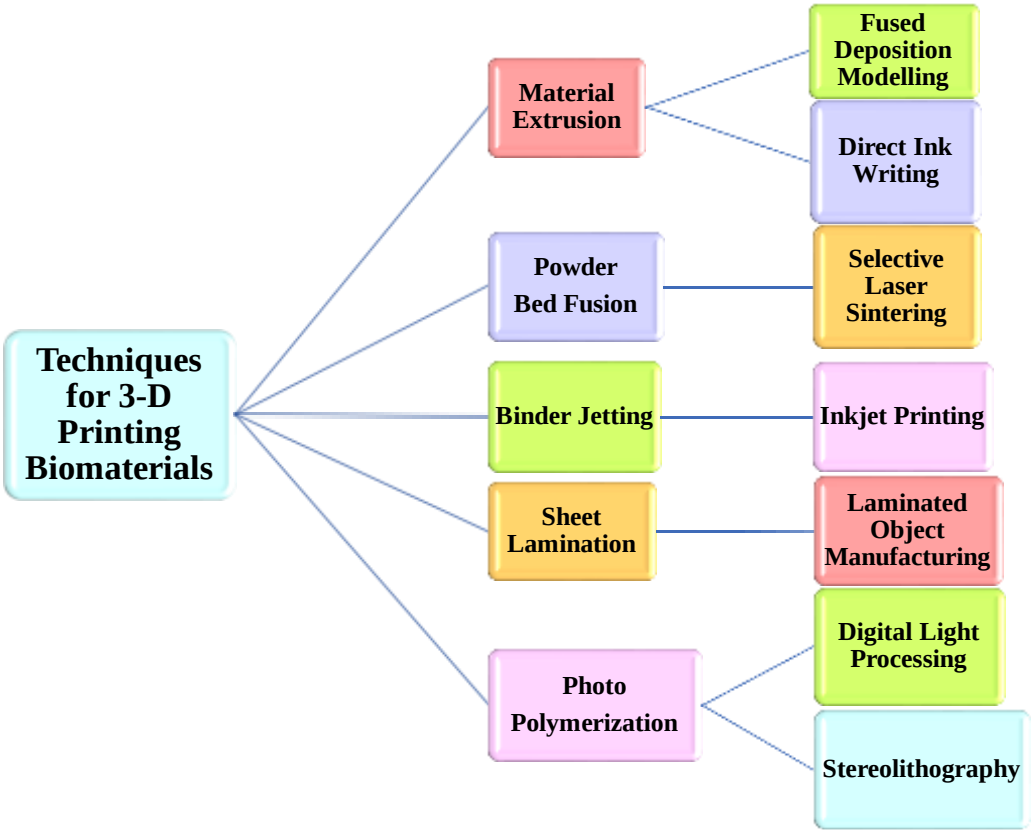

Figure 3. Different types of techniques 3-D printing biomaterials [60].

To solve this, 4D printing has been introduced for tissue regeneration. Oladapo and colleagues used CMC to create a nanostructured hydrogel composite using 4D printing. However, both 3D and 4D printing need to be user-friendly for wound dressing [60, 61]. Tissue-engineered scaffolds frequently fail to adequately support the biomimetic growth of cells in three dimensions due to the lack of natural architecture and vasculature [62]. In contrast, 3D bioprinting has emerged as a viable method for creating tissue constructs with precise micro/nano designs by combining scaffolds with cells and bioactive growth factors [63]. 3D bioprinting is a precise method of additive manufacturing that creates tissue scaffolds with human-scale cellular structure. Additive manufacturing, also known as 3D printing, is a computer-controlled process used to create 3D objects layer by layer. It has been used in industries like automotive, aerospace, fashion, and household goods for over three decades [60].

Advancements in 3D bioprinting have allowed for the creation of biomimetic microarchitecture using patient-specific tissues, solving problems with transplantation and donor-host compatibility. Electrically conductive bioink (ECB) is particularly effective in promoting cell growth by enhancing electrical coupling within 3D scaffolds. Sathish and his coworkers focused their efforts on creating an ECB that is immobilized with gold

nanospheres (GNS) within the carboxymethyl cellulose (CMC) polymer. The objective of this study is to address the challenges related to ECB preparation. Through the reduction of gold in situ, stable gold nanoparticles are generated within the CMC hydrogel polymer matrix. This method improves conductivity without compromising the favorable characteristics of the bioink used in 3D bioprinting technology [64]. Harshavardhan *et al.* developed a composite bioink by combining CMC and agarose in different ratios. The 5:5 ratio showed the best gel formation at 37 °C and was further analyzed. The cytocompatibility of this bioink was tested using skin fibroblast cells. Intricate 3D structures were successfully printed with this bioink, maintaining cell viability of over 80% for seven days. At room temperature, the gelation studies have verified the robust gel formation of 4% L-CMC and M-CMC with 2% agarose. Moreover, the analysis of mechanical strength revealed that the 5:5 ratio exhibited a notable enhancement in mechanical properties when compared to all other ratios [65].

3. Conclusion

Carboxymethyl Cellulose (CMC) has proven to be a versatile and vital material in the biomedical field, owing to its excellent physicochemical properties and biocompatibility. Recent developments have expanded its use, especially in wound management, drug delivery, and tissue engineering. In wound management, CMC's ability to form hydrogels promotes a moist healing environment, enhances the absorption of exudates, and boosts antimicrobial effectiveness. In the realm of drug delivery, CMC-based systems facilitate controlled and targeted therapeutic release, enhancing drug effectiveness and patient adherence. The incorporation of CMC into 3D bioprinting represents a major leap in tissue engineering, offering scaffolds that support cell growth and differentiation, aiding the creation of intricate tissue structures. Nevertheless, there are still hurdles to overcome in optimizing CMC for specific clinical applications and scaling up its commercial use. In summary, CMC is a pivotal element in contemporary healthcare, propelling innovations in wound management, drug delivery, and tissue engineering. With continued research and development, CMC is set to further advance medical treatments and improve patient outcomes.

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