



The fate of carboxymethyl cellulose as a polymer of pharmaceutical importance

Arghya Paria¹, Vineet Kumar Rai^{2*}

¹Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab 142001, India.

²School of Pharmaceutical Science, Siksha 'O' Anusandhan University, Bhubaneswar, Odisha, 751003, India.

ARTICLE HISTORY

Received: 07-04-2022
Revised: 21-05-2022
Accepted: 24-05-2022
Online: 14-06-2022

KEYWORDS

CMC
Pharmaceutical industry
Hydrophilicity
Mechanical strength
Muco-adhesiveness
Non-medical
Degree of Substitution
Bioadhesive

ABSTRACT

Carboxymethyl cellulose (CMC) is one of the most widely used cellulose derivatives. This polymer is commonly used in several sectors, such as food, paper mills, textile, and pharmaceutical industries. CMC also has versatile applications in biomedical engineering, treatment of wastewater, energy production units, and many more. The main reason for selecting this polymer is its characteristic surface properties, mechanical/tensile strength, hydrophilicity, viscous properties, and majorly abundance source of raw materials. CMC production is a low-cost process that can be carried out quickly on a lab scale. Several research publications have been published on CMC, depending on the origins and application domains. This review provides general information on this material's properties, which justifies its applications in several medical and non-medical sectors.

Introduction

Carboxymethyl cellulose (CMC) is a water-soluble anionic derivative of cellulose, an anhydrous-glucose linear polysaccharide, -1,4-glycosidic linkages connect the repeating units. The primary distinction between CMC and cellulose at the molecular level is that some anionic carboxymethyl groups (i.e., CH₂COOH) replace the hydrogen atoms of some hydroxyl groups present in the CMC structure in the pure cellulose architecture. CMC was created for the

first time in 1918. However, in Germany in the early 1920s, commercial manufacture of these vital polymer materials was first proven (1).


Since the original celluloses were majorly obtained from wood and other vegetable precursors, containing a high proportion of cellulose fibers, the production of CMC became dependent on such specific wood-based plants (2). However, after multiple surveys, many more cellulosic materials have been introduced to the literature daily by many researchers who act as adequate substitutes in this context. These included some vegetable precursors such as sago palm (3), corn cobs (4), corn husks (5), corn stalks, durian rind (6), banana pseudostems (7), corn stalks, cocoa pods, the pulp of Eucalyptus globulus (8), orange peel, pineapple peel, bagasse, Asparagus officinalis stalk end, as well as some waste materials Wastepaper, knitted rags, used textiles, gin waste and waste linters from the textile industry. Extraction of CMC from waste has inspired researchers to commence mass or commercial

*Address for correspondence

Dr. Vineet Kumar Rai, Project Scientist II, Department of Pharmaceutics, School of Pharmaceutical Science, Siksha 'O' Anusandhan University, Bhubaneswar, Odisha, 751003, India. Email: raivk.gkp@gmail.com.

DOI: <https://doi.org/10.55006/biolsciences.2022.2204>

Published by [IR Research Publication](https://irrespub.com); Copyright ©

2022 by Authors is licensed under [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/) 

production of CMC (9).

CMC and CMC-based materials have a wide range of applications in biomedicine, pharmaceuticals, textiles, construction, food, plastics, cosmetics, paper, and oil industries due to their simple and inexpensive synthesis process, adequate supply of raw materials, characteristic surface properties, mechanical strength, different formability, adjustable hydrophilicity, viscosity, rheological properties, and hundreds of other opposing aspects.

CMC and its composites are frequently used in tissue engineering (10), bone tissue engineering (11), wound dressings (12), absorbent nonwovens (13), production of 3D scaffolds for biocompatible implants (14), artificial organs or extracellular polymer matrix imitators, diagnosis of various diseases, and other biomedical fields for a variety of purposes (15). Construction, cosmetics, dentistry, liquid detergent, fertilizer, oil, and other industries have all used CMC. However, the performance of the resultant products, such as solubility, particle size, viscosity, and rheological properties, is strongly dependent on purity, degree of polymerization (DP), degree of substitution (DS), and uniformity, which define the efficacy of the producing products.

CMC products are typically classified into three classifications depending on purity and DS: food grade, pharmaceutical grade, and industrial grade CMC (16); due to their impure chemical compositions and qualities, industrial-grade CMCs cannot be employed for pharmaceutical or biomedical purposes like as in drug administration, tissue or organ implantation in vivo, wound dressing, and so on. In contrast, high-priced, pharmaceutical-grade pure CMC products are not required for construction, plastics, and oil applications in favor of the less expensive alternatives (i.e., industrial-grade products). Furthermore, mechanical strength, viscosity, and rheological qualities severely limit the applications of synthetic CMC compounds. Characterizing a CMC product is thus an essential step in deciding its future applications and marketing in various fields. Herein, this review highlights the general information about the properties of CMC, which justifies its applications in different medical and non-medical sectors.

Properties of CMC

Hydrophilicity

CMC and other cellulose derivatives differ primarily in two ways. Firstly, the presence of hydrophilic groups (CH₂COO) impacts water intake and

hydrogen bonding; second is the homogenous substitution of the CH₂COO groups both in the substituted position and, in the degree, increases the complexity of hydrogen bonds. Thermogravimetric tests reveal that CMC retained water molecules even after drying for 24 hours at 50 °C in a vacuum oven, indicating that CMC has high hydrophilicity (17). Hydrogen bonds are formed between water molecules and other polymer chains when water is present (hydrophilic OH and COO groups) (18).

Bioadhesive

Based on bioadhesive property, the Food and Drug Administration (FDA) allows up to 10.95 mg CMC for making buccal formulations, up to 0.5 percent for visual solutions, and up to 242 mg for solid oral dosage (OSD) formulations (19). CMC is a type of polyanionic polymer discovered to have bioadhesive characteristics. Compared to most non-ionic cellulose derivatives, CMC more strongly adheres to some biological surfaces. CMC has this feature, making it a perfect excipient for formulating transdermal and transmucosal dosage forms. CMC tablets were created to administer sotalol HCl, a water-soluble medication. Pills with a 14-hour in-vitro drug release examination showed good bioadhesive ex vivo adhesion to rabbit stomachs or small intestine tissue (20). The CMC coating of polymers and acetylsalicylic acid improved the mucosal surface adhesion capability in an adhesion test. In low pH gastrointestinal tract circumstances, bioadhesive CMC matrixes were used to investigate the stability of ciprofloxacin as a water-soluble medication (21). CMC tablets have been developed for the oral mucosal distribution of poorly water-soluble drugs such as pindolol (22) and glipizide (23), as well as water-soluble pharmaceuticals, including miconazole nitrate (24) and lignocaine HCl (25), and triamcinolone acetonide (26). Losartan potassium, ketorolac tromethamine, and diltiazem hydrochloride have been developed as buccal mucoadhesive CMC films for oral mucosal delivery. Mucoadhesive buccal patches of atenolol were also developed for local administration of the medicament to the oral cavity (27).

Nontoxicity

Various salts of CMC are interesting medication delivery possibilities since they have a lot of potential to be used as structural building blocks for living cell polysaccharides. Biopolymer carriers have several appealing characteristics that could lead to the creation of potential transportation systems. As multifunctional active ingredient carriers, these carriers reduce the toxicity of the therapeutic agent, and the pharmacokinetic profile of the active ingredient should improve with the stabilization of

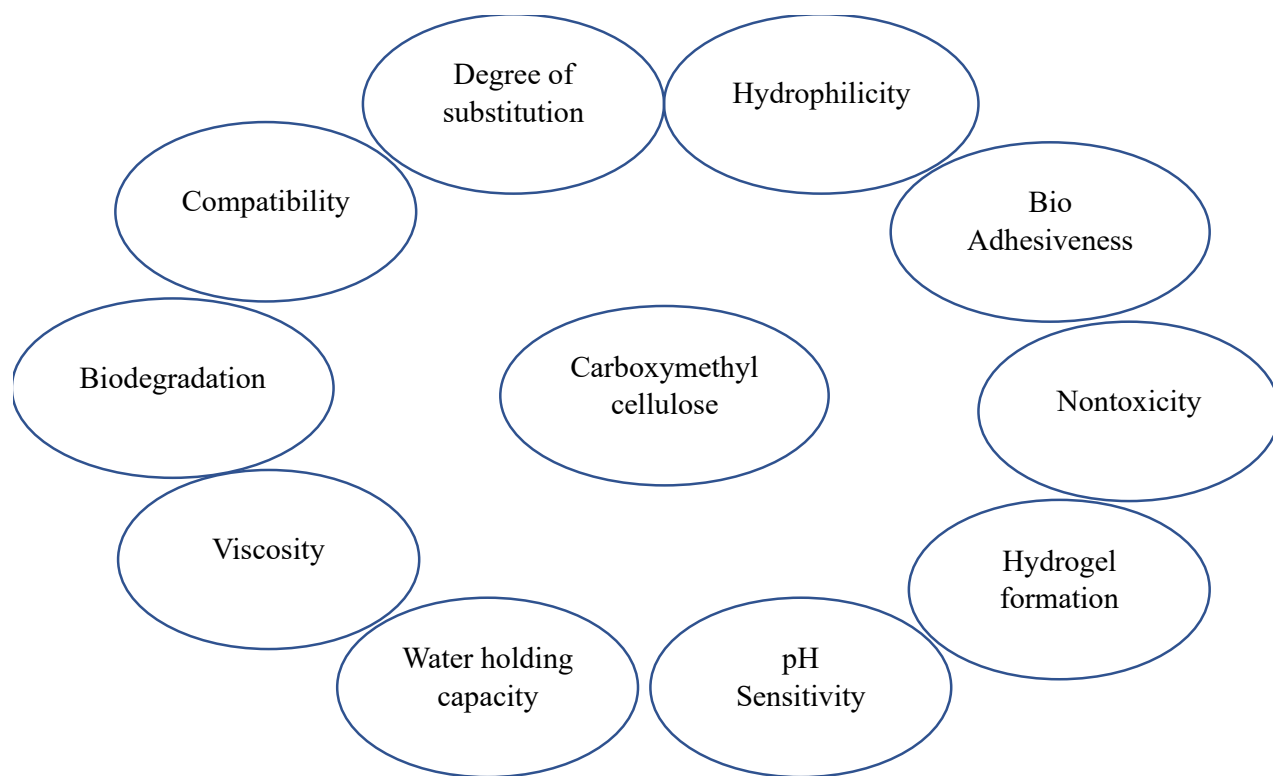


Figure 1. Ideal properties of carboxymethyl cellulose

the active ingredient carrier. Although nanoscale delivery systems such as nanoparticles and dendrimers have made significant progress in drug delivery, their specific and compelling interactions with vital cellular components such as mitochondria, plasma membrane, endosome, enzymes, and nucleus have made significant progress resulting in toxicity (28). One strategy for controlling these toxicities is to modify these carriers with various non-toxic, biodegradable, and biocompatible substances. CMC biopolymers have been coupled to multiple drug delivery methods and have significantly lower toxicity (29).

Hydrogel formation

CMC is the most critical cellulose-derived component utilized in superabsorbent polymers (30). Three-dimensional hydrophilic CMC networks can be constructed as polymer hydrogels capable of absorbing enormous volumes of biological fluids or water and releasing medications at a precise dosage. Crosslinking of polymers can be accomplished using polyvalent carboxylic acids like citric acid (31), gamma irradiation (32), or chloromethylene iodide (33). Due to physical or chemical cross-linking, homopolymer or copolymer networks can be formed that are insoluble in water. Superabsorbent polymers have been created by combining CMC with several synthetic and natural

polymers (polyvinyl alcohol, chitosan (CS), alginate, starch, and polyvinylpyrrolidone, for example) (34). On the other hand, increased CMC concentration improves diffusion constants and solvent front rates due to CMC's hydrophilic nature. The ability of hydrogels to swell is determined by the hydrophilic functional groups that allow water to form hydrogen bonds and the size of the hydrodynamic free volume. As a result of CMC's very hydrophilic nature, the swelling rate increases as the CMC content in the polymer matrix increases (35). Alternatively, with various nanoparticles, CMC-based nanocomposite hydrogels have been prepared to achieve the desired feature.

pH sensitivity

In the hydrogel form, CMC exhibits pH-sensitive characteristics. The CMC hydrogel is an anionic polyelectrolyte with carboxyl groups that is pH sensitive. CMC-based hydrogel carriers have attracted increased interest in biological applications due to this characteristic. Swelling behaviors were one of the critical challenges that hampered the application of the hydrogels. The achieved swelling rate is influenced by various parameters such as pH, composition, temperature, ionic strength, and the level of crosslinking in the polymeric network. CMC hydrogels have negatively charged moieties with carboxylic pendant groups

(36). In anionic hydrogels, the ionized structure leads to increased electrostatic repulsion between chains and, as a result, increases the size of the network at pH values higher than its pKa. Hydrogels that can absorb significant volumes of water and form a highly loose structure are ideal in these situations (37). The ionization of CMC pendant groups (COO) and the creation of significant osmotic phenomena at pH above the polymeric pKa cause an increase in the swelling rate of hydrogels (38). The deionization of carboxylate groups in CMC hydrogel causes shrinkage in the polymeric network at pH below the polymeric pKa of different nanoparticles, such as copper complexes, silver nanoparticles, Fe₃O₄, calcium carbonate, ZnS, and cellulose nanocrystal, graphene quantum dot, and metal-organic framework. This property has been used to improve the pH-sensitivity features of CMC (39).

Water holding capacity

CMC has a water holding capacity of 5.11 g/g and an oil carrying capacity of 1.59 g/g, making it ideal for pharmaceutical and food additive applications. Low viscosity CMC is utilized as a moisture binder in the food business, whereas high viscosity CMC is employed as a gelation agent (40). The reduced viscosity-based CMC is used with sodium bentonite as a viscosity modifier or dispersion media in a drilling mud system. CMC's water-holding capability improves bentonite dispersion viscosity and lowers fluid losses in drilling systems. CMC's water holding capacity provides the needed rheological qualities in biomedical, tissue engineering, pharmaceutical, textile dye processing, meals, and cosmetic applications. CMC hydrogels offer a softer feel in soft tissue filler engineering due to their great spreading accessibility. CMC/MCC (microcrystalline cellulose) is a bio-composite film-forming substance utilized in drug delivery vehicles for medication delivery (such as hard capsules). CMC is a filler that improves the film's strength and stability by acting as a filler (41).

Viscosity

The internal friction of a moving fluid is defined by viscosity, which measures a fluid's resistance to movement. Because of its excellent solubility in water, CMC is a polymeric substance that provides a viscous solution in an aqueous media. As a result, the viscosity parameter is critical in characterizing aqueous Na-CMC (or H-CMC) fluid behavior, characteristics (thickening, emulsifying, etc.), and property-based applications.

The viscosity of any formulation where CMC is applied is maintained with increasing or decreasing

CMC concentration. Even the viscosity of CMC depends on its sources and synthesis conditions, such as NaOH concentration, the temperature throughout the experiment, and the pH of the solution. CMC extracted from plant-based cellulose is mainly high viscosity grade and is used in supplementary materials. Viscosity is the essential property of this polymer for various applications. For example, high viscous CMC is employed in the food industries as gelation agents, whereas the low viscous CMC functions as a moisture binder (42).

The low viscous CMC uses sodium bentonite to act as a viscosity modifier or dispersion media in a drilling mud system. CMC improves bentonite dispersion viscosity and lowers fluid losses in drilling systems (43). The thickness of CMC gives the recommended rheological qualities in biomedical sectors, tissue engineering, pharmaceutical industries, textile dye processing units, meals, and cosmetic applications. The lower-viscosity CMC hydrogels provide a softer feel in soft tissue filler engineering due to their increased spreading accessibility. CMC hydrogels with a higher viscosity give a firmer feel due to reduced spreading accessibility (44).

CMC/MCC (microcrystalline cellulose) is a bio-composite film-forming substance utilized in drug delivery vehicles for medication delivery (such as hard capsules). CMC works as a filler and adds strength to the film by increasing viscosity (45). CMC has also been employed to maintain the intrinsic viscosity of CMC/rosin/PEG (polyethylene glycol) medicinal nano-carriers lately (46). CMCs are commonly utilized in meals because of their viscosity properties, which provide the desired rheological properties, texture, and mouthfeel. CMC is used as a highly viscous material in emulsified food or thickening juice (47). Furthermore, it is utilized to adjust the viscoelastic qualities of semisolid dairy products based on their viscosity (low or high). CMC has been combined with hyaluronic acid to form a gel for use in cosmetics due to its ability to manage thixotropy and pseudoplastic behavior. CMC gives the gel a superior viscosity and textural profile (48).

Biodegradation

CMC is widely used in the formulation of pharmaceutical products because of its nontoxic behavior in the body. CMC is a complex carbohydrate broken down by the glucosidase enzyme in the body. -Glucosidase attacks the 1,4-bond and breaks it down into simple sugar, which helps in the digestion of dietary carbohydrates and produces glucose which is further broken in the intestinal tract via absorption to raise blood glucose levels in the body. In carboxymethyl cellulose, the

CH₂COOH- group in macromolecules is linked by a -1,4 bond (49).

Energy is released in the body when complex CMC is broken down into simple glucose. The unhydrolyzed portion is broken down by a trace amount of cellulase in mitochondria's endoplasmic reticulum and excreted in the feces. CMC, which is insoluble in stomach acid but soluble in alkaline intestinal fluids, is a functional enteric coating for powders and tablets because of its consistent quality. It's a gentle but powerful bulk laxative. It's often utilized in geriatric and weight-loss formulations due to its capacity to retain water without causing digestion or intestinal irritation. Its ability to suspend calamine, antibiotics, and barium salts in aqueous environments is valid (for x-ray contrast media).

It is frequently used as a binder in cosmetic products and a stabilizer for hand lotions and vitamin-oil emulsions. It has been discovered to have the demulcent characteristics required for cough syrups. It can be used to make a dental impression material when combined with gelling agents and fillers. Its grease resistance is used in the creation of anti-aging hand lotions. CMC may be quickly tableted due to its adhesive properties. It's used as a thickening and suspending agent for mild abrasives in toothpaste. It has been utilized in denture adhesives because of its ability to form wet tack quickly and dissolve slowly when in a gel condition (50).

Compatibility

Most water-soluble non-ionic/ anionic polymers, gums, proteins, carbohydrates, salts, and solvents are compatible with CMC in solution. The ability of the additional cation to generate a soluble carboxymethylcellulose salt determines CMC compatibility in salt solutions. Monovalent cations that produce soluble salts of carboxymethylcellulose do not affect the solution's viscosity, transparency, or other qualities. Divalent cations are on the edge of having a viscosity-reduced solution.

Trivalent cations form insoluble salts. The effect of salt is dependent on the type of salt, its concentration, the pH of the solution, the DS of the CMC, and how the salt and CMC come into contact. CMCs that have been heavily and consistently replaced have a higher salt tolerance. By dissolving the CMC before adding the salt, you can increase your salt tolerance. Compatibility is reduced when dry CMC is added to a salt solution or when the salt and gum are dissolved simultaneously. Monovalent cations usually form soluble salts. The order in which

the gum and salt are added determines the viscosity (51).

There is little influence on viscosity if CMC is well dissolved in water before adding salt. However, when the gum is introduced to a salt solution, the thickness is substantially reduced. Salts of monovalent cations do not affect the viscosity created by a highly and uniformly substituted kind of CMC, independent of the addition sequence. High shear improves viscosity growth in all circumstances. Divalent cations, in general, do not form crosslinked gels with CMC. However, when divalent cations are added to the cellulose gum solution, viscosity is reduced, and haze may form. Cations such as calcium, barium, cobalt, magnesium, iron, and manganese work in this way. When moderate divalent cations are added to the CMC solution, highly and evenly substituted forms of CMC are only marginally affected (52).

Degree of Substitution

Their substituted reactive groups determine the chemical activity of cellulose derivatives. Anhydro-glucose unit of cellulose has three hydroxyls, reactive groups, with the property of degree of substitution (DS). The degree of substitution is defined as the number of reactive groups which have the potential to be substituted by other active molecules. During CMC synthesis, the value of DS is calculated by identifying the number of carboxymethyl groups attached to the anhydrous glucose unit. It affects CMC's properties like solubility, emulsibility, viscosity, stability, and salt tolerance (53). The properties of CMC determined by its DS value are given in table 1. Recent findings have shown that the source from which CMC is produced and its synthesis techniques have an effect on determining the DS value. Variances of DS of CMC due to extraction from the different sources are given in table 2. This wide range of DS makes CMC widely applicable in various sectors, such as the food and pharmaceutical industries. The well-suited application of CMC in multiple sectors is given in table 3.

Application of CMC

Application of CMC in Pharmaceutical Industries

CMC and its derivatives have been widely used in pharma industries due to their biocompatibility, nontoxicity, stability, and drug binding ability (63). It is used as a binder, stabilizer, and emulsifier to make different pharmaceutical dosage forms. The versatile use of this polymer is due to its extensive range of DS value, solubility, and high purity. Several examples of CMC and its derivatives are applied as

Table 1. Properties of CMC affected by the DS value

Properties	Effect of degree of substitution on these properties	Reference
Solubility	CMC of DS value 0.4 is swellable but insoluble in water. However, it is fully soluble beyond 0.4 DS.	(54)
	CMC with DS value 0.1-0.4 is soluble in 4-8% NaOH.	(55)
Viscosity	Increasing DS increases the viscosity of CMC.	(54)
Hygroscopicity	Increasing DS increases the hygroscopicity of CMC.	(56)
Salt tolerance	Increasing DS increases the salt tolerance of CMC.	(56)
crystallinity	CMC is crystalline at a DS of 0.82, and crystallinity disappears above the DS value of 1.	(57)

*DS-Degree of Substitution, CMC-carboxymethyl cellulose

Table 2. DS value of CMC according to its source

Source of CMC	DS value of CMC
Banana fruit	0.17
Banana stem	0.28
Oil palm fiber	0.29
Palm kernel cake	0.31
Sunflower stalk	0.33
M. Sinensis	0.35
Cotton fiber	0.3-0.4
Seaweed	0.51
Sugar beet pulp	0.67
C. Papyrus	0.76
Water hyacinth	1.76
Corn leaves	2.39
Cornhusk	2.41

*DS- Degree of substitution

Table 3. Application of CMC in various sectors

Range of DS	Applications	Ref.
0.5-1.2	food additives, paper size, paints, coatings agents, and detergents.	(58)
0.6-0.95	Preservative to increase the durability of acidic milk drinks. Stabilizer and improves the stability of milk.	(59)
0.3-0.4	Manufacturing of carboxymethyl gauze for wound dressing and antimicrobial treatment.	(60)
0.62-0.79	Hydrogel formation (Na-CMC/propylene glycol/H ₂ O hydrogel).	(61)
1.2-1.4	Production of lithium-ion batteries (suitable binder in anode).	(62)

*DS- Degree of substitution

efficient excipients and drug carriers. CMC beads derived from sago biomass encapsulate red palm oil to form controlled release medicament to the target intestine (64). Leaf extract of white jute is combined with CMC to formulate ulcer control media (65). Anionic CMC is used as a binder to make turmeric formulations. Additionally, it acts as a natural emulsifier and stabilizer in the formulation of Zein protein products and Pickering emulsions (66).

CMC is not only used as an active pharmaceutical excipient but also as an effective drug carrier in various diseases. It is a reliable carrier for anticancer chemotherapy drugs. Na-CMC-graft-histidine and D- α -Tocopheryl polyethylene glycol 1000 succinate are used to formulate nano-particle-based copolymers that efficiently encapsulate the

docetaxel drug and overcome its drawbacks such as multidrug resistance and reduce allergic actions (67). Graft polymers of Na-CMC and N, N-Dimethyl aminoethyl methacrylate show antitumor activity on cancerous cells (68). CMC-ursolic acid encapsulated with hydroxycamptothecin is used to form nanoparticles that target the tumor cells with high efficiency (69).

CMC-Bowman Birk inhibitor conjugate and CMC protease inhibitor conjugate are used to formulate mucoadhesive paste for delivering insulin via the oral route. These conjugates make a protective layer around insulin and enhance drug delivery. This formulation aid in overcoming the drawbacks such as enzymatic degradation of insulin in the gastrointestinal tract (70). In formulations of oral

solid dosage forms, CMC biocomposite now acts as a cost-reducing agent by replacing gelatine to formulate hard shell capsules (45).

Apart from oral delivery, CMC is also used as viscous polymer material for ophthalmic drug delivery systems. CMC acts as a biocompatible emulsifier to formulate emulsified Tilisolol-CMC ophthalmic drug solution. This solution is used to make an ocular injection system. CMC tends to decrease the excess leakage of the drug in the target area and improve drug delivery in sustained release form (71).

The formulation of microneedles using CMC is now in trend. It has acted as a boon in the transdermal drug delivery system (TDDS). CMC-Amylopectin microneedles are biocompatible and are used to deliver protein and vaccines via the transdermal route. CMC increases the permeability of the drug and enhances the microneedle array's dissolution property, which further improves the efficiency of the delivery system (72). CMC is used in the manufacturing of wound dressing gauges. They are added in meters to increase water/antimicrobial liquid retention for adsorbent and wound dressing (73,74). Furthermore, CMC hydrogels are used as

environment-friendly adsorbents to remove dyes from wastewater solutions and make them potable (75). CMC derivatives are found to have antimicrobial activities (76). CMC-based silver nanocomposites have excellent antimicrobial activity. For this reason, CMC is used as a coating material on nonwoven fabrics for making favorable antimicrobial textiles. Such textiles are tested on rat skin which showed depletion of microbe growth in it (77).

Nonmedical Applications of CMC

CMC nowadays are used as thickening agents in paints and textile printing. The CMC extracted from lignocellulosic waste is used as thickeners in vat dyes for cloth printing (78). CMC increases the viscosity of dye and holds dye particles in the printing area. Crude CMC has a prominent position in adjusting the size of thread and yarns in textile industries. Its properties, such as water solubility and ease of removal on washing, have contributed to textile sizing applications. CMC obtained from starch acts as a sizing agent in cotton fiber (79). They enhance the adhesion of starch to cotton blend. CMC derivatives such as CMC-g-polyvinyl alcohol and CMC-g-polymethyl methacrylate are used in textile industries as sizing agents (80).

Besides size-controlling agents, CMC is also used to improve color quality in silk fabrics and digital printing. CMC is added to color dyes to maintain

color uniformity, viscosity, hydrophilicity, and dye penetration property (81). CMC/sodium alginate/dextrin mixture is used to develop superior quality digital printing of textiles (82).

CMC is widely used in food industries as a bulking agent, apart from textile mills. It is tasteless, odorless, noncaloric, and physiologically inert, and it forms a clear solution without opacity. These properties improve food quality and safety and provide desired mouthfeel (83,84). CMC is used to enhance food texture and act as a thickener, emulsion stabilizer, moisture binder, etc. In addition, it is also used as packaging material to confirm the long time safety of food products (85). CMC acts as a thickener in nano-emulsion-based olive oil to improve stability (86). Low viscous CMC acts as a moisture binder, and high viscous CMC acts as a gelling agent (87).

Production of dairy products and fruit syrups requires CMC as a thickener (88). It acts as a dewatering agent in producing fruit syrup (89) and an emulsifier in the production of cream products, condiments, bakery food, and beverages (90). 0.5% CMC is used as a stabilizer to produce ice cream. It increases the creamy mouthfeel and eliminates the over-crystal growth of lactose in ice cream. CMC also prevents the sedimentation of milk drinks in low and high temperatures (91).

CMC is also nowadays used as a fat replacer in making dietary food in dairy and energy drinks. 0.5% of CMC-MCC is used to make meat patties with low calories, and CMC acts as a fat replacer in the process (92). CMC and other dietary fibers such as chitosan and pectin are used to design high nutrition, low fat-based, healthier meat products (93).

Conclusion

Due to the abundance and versatility of CMC, it has made its way into various medical and non-medical sectors. Earlier only wood-based materials were used to extract cellulose further modified to form CMC. However, recent developments portray the most significant changes in the cellulose extraction process. The formulators are now able to remove cellulose from waste and rag products. CMC is given maximum importance among multiple cellulose derivatives due to its unique physicochemical properties. Its hydrophilicity, nontoxicity, biodegradability, pH sensitivity, and compatibility with numerous other components have been applicable in biomedical engineering, food industries, pharma sectors, and textile mills. Multiple hybrid materials based on CMC have been

manufactured to date. However, there is a vast scope for developing more alternatives in the future.

Contribution of authors

Nil

Acknowledgments

ISF College is thankfully acknowledged for providing the necessary infrastructure and facilities to carry out this work.

Conflict of interest

None declared

References

1. Heinze T, Pfeiffer K. Studies on the synthesis and characterization of carboxymethylcellulose. *Die Angewandte Makromolekulare Chemie*. 1999 May 1;266(1):37-45.
2. Revol JF, Goring DA. On the mechanism of the mercerization of cellulose in wood. *Journal of Applied Polymer Science*. 1981 Apr;26(4):1275-82.
3. Pushpamalar V, Langford SJ, Ahmad M, Lim YY. Optimization of reaction conditions for preparing carboxymethyl cellulose from sago waste. *Carbohydrate Polymers*. 2006 May 11;64(2):312-8.
4. Singh RK, Singh AK. Optimization of reaction conditions for preparing carboxymethyl cellulose from corn cobic agricultural waste. *Waste and Biomass Valorization*. 2013 Mar;4(1):129-37.
5. Mondal MI, Yeasmin MS, Rahman MS. Preparation of food grade carboxymethyl cellulose from corn husk agrowaste. *International Journal of Biological Macromolecules*. 2015 Aug 1;79:144-50.
6. Rachtanapun P, Luangkamin S, Tanprasert K, Suriyatem R. Carboxymethyl cellulose film from durian rind. *LWT-Food Science and Technology*. 2012 Sep 1;48(1):52-8.
7. Adinugraha MP, Marseno DW. Synthesis and characterization of sodium carboxymethylcellulose from cavendish banana pseudo stem (*Musa cavendishii* LAMBERT). *Carbohydrate Polymers*. 2005 Nov 10;62(2):164-9.
8. Dapía S, Tovar CA, Santos V, Parajó JC. Rheological behaviour of carboxymethylcellulose manufactured from TCF-bleached milox pulps. *Food hydrocolloids*. 2005 Mar 1;19(2):313-20.
9. Revol JF, Goring DA. On the mechanism of the mercerization of cellulose in wood. *Journal of Applied Polymer Science*. 1981 Apr;26(4):1275-82.
10. Verma N, Pramanik K, Singh AK, Biswas A. Design of magnesium oxide nanoparticle incorporated carboxy methyl cellulose/poly vinyl alcohol composite film with novel composition for skin tissue engineering. *Materials Technology*. 2021 Jan 18:1-1.
11. Sharmila G, Muthukumaran C, Kirthika S, Keerthana S, Kumar NM, Jeyanthi J. Fabrication and characterization of *Spinacia oleracea* extract incorporated alginate/carboxymethyl cellulose microporous scaffold for bone tissue engineering. *International Journal of Biological Macromolecules*. 2020 Aug 1; 156:430-7.
12. Parikh DV, Fink T, Rajasekharan K, Sachinvala ND, Sawhney AP, Calamari TA, Parikh AD. Antimicrobial silver/sodium carboxymethyl cotton dressings for burn wounds. *Textile Research Journal*. 2005 Feb;75(2):134-8.
13. Easson M, Villalpando A, Condon BD. Absorbent Properties of Carboxymethylated Fiber, Hydroentangled Nonwoven and Regenerated Cellulose: A Comparative Study. *Journal of Engineered Fibers and Fabrics*. 2017 Dec;12(4):155892501701200408.
14. Singh BN, Panda NN, Mund R, Pramanik K. Carboxymethyl cellulose enables silk fibroin nanofibrous scaffold with enhanced biomimetic potential for bone tissue engineering application. *Carbohydrate polymers*. 2016 Oct 20; 151:335-47.
15. Saladino ML, Markowska M, Carmone C, Cancemi P, Alduina R, Presentato A, Scaffaro R, Biały D, Hasiak M, Hreniak D, Wawrzyńska M. Graphene oxide carboxymethylcellulose nanocomposite for dressing materials. *Materials*. 2020 Jan;13(8):1980.
16. Mondal MI, Yeasmin MS, Rahman MS. Preparation of food grade carboxymethyl cellulose from corn husk agrowaste. *International Journal of Biological Macromolecules*. 2015 Aug 1; 79:144-50.
17. Li W, Sun B, Wu P. Study on hydrogen bonds of carboxymethyl cellulose sodium film with two-dimensional correlation infrared spectroscopy. *Carbohydrate polymers*. 2009 Oct 15;78(3):454-61.
18. Adinugraha MP, Marseno DW. Synthesis and characterization of sodium carboxymethylcellulose from cavendish banana pseudo stem (*Musa cavendishii* LAMBERT). *Carbohydrate Polymers*. 2005 Nov 10;62(2):164-9.

19. Arca HC, Mosquera-Giraldo LI, Bi V, Xu D, Taylor LS, Edgar KJ. Pharmaceutical applications of cellulose ethers and cellulose ether esters. *Biomacromolecules*. 2018 Jun 5;19(7):2351-76.
20. Jiménez-Castellanos MR, Zia H, Rhodes CT. Design and testing in vitro of a bioadhesive and floating drug delivery system for oral application. *International Journal of Pharmaceutics*. 1994 Apr 25;105(1):65-70.
21. Varshosaz J, Tavakoli N, Roozbahani F. Formulation and in vitro characterization of ciprofloxacin floating and bioadhesive extended-release tablets. *Drug delivery*. 2006 Jan 1;13(4):277-85.
22. Dortunç B, Özer L, Uyanik N. Development and in vitro evaluation of a buccoadhesive pindolol tablet formulation. *Drug development and industrial pharmacy*. 1998 Jan 1;24(3):281-8.
23. Semalty M, Semalty A, Kumar G. Formulation and characterization of mucoadhesive buccal films of glipizide. *Indian journal of pharmaceutical sciences*. 2008 Jan;70(1):43.
24. Mohammed FA, Khedr H. Preparation and in vitro/in vivo evaluation of the buccal bioadhesive properties of slow-release tablets containing miconazole nitrate. *Drug development and industrial pharmacy*. 2003 Jan 1;29(3):321-37.
25. Parviez N, Ahuja A, Khar RK. Development and evaluation of muco-adhesive buccal tablets of lignocaine hydrochloride. *Indian journal of pharmaceutical sciences*. 2002;64(6):563.
26. Ali J, Khar RK, Ahuja A. Formulation and characterisation of a buccoadhesive erodible tablet for the treatment of oral lesions. *Die Pharmazie*. 1998 May 1;53(5):329-34.
27. Verma N, Wahi AK, Verma A, Chattopadhyay P. Evaluation of a mucoadhesive buccal patch for delivery of atenolol: in vitro screening of bioadhesion. *J Pure Appl Microbiol*. 2007 Apr;1(115):8.
28. Baun A, Hartmann NB, Grieger K, Kusk KO. Ecotoxicity of engineered nanoparticles to aquatic invertebrates: a brief review and recommendations for future toxicity testing. *Ecotoxicology*. 2008 Jul;17(5):387-95.
29. Javanbakht S, Nazari N, Rakhshaei R, Namazi H. Cu-crosslinked carboxymethylcellulose /naproxen/graphene quantum dot nanocomposite hydrogel beads for naproxen oral delivery. *Carbohydrate polymers*. 2018 Sep 1; 195:453-9.
30. Oppermann W. Superabsorbent materials based on cellulose. *Papier*. 1995 Dec 1;49(12):765-769.
31. Demitri C, Del Sole R, Scalera F, Sannino A, Vasapollo G, Maffezzoli A, Ambrosio L, Nicolais L. Novel superabsorbent cellulose-based hydrogels crosslinked with citric acid. *Journal of Applied Polymer Science*. 2008 Nov 15;110(4):2453-60.
32. Liu P, Peng J, Li J, Wu J. Radiation crosslinking of CMC-Na at low dose and its application as substitute for hydrogel. *Radiation Physics and Chemistry*. 2005 Apr 1;72(5):635-8.
33. Barbucci R, Magnani A, Consumi M. Swelling behavior of carboxymethylcellulose hydrogels in relation to cross-linking, pH, and charge density. *Macromolecules*. 2000 Oct 3;33(20):7475-80.
34. El Salmawi KM. Application of polyvinyl alcohol (PVA)/carboxymethyl cellulose (CMC) hydrogel produced by conventional crosslinking or by freezing and thawing. *Journal of Macromolecular Science, Part A: Pure and Applied Chemistry*. 2007 Apr 1;44(6):619-24.
35. Rokhade AP, Agnihotri SA, Patil SA, Mallikarjuna NN, Kulkarni PV, Aminabhavi TM. Semi-interpenetrating polymer network microspheres of gelatin and sodium carboxymethyl cellulose for controlled release of ketorolac tromethamine. *Carbohydrate polymers*. 2006 Aug 15;65(3):243-52.
36. Qiu Y, Park K. Environment-sensitive hydrogels for drug delivery. *Advanced drug delivery reviews*. 2001 Dec 31;53(3):321-39.
37. Ullah F, Othman MB, Javed F, Ahmad Z, Akil HM. Classification, processing and application of hydrogels: A review. *Materials Science and Engineering: C*. 2015 Dec 1; 57:414-33.
38. Das N. Preparation methods and properties of hydrogel: A review. *Int. J. Pharm. Pharm. Sci*. 2013 Jan;5(3):112-7.
39. Javanbakht S, Pooresmaeil M, Hashemi H, Namazi H. Carboxymethylcellulose capsulated Cu-based metal-organic framework-drug nanohybrid as a pH-sensitive nanocomposite for ibuprofen oral delivery. *International journal of biological macromolecules*. 2018 Nov 1; 119:588-96.
40. Mondal MI, Yeasmin MS, Rahman MS. Preparation of food grade carboxymethyl cellulose from corn husk agrowaste. *International Journal of Biological Macromolecules*. 2015 Aug 1;79:144-50.
41. Huan Y, Zhang S, Vardhanabhuti B. Effect of CMC molecular weight on acid-induced gelation of heated WPI-CMC soluble complex. *Journal of food science*. 2016 Feb;81(2):N502-7.

42. Theeuwes C, Dijk B, inventors; Akzo Nobel NV, assignee. Use of carboxymethyl cellulose (cmc) in fruit-based products. United States patent application US 10/537,199. 2006 Feb 9.
43. Abu-Jdayil B, Ghannam M. The modification of rheological properties of sodium bentonite-water dispersions with low viscosity CMC polymer effect. *Energy Sources, Part A: Recovery, Utilization, and Environmental Effects*. 2014 May 19;36(10):1037-48.
44. Sundaram H, Voigts B, Beer K, Meland M. Comparison of the rheological properties of viscosity and elasticity in two categories of soft tissue fillers: calcium hydroxylapatite and hyaluronic acid. *Dermatologic Surgery*. 2010 Nov; 36:1859-65.
45. Hamdan MA, Ramli NA, Othman NA, Amin KN, Adam F. Characterization and property investigation of microcrystalline cellulose (MCC) and carboxymethyl cellulose (CMC) filler on the carrageenan-based biocomposite film. *Materials Today: Proceedings*. 2021 Jan 1; 42:56-62.
46. Karakus S, Ilgar M, Tan E, Kahyaoglu IM, Tasaltin N, Albayrak I, Insel MA, Kilislioglu A. Preparation and characterization of carboxymethyl cellulose/poly (ethylene glycol)-rosin pentaerythritolester polymeric nanoparticles: Role of intrinsic viscosity and surface morphology. *Surfaces and Interfaces*. 2020 Dec 1; 21:100642.
47. Arancibia C, Navarro-Lisboa R, Zúñiga RN, Matiacevich S. Application of CMC as thickener on nanoemulsions based on olive oil: Physical properties and stability. *International Journal of Polymer Science*. 2016 Jan 1;2016.
48. Birsan M, Bibire N, Panainte AD, Silasi O, Antonoaea P, Ciurba A, Cristofor AC, Wroblewska M, Sosnowska K. The Influence of the Preparation Method on the Characteristics of a New Cosmetic Gel Based on Hyaluronic Acid and Matrix-Forming Polymers. *network*. 2020 Jun 1;7:9. Roy N, Saha N, Kitano T, Saha P. Biodegradation of PVP-CMC hydrogel film: A useful food packaging material. *Carbohydrate polymers*. 2012 Jun 20;89(2):346-53.
49. Aboagye IA. Use of Exogenous Fibrolytic Enzymes to Improve the Nutritive Value of Preserved Forage for Ruminants (Doctoral dissertation, Thompson Rivers University).
50. Feddersen RL, Thorp SN. Sodium carboxymethylcellulose. In *Industrial gums* 1993 Jan 1 (pp. 537-578). Academic Press.
51. Wanchoo RK, Sharma PK. Viscometric study on the compatibility of some water-soluble polymer-polymer mixtures. *European Polymer Journal*. 2003 Jul 1;39(7):1481-90.
52. Whistler R, editor. *Industrial gums: polysaccharides and their derivatives*. Elsevier; 2012 Dec 2.
53. Casaburi, A.; Rojo, Ú.M.; Cerrutti, P.; Vázquez, A.; Foresti, M.L. Carboxymethyl cellulose with tailored degree of substitution obtained from bacterial cellulose. *Food Hydrocoll*. 2018, 75, 147-156
54. Yeasmin MS, Mondal MI. Synthesis of highly substituted carboxymethyl cellulose depending on cellulose particle size. *International journal of biological macromolecules*. 2015 Sep 1;80:725-31.
55. Hon, D.N.-S. Cellulose: Chemistry and Technology. In *Encyclopedia of Materials: Science and Technology*, 1st ed.; Buschow, K.H.J., Cahn, R., Flemings, M., Ilchner, B., Kramer, E., Mahajan, S., Veyssiere, P., Eds.; Elsevier: Amsterdam, The Netherlands, 2001; pp. 1039-1045.
56. Bemiller JN. Cellulose and Cellulose-Based Hydrocolloids: Carbohydrate Chemistry for Food Scientists.
57. Xiquan L, Tingzhu Q, Shaoqui Q. Kinetics of the carboxymethylation of cellulose in the isopropyl alcohol system. *Acta Polymerica*. 1990 Apr;41(4):220-2.
58. Jett. C, Arthur, J. Chemical Modification of Cellulose and its Derivatives. In *Comprehensive Polymer Science and Supplements*; Elsevier: Amsterdam, The Netherlands, 1989; Volume 6, pp. 49-80
59. Du B, Li J, Zhang H, Huang L, Chen P, Zhou J. Influence of molecular weight and degree of substitution of carboxymethylcellulose on the stability of acidified milk drinks. *Food Hydrocolloids*. 2009 Jul 1;23(5):1420-6.
60. Parikh DV, Fink T, Rajasekharan K, Sachinvala ND, Sawhney AP, Calamari TA, Parikh AD. Antimicrobial silver/sodium carboxymethyl cotton dressings for burn wounds. *Textile Research Journal*. 2005 Feb;75(2):134-8.
61. Komorowska P, Rózańska S, Rózański J. Effect of the degree of substitution on the rheology of sodium carboxymethylcellulose solutions in propylene glycol/water mixtures. *Cellulose*. 2017 Oct;24(10):4151-62.
62. Lee BR, Oh ES. Effect of molecular weight and degree of substitution of a sodium-carboxymethyl cellulose binder on Li4Ti5O12 anodic performance. *The Journal of Physical Chemistry C*. 2013 Mar 7;117(9):4404-9.
63. Sorokin AV, Kuznetsov VA, Lavlinskaya MS. Synthesis of graft copolymers of carboxymethyl cellulose and N, N-

- dimethylaminoethyl methacrylate and their study as Paclitaxel carriers. *Polymer Bulletin*. 2021 Jun;78(6):2975-92.
64. Sathasivam T, Muniyandy S, Chuah LH, Janarthanan P. Encapsulation of red palm oil in carboxymethyl sago cellulose beads by emulsification and vibration technology: Physicochemical characterization and in vitro digestion. *Journal of food engineering*. 2018 Aug 1; 231:10-21.
 65. Al Batran R, Al-Bayaty F, Ameen Abdulla M, Jamil Al-Obaidi MM, Hajrezaei M, Hassandarvish P, Fouad M, Golbabapour S, Talaei S. Gastroprotective effects of *C. orchorus olitorius* leaf extract against ethanol-induced gastric mucosal hemorrhagic lesions in rats. *Journal of Gastroenterology and Hepatology*. 2013 Aug;28(8):1321-9.
 66. Babazadeh A, Tabibiazar M, Hamishehkar H, Shi B. Zein-CMC-PEG multiple nanocolloidal systems as a novel approach for nutraceutical applications. *Advanced pharmaceutical bulletin*. 2019 Jun;9(2):262.
 67. Jiang W, Yang L, Qiu L, Xu J, Yang X, Wang J, Zhou H, Wang D. Multifunctional hybrid nanoparticles based on sodium carboxymethylcellulose-graft-histidine and TPGS for enhanced effect of docetaxel. *RSC Advances*. 2015;5(66):53835-45.
 68. Uglea CV, Pârva A, Corjan M, Dumitriu AD, Ottenbrite RM. Biodistribution and antitumor activity induced by carboxymethylcellulose conjugates. *Journal of bioactive and compatible polymers*. 2005 Nov;20(6):571-83.
 69. Liu YX, Liu KF, Li CX, Wang LY, Liu J, He J, Lei J, Liu X. Self-assembled nanoparticles based on a carboxymethylcellulose-ursolic acid conjugate for anticancer combination therapy. *RSC advances*. 2017;7(58):36256-68.
 70. Marschütz MK, Bernkop-Schnürch A. Oral peptide drug delivery: polymer-inhibitor conjugates protecting insulin from enzymatic degradation in vitro. *Biomaterials*. 2000 Jul 1;21(14):1499-507.
 71. Sasaki H, Kashiwagi S, Mukai T, Nishida K, Nakamura J, Nakashima M, Ichikawa M. Topical Delivery System of Ophthalmic Drugs by Periocular Injection with Viscous Solution. *Biological and Pharmaceutical Bulletin*. 1999 Sep 15;22(9):961-5.
 72. Park YH, Ha SK, Choi I, Kim KS, Park J, Choi N, Kim B, Sung JH. Fabrication of degradable carboxymethyl cellulose (CMC) microneedle with laser writing and replica molding process for enhancement of transdermal drug delivery. *Biotechnology and bioprocess engineering*. 2016 Jan;21(1):110-8.
 73. Easson M, Villalpando A, Condon BD. Absorbent Properties of Carboxymethylated Fiber, Hydroentangled Nonwoven and Regenerated Cellulose: A Comparative Study. *Journal of Engineered Fibers and Fabrics*. 2017 Dec;12(4):155892501701200408.
 74. Parikh DV, Fink T, Rajasekharan K, Sachinvala ND, Sawhney AP, Calamari TA, Parikh AD. Antimicrobial silver/sodium carboxymethyl cotton dressings for burn wounds. *Textile Research Journal*. 2005 Feb;75(2):134-8.
 75. Varaprasad K, Jayaramudu T, Sadiku ER. Removal of dye by carboxymethyl cellulose, acrylamide and graphene oxide via a free radical polymerization process. *Carbohydrate polymers*. 2017 May 15;164:186-94.
 76. Bozaci E, Akar E, Ozdogan E, Demir A, Altinisik A, Seki Y. Application of carboxymethylcellulose hydrogel based silver nanocomposites on cotton fabrics for antibacterial property. *Carbohydrate Polymers*. 2015 Dec 10;134:128-35.
 77. Montaser AS, Jlassi K, Ramadan MA, Sleem AA, Attia MF. Alginate, gelatin, and carboxymethyl cellulose coated nonwoven fabrics containing antimicrobial AgNPs for skin wound healing in rats. *International Journal of Biological Macromolecules*. 2021 Mar 15;173:203-10.
 78. Sheikh J, Bramhecha I, Teli MD. Recycling of terry towel (cellulosic) waste into carboxymethyl cellulose (CMC) for textile printing. *Fibers and Polymers*. 2015 May;16(5):1113-8.
 79. Hebeish A, Higazy A, El-Shafei A, Sharaf S. Synthesis of carboxymethyl cellulose (CMC) and starch-based hybrids and their applications in flocculation and sizing. *Carbohydrate Polymers*. 2010 Jan 5;79(1):60-9.
 80. Mohamed ZE, Amr A, Knittel D, Schollmeyer E. Synthesis and application of new sizing and finishing additives based on carboxymethyl cellulose. *Carbohydrate polymers*. 2010 Jul 23;81(4):769-74.
 81. Obele CM, Ibenta ME, Chukwuneke JL, Nwanonyi SC. Carboxymethyl cellulose and cellulose nanocrystals from cassava stem as thickeners in reactive printing of cotton. *Cellulose*. 2021 Mar;28(4):2615-33.
 82. Jeong DS, Chun TI. Color Fastness of Digital Textile Printing on Silk Fabrics-The effect of the mixed pre-treatment agent. *Fashion & Textile Research Journal*. 2013;15(5):808-14.
 83. Zhang LM. New water-soluble cellulosic polymers: a review. *Macromolecular*

- Materials and Engineering. 2001 May 1;286(5):267-75.
84. McClements DJ. Emulsion stability. In Food emulsions 2015 Aug 21 (pp. 314-407). CRC Press.
 85. Mirhosseini H, Tan CP, Aghlora A, Hamid NS, Yusof S, Chern BH. Influence of pectin and CMC on physical stability, turbidity loss rate, cloudiness and flavor release of orange beverage emulsion during storage. Carbohydrate Polymers. 2008 Jul 4;73(1):83-91.
 86. Arancibia C, Navarro-Lisboa R, Zúñiga RN, Matiacevich S. Application of CMC as thickener on nanoemulsions based on olive oil: Physical properties and stability. International Journal of Polymer Science. 2016 Jan 1;2016.
 87. Theeuwes C, Dijk B, inventors; Akzo Nobel NV, assignee. Use of carboxymethyl cellulose (cmc) in fruit-based products. United States patent application US 10/537,199. 2006 Feb 9.
 88. Arancibia C, Bayarri S, Costell E. Comparing carboxymethyl cellulose and starch as thickeners in oil/water emulsions. Implications on rheological and structural properties. Food Biophysics. 2013 Jun;8(2):122-36.
 89. Islam M, Alam MN, van de Ven T. Sustainable cellulose-based hydrogel for dewatering of orange juice. Cellulose. 2020 Sep;27(13):7637-48.
 90. Bosso A, Salmasso D, De Faveri E, Guaita M, Franceschi D. The use of carboxymethylcellulose for the tartaric stabilization of white wines, in comparison with other oenological additives. Vitis. 2010 Jan 1;49(2):95-9.
 91. Sebayang F, Sembiring H. Synthesis of CMC from palm midrib cellulose as stabilizer and thickening agent in food. Oriental Journal of Chemistry. 2017;33(1):519.
 92. Gibis M, Schuh V, Weiss J. Effects of carboxymethyl cellulose (CMC) and microcrystalline cellulose (MCC) as fat replacers on the microstructure and sensory characteristics of fried beef patties. Food Hydrocolloids. 2015 Mar 1;45:236-46.
 93. Han M, Bertram HC. Designing healthier comminuted meat products: Effect of dietary fibers on water distribution and texture of a fat-reduced meat model system. Meat Science. 2017 Nov 1; 133:159-65.