CROSSLINKED CARBOXYMETHYL CELLULOSE-SiO₂ HYDROGELS FABRICATION: COMPOSITION AND THERMAL STABILITY TOWARDS BIOMEDICAL APPLICATIONS

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Abstract - Novel and innovative materials for biomedical and pharmaceutical applications have to consider several factors during their fabrication, such as the material composition and thermal stability, aiming to establish the promising physicochemical properties towards efficient and controlled drug release systems. In this study, carboxymethyl cellulose (CMC) hydrogels are prepared by incorporating silica dioxide (SiO₂) nanoparticles previously modified with primary amine (-NH₂) functional groups, aiming to evaluate the chemical composition and to improve the thermal efficiency. The carbodiimide chemistry method is performed to promote the crosslinking of the CMC structure through the formation of amide bonds from the activation of carboxyl (C=O) groups and further covalent binding with -NH₂ groups. The morphology information displays high dispersed SiO₂ nanoparticles with a smooth surface, regular shape, and an average particle size of 104 nm. The material composition and thermal stability are evaluated using the Fourier transform infrared spectroscopy and thermogravimetric analysis to establish a preliminary overview of a functional hydrogel for biomedical and pharmaceutical applications. The formation of amide bonds is confirmed indicating the successful crosslinking of the CMC structure with SiO₂-NH₂ nanoparticles, which is attributed to the activation of the C=O groups and its strong affinity to the -NH₂ groups. This interaction enhanced the thermal stability of the crosslinked CMC-SiO₂ hydrogels up to 469°C which was the last decomposition event, outstanding the contribution of major content of SiO₂-NH₂ nanoparticles. These results suggest a suitable procedure for the fabrication of crosslinked CMC-SiO₂ hydrogels as novel materials with promising physicochemical properties, which can contribute to the biomedical and pharmaceutical fields in controlled drug release and delivery systems.

Keywords: Carboxymethyl cellulose hydrogel; silica dioxide nanoparticles; amine functionalization; carbodiimide crosslinker chemistry; material composition; thermal stability; biomedicine

FABRICACIÓN DE HIDROGELES ENTRECRUZADOS DE CARBOXIMETIL CELULOSA-SiO₂: COMPOSICIÓN Y ESTABILIDAD TÉRMICA HACIA APLICACIONES BIOMÉDICAS

Resumen - Nuevos e innovadores materiales para aplicaciones biomédicas y farmacéuticas deben considerar factores como la composición y la estabilidad térmica para establecer las propiedades fisicoquímicas adecuadas para sistemas eficientes de liberación controlada de fármacos. En este estudio, hidrogeles de carboximetilcelulosa (CMC) son preparados incorporando nanopartículas de dióxido de sílice (SiO₂) previamente modificadas con grupos de aminas primarias (-NH₂), buscando evaluar

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la composición química y mejorar la estabilidad térmica. El método de carbodiimidas es utilizado para promover el entrecruzamiento de la CMC con la formación de enlaces amidas a partir grupos carboxilo (C=O) activados y su posterior enlace con grupos -NH₂. La información morfológica muestra nanopartículas de SiO₂ dispersas con superficie lisa, forma regular, y diámetro promedio de 104 nm. La composición del material y la estabilidad térmica son evaluadas usando la espectroscopia infrarroja de la transformada de Fourier y el análisis termogravimétrico para establecer una perspectiva preliminar de hidrogeles funcionales para aplicaciones biomédicas y farmacéuticas. La formación de enlaces amidas es confirmado indicando el entrecruzamiento exitoso de la estructura de la CMC con nanopartículas de SiO₂-NH₂, el cual es atribuido a la activación de los grupos C=O y su fuerte afinidad a los grupos -NH₂. Esta interacción mejoró la estabilidad térmica de los hidrogeles entrecruzados de CMC-SiO₂ hasta 469°C la cual fue el último evento de descomposición, resaltando la contribución de una mayor presencia de nanopartículas de SiO₂-NH₂. Estos resultados sugieren un adecuado proceso de fabricación de hidrogeles entrecruzados de CMC-SiO₂ como material novedoso con propiedades fisicoquímicas prometedoras, permitiendo contribuir en el campo biomédico y farmacéutico en sistemas de administración controlada de fármacos.

Palabras clave: Hidrogel de carboximetilcelulosa; nanopartículas de dióxido de sílice; funcionalización con aminas; entrecruzamiento con química de carbodiimida; composición del material; estabilidad térmica; biomedicina.

Introduction

In recent years, nanotechnology has been focusing on the development of innovative nanomaterials with exceptional physicochemical properties for a wide number of applications, outstanding the biomedicine and pharmaceutical fields (Tang et al., 2020). Among these nanomaterials, the silica dioxide (SiO₂) nanoparticles are extensively explored due to the advantages offered by their biocompatibility, chemical, and enzymatical stability, reactive surface area, environmentally friendly, and good cost-effectiveness (Abeer et al., 2020). The SiO₂ nanoparticles are synthesized through different physical and chemical methods, which is highlighted the Stöber method due to its simplicity and effectiveness. However, the presence of silanol (Si-OH) groups on the surface after the synthesis represent a challenge, reducing the advantages of using this type of nanoparticles (Sepulveda et al., 2020). This can be solved by functionalizing the surface of the SiO₂ nanoparticles using different functional groups, such as primary amines (NH₂), allowing also to increase the selectivity and affinity (Mahmoodi, Khorramfar, & Najafi, 2011).

Also, biopolymers are being studied along with the nanomaterials for developing and designing different drug delivery systems, in which the combination provides superior characteristics, such as non-toxicity, biodegradability, and high loading cargo and sustained release (Gholamali & Yadollahi, 2020). Carboxymethyl cellulose (CMC) is a promising example of these explored biopolymers and has proven to be efficient in therapeutic systems for biomedical and pharmaceutical applications (Rao et al., 2018). These CMC biopolymers have been explored in industries and academia for their promising physicochemical properties, including hydrophilicity, non-toxicity, and pH-sensitivity (Javanbakht & Shaabani, 2019). The ability to hydrogel-forming using CMC is mainly attributed to the ionic nature and a large amount of carboxyl (C=O) and hydroxyl (-OH) groups in the structure (Jeong, Kim, Kim, & Jung, 2020). However, a few but important limitations, such as the mechanical, thermal, and chemical stability, need to be addressed in the CMC hydrogels to compete with synthetic and non-biodegradable polymers (Shahbazi, Ahmadi, Seif, & Rajabzadeh, 2016).

Physical, chemical (Lin et al., 2020), and enzymatic crosslinking methods arose to overcome the mentioned limitation in the CMC hydrogels formation, improving their physicochemical properties (Zhong et al., 2019). Among the crosslinking agents, citric acid, polyacrylamide, antibacterial Propolis honey, polyethylene glycol (Kanikireddy, Varaprasad, Jayaramudu, Karthikeyan & Sadiku, 2020), glutaraldehyde, formaldehyde, carbodiimide (Jiang et al., 2016), calcium, and aluminum have been widely explored (Mahmoud, Abdou, Sobhy & Fekry, 2017). Although the crosslinking of CMC hydrogel represent a good alternative, there are still challenges regarding the biocompatibility (Jiang et al., 2016), swelling (Jeong et al., 2020), and drug release (Kadry, 2019), which reports suggest their decreasing when using crosslinking agents. Carbodiimide crosslinker chemistry has been reported to be suitable for the hydrogel formation through the covalent binding between NH₂ and C=O groups, resulting in an amide crosslinked bonds in the polymer's structure, including poly (dimethylsiloxane) (Mapkar, Iyer, & Coleman, 2009), and β -cyclodextrin (Tang et al., 2020).

This study reports the synthesis of SiO₂ nanoparticles using the Stöber method, and the surface modification with primary -NH₂ functional groups. These SiO₂-NH₂ nanoparticles were used for the first time, during the formation of CMC hydrogels via the carbodiimide crosslinker chemistry method. This study aims to evaluate the chemical composition and thermal stability of the resulting CMC hydrogels compared to similarly reported CMC hydrogels using other crosslinking agents. In this method, amides bonds were formed from the activation of C=O groups in the CMC structure and the further binding with -NH₂ groups grafted on the surface of the SiO₂ nanoparticles. The material composition was corroborated using the Fourier transform infrared (FTIR) spectroscopy, allowing to identify the successful formation of amide bonds. Whereas the thermogravimetric analysis (TGA) confirmed the high thermal stability due to the presence of uniform and spherical SiO₂ nanoparticles. These results are promising for the preparation of crosslinked CMC-SiO₂ hydrogels with enhanced physicochemical properties, aiming to contribute with a suitable biomaterial for applications in the biomedicine and pharmaceutical fields as an efficient and controlled drug release system.

Experimental Methods

Materials

Carboxymethyl cellulose sodium salt (CMC), tetraethyl orthosilicate (TEOS, 98%), dimethyl sulfoxide (DMSO, 99%), and (3-Aminopropyl)triethoxysilane (APTES, 98%) were acquired from Alfa Aesar by Thermo Fisher Scientific. Ammonium hydroxide (NH₄OH, 30%) and absolute ethanol were purchased from Merck. 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC), N-Hydroxysuccinimide (NHS, 98%), acetic acid (99%), and nitric acid (HNO₃, 70%) were acquired from Sigma-Aldrich. Distilled water and deionized water were used in all the experiments.

Synthesis of SiO₂ nanoparticles

The SiO₂ nanoparticles were synthesized via the Stöber method consisted of the hydrolysis/condensation using the TEOS precursor (Sepulveda et al., 2020). Initially, 1.1 mL of TEOS was added into 50 mL of absolute ethanol followed by sonication at room temperature for 10 min. Afterward, the hydrolysis of TEOS was carried out by adding 1.53 mL of distilled water dropwise into the previous solution and left to react for 5 min in the ultrasound bath at room temperature. The condensation and further nucleation were

promoted using 5.71 mL of NH₄OH as the catalyst, allowing to react for another 15 min at the same operating conditions. After completing the reaction time, the solution was taken out of the ultrasound and left for solidification during 1 h, consisting of the stable growth of the colloids. The resulting SiO₂ nanoparticles were collected by centrifugation at 15000 g-force and room temperature for 15 min and then washed with distilled water and absolute ethanol to eliminate remaining TEOS and other impurities. Finally, the SiO₂ nanoparticles were dried in a conventional oven at 70°C for 2 h.

Amine functionalization of SiO₂ nanoparticles

The surface of the SiO₂ nanoparticles was modified by grafting amine (-NH₂) functional groups from APTES molecules (Z. Zhang et al., 2018). Here, 1.5 g of SiO₂ nanoparticles were suspended in 80 mL of DMSO using an ultrasound bath and then vigorous stirring. Afterward, 5 mL of APTES, 1.25 mL of distilled water, and 0.1 mL of acetic acid were added dropwise and the solution was left to react for 72 h at room temperature. The SiO₂-NH₂ nanoparticles were separated from the solution centrifuging at 15000 g-force and room temperature for 15 min followed by washes with distilled water and ethanol. Then, 0.1 or 0.5 g of the as-synthesized SiO₂-NH₂ nanoparticles were dispersed in 10 mL of deionized water using an ultrasound bath for 15 min and the pH was adjusted to 4 adding drops of a 2 M HNO₃ solution. The suspension was stored at 4°C for further crosslinking with CMC.

Preparation of crosslinked CMC-SiO₂ hydrogel

The crosslinked CMC-SiO₂ hydrogel was prepared through carbodiimide crosslinker chemistry between carboxylic acid and primary amine functional groups (Tang et al., 2020). Initially, the hydrogel was prepared by adding 0.1 g of CMC sodium salt in 7.5 mL of deionized water under 125 rpm of stirring at room temperature. Once the solution is homogenized, the pH was adjusted to 5 using drops of a 0.1 M NaOH solution. Then, the carboxyl groups of the CMC sodium salt were activated adding 12.5 mg of EDC and 7.5 mg of NHS, keeping the same operating conditions. Afterward, the formation of amide bonds was performed adding the SiO₂-NH₂ nanoparticles suspension into the previous hydrogel solution, which was left to react at 125 rpm and room temperature for 48 h. Finally, the crosslinked CMC-SiO₂ hydrogel was dried using an electric oven at 38°C for 7 h.

Characterizations

The morphology of the CMC and SiO₂ nanoparticles was investigated using a scanning electron microscope (SEM) QUANTA FEG 650 with an acceleration voltage of 7 kV. The identification of the functional groups and the crosslinked structure was performed using the Fourier transform infrared (FTIR) spectroscopy in an IR Affinity Shimadzu S/N A213749 equipment. The KBr dispersion method was used in a wave number range between 4000 and 400 cm⁻¹ at room temperature for 10 min. The thermogravimetric analysis (TGA) and derivative thermogravimetric (DTG) curve were performed in a TA Instruments SDT Q600 using a 100 mL/min airflow in the temperature range of 26 and 600°C with a heating ramp of 10°C/min.

Results and Discussion

The scanning electronic microscopy (SEM) was used to evaluate the morphology information of the as-synthesized SiO₂ nanoparticles. According to **Figure 1**, the SiO₂ nanoparticles exhibit a regular smooth surface and sphere shape, which is attributed to the controlled hydrolysis/condensation procedure of TEOS precursor. Although some nanoparticles possess irregular shape, it can be stated that the SiO₂ nanoparticles are regular with an average particle size of 104 ± 12 nm as seen in **Figure 2**. Here, the solidification stage during SiO₂ nanoparticles synthesis plays an important role since it allows controlling the particle size, and it has been reported that the longer is the solidification stage the larger is the particle size. Additionally, no agglomeration was noted in the SEM image allowing the confirm the high dispersion of the SiO₂ nanoparticles. This is mainly attributed to the *in-situ* surface functionalization of the SiO₂ nanoparticles with hydroxyl (-OH) groups during the condensation of the silica matrix, which is typical for this nucleation method. The high dispersion of SiO₂ nanoparticles represents a suitable feature when applying in the biomedicine field, which is used as nanoplatfroms to bind different molecules for cell targeting (Giner-Casares, Henriksen-Lacey, Coronado-Puchau, & Liz-Marzán, 2016), and drug delivery (Lee et al., 2020).

Figure 1. SEM image of SiO₂ nanoparticles synthesized via the Stöber method

Source: own elaboration (2020)
Figure 2. SiO₂ nanoparticles size distribution

Source: own elaboration (2020)

The main functional groups of the crosslinked CMC-SiO₂ hydrogels were determined in the Fourier transform infrared (FTIR) spectra shown in **Figure 3**. Here, hydroxyl, carboxyl, and amine functional groups were identified after performing the carbodiimide crosslinker chemistry and using EDC and NHS. The intense and broadband between 3700 and 2500 cm⁻¹ corresponds to the stretching vibrations of -OH groups. This broadband appeared due to the large number of -OH groups composing the CMC structure, which was highlighted a specifically centered peak around 3000 cm⁻¹ ascribed to the carboxylic acid content (Zhu, Bao, Wei, Ma, & Kong, 2016). In addition to this peak, high intensity but sharper peak located between 1440 and 1395 cm⁻¹ was also related to the presence of the carboxylic acid content widely available in the CMC structure. A strong peak was noted at around 1640 cm⁻¹ attributed to the presence of C=O (Kamel, El-Gendy, Hassan, El-Sakhawy, & Kelnar, 2020), and -NH bonds from the secondary amides (Rao et al., 2018), that were formed during the carbodiimide crosslinker chemistry (see **Figure 4**).

Figure 3. Fourier transform infrared (FTIR) spectra for the identification of the functional groups in the crosslinked CMC-SiO₂ hydrogels.

Source: own elaboration (2020)

In this process, the EDC allowed the formation of intermediates with the carboxyl groups in the CMC structure, such as the O-acylisourea (see **Figure 4a**), which is an unstable molecule. Then, the NHS was used to activate the carboxyl groups linked to the EDC molecules by displacing the O-acylisourea as isourea, promoting the formation of amine-reactive NHS ester (see **Figure 4b**) as another intermediate but more stable molecule. The activated carboxyl group was then able to interact with the primary amine group grafted on the surface of the SiO₂ nanoparticles, completing the crosslinking of the CMC structure through the formation of secondary amides (see **Figure 4c**). Therefore, the successful crosslinking of CMC with the SiO₂ nanoparticles was confirmed with the peak around 1640 cm⁻¹, along with another one located between 1250 and 1020 cm⁻¹ ascribed to C-N stretching vibrations (Asere et al., 2019).

On the other hand, the representative peaks of the SiO₂ nanoparticles are evidenced in the wavenumber region of 1100 and 400 cm⁻¹, which is attributed to the silanol (Si-OH) and siloxane (Si-O-Si) functional groups. The peaks around at 1069 and 687 cm⁻¹ corresponded to the asymmetric and symmetric Si-O bonds for the SiO₂ structure (Pourrajab, Noghrehabadi, Hajidavalloo, & Behbahani, 2020), whereas the medium intensity and broadband between 650 and 450 cm⁻¹ were attributed to the bending Si-O-Si vibration (Asri Mohd Esa & Sapawe, 2020). An additional band was noted in the wavenumber region from 966 to 819 cm⁻¹, which indicates remaining Si-OH groups available on the large surface area of the SiO₂-NH₂ nanoparticles (Pourrajab et al., 2020). This represents a suitable surface for enhanced grafting with NH₂ groups, providing a major crosslinking area for the interaction and binding with the carboxyl group from the CMC structure.

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Figure 4. Carbodiimide chemistry procedure for the crosslinking of CMC hydrogels and the incorporation of SiO₂ nanoparticles.

Source: own elaboration (2020)

The thermogravimetric analysis (TGA) and derivative thermogravimetric (DTG) curves are displayed in **Figure 5** and **Figure 6**. The CMC was crosslinked using different concentrations of SiO₂-NH₂ nanoparticles to evaluate the thermal stability, considering as an important factor for applications in the biomedicine field. In **Figure 5**, the crosslinked CMC-SiO₂ hydrogel using 0.1 g of SiO₂-NH₂ nanoparticles exhibited two main weight loss stages with several thermal events and maximum decomposition peaks. The three first event at 53, 102, and 164°C were mainly attributed to moisture or some water content in the crosslinked CMC-SiO₂ hydrogel with a weight loss of about 27%, in which water is evaporated at 164°C due to the strong binding between the CMC and SiO₂-NH₂ nanoparticles. Afterward, the weight was reduced up to 33% with a maximum decomposition at 250 and 279°C attributed to the release of CO₂ from the carboxyl groups contained in the cellulose backbone(Jiang et al., 2016), which promote the cleavage and fragmentation of the main bonds in the structure(C. Zhang et al., 2020). However, two more events occurred at 352 and 430°C,suggesting the decomposition of more stable organic content, which is related to the presence of SiO₂-NH₂ nanoparticles that provides higher thermal stability.

Figure 5. Thermogravimetric analysis (TGA) and derivative thermogravimetric (DTG) curve of the hydrogels crosslinked with 0.1 g of SiO₂-NH₂ nanoparticles to determine changes in the sample weight over time as the temperature increases.

Source: own elaboration (2020)

In the case of the hydrogels crosslinked with 0.5 g of SiO₂-NH₂ nanoparticles shown in **Figure 6**, a two-stage thermal decomposition was also observed. The decomposition events are reduced attribute to the presence of SiO₂-NH₂ nanoparticles, in which the evaporation of water content occurred up to 107°C instead of 164°C since the availability of -OH decreased due to the interaction with primary -NH groups. However, the weight loss was around 37% in this first stage, which was 10% more compared to the crosslinked CMC-SiO₂ hydrogel using 0.1 g of SiO₂-NH₂ nanoparticles. This effect is attributed to a major content of water that was adsorbed on the surface of the SiO₂-NH₂ nanoparticles, considering that the concentration was increased to 0.5 g which promotes a larger available surface area. In the second stage, the total number of decomposition events decreased, as well as the decomposition area, indicating major thermal stability in the crosslinked CMC-SiO₂ hydrogel structure. This is observed from the total remaining weight of 56% at 485°C, in which the last thermal event 469°C related to the decomposition of more stable organic content, suggests an enhancement of about 30°C concerning the crosslinked hydrogels using 0.1 g of SiO₂-NH₂ nanoparticles. These two-stages decomposition results are highlighted in comparison with others studies in the literature for crosslinked CMC hydrogels using complex crosslinking agents, such as polyacrylamide (Jeong et al., 2020), ZnO nanoparticles (Gholamali & Yadollahi, 2020), and TiO₂ nanoparticles (Mahmoud et al., 2017) with a total remaining weight around 21, 30, and 60%, respectively. Accordingly, the formation of amide covalent bonds using the carbodiimide crosslinker chemistry between the carboxylic acid from the CMC and the primary amine functional groups from the SiO₂-NH₂ nanoparticles, represent a more efficient alternative for the fabrication of hydrogels by increasing the thermal stability up to 35%.

Figure 6. TGA and DTG curve of the hydrogels crosslinked with 0.5 g of SiO₂-NH₂ nanoparticles.

Source: own elaboration (2020)

Conclusions

This study reported the synthesis and amine-functionalization of SiO₂ nanoparticles for the incorporation in crosslinked CMC hydrogels via the carbodiimide crosslinker chemistry. The material composition and thermal stability were deeply evaluated and analyzed, aiming to establish the potential application of the crosslinked CMC-SiO₂ hydrogels in controlled drug release and delivery systems. The primary NH₂ groups grafted on the surface of the SiO₂ nanoparticles provided high affinity and strong interaction with the activated C=O groups from the carboxylic acid in the CMC structure. This allowed the formation of stable amide bonds, which promoted enhanced thermal stability when increasing the temperature, as was observed in the DTG curves. Moreover, the content of SiO₂-NH₂ nanoparticles played an important role in the thermal stability of the CMC hydrogels, decreasing the percentage of decomposition and reducing the number of thermal events. According to these results, the crosslinked CMC-SiO₂ hydrogels showed to be a promising material compared to similar reported in the literature with lower thermal efficiencies.

Additional future research work involves a profound determination of the physicochemical properties, including chemical stability, drug loading and release capacities, swelling percentage, and the influence of

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parameters such as pH, temperature, and enzyme content on the efficiency of the controlled drug release systems.

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References

- Abeer, M. M., Rewatkar, P., Qu, Z., Talekar, M., Kleitz, F., Schmid, R.,... Popat, A. (2020). Silica nanoparticles: A promising platform for enhanced oral delivery of macromolecules. *Journal of Controlled Release*, 326(April), 544–555. <https://doi.org/10.1016/j.jconrel.2020.07.021>
- Asere, T. G., Mincke, S., Folens, K., Vanden Bussche, F., Lapeire, L., Verbeken, K., ... Stevens, C. V. (2019). Dialdehyde carboxymethyl cellulose cross-linked chitosan for the recovery of palladium and platinum from aqueous solution. *Reactive and Functional Polymers*, 141(January), 145–154. <https://doi.org/10.1016/j.reactfunctpolym.2019.05.008>
- Asri Mohd Esa, Y., & Sapawe, N. (2020). Removal of methylene blue from aqueous solution using silica nanoparticle extracted from skewer coconut leaves. *Materials Today: Proceedings*, 31, 398–401. <https://doi.org/10.1016/j.matpr.2020.07.192>
- Gholamali, I., & Yadollahi, M. (2020). Doxorubicin-loaded carboxymethyl cellulose/Starch/ZnO nanocomposite hydrogel beads as an anticancer drug carrier agent. *International Journal of Biological Macromolecules*, 160, 724–735. <https://doi.org/10.1016/j.ijbiomac.2020.05.232>
- Giner-Casares, J. J., Henriksen-Lacey, M., Coronado-Puchau, M., & Liz-Marzán, L. M. (2016). Inorganic nanoparticles for biomedicine: Where materials scientists meet medical research. *Materials Today*, 19(1), 19–28. <https://doi.org/10.1016/j.mattod.2015.07.004>
- Javanbakht, S., & Shaabani, A. (2019). Carboxymethyl cellulose-based oral delivery systems. *International Journal of Biological Macromolecules*, 133, 21–29. <https://doi.org/10.1016/j.ijbiomac.2019.04.079>
- Jeong, D., Kim, C., Kim, Y., & Jung, S. (2020). Dual crosslinked carboxymethyl cellulose/polyacrylamide interpenetrating hydrogels with highly enhanced mechanical strength and superabsorbent properties. *European Polymer Journal*, 127(December 2019), 109586. <https://doi.org/10.1016/j.eurpolymj.2020.109586>
- Jiang, X., Yang, Z., Peng, Y., Han, B., Li, Z., Li, X., & Liu, W. (2016). Preparation, characterization and feasibility study of dialdehyde carboxymethyl cellulose as a novel crosslinking reagent. *Carbohydrate Polymers*, 137, 632–641. <https://doi.org/10.1016/j.carbpol.2015.10.078>
- Kadry, G. (2019). Comparison between gelatin/carboxymethyl cellulose and gelatin/carboxymethyl nanocellulose in tramadol drug loaded capsule. *Heliyon*, 5(9), e02404. <https://doi.org/10.1016/j.heliyon.2019.e02404>
- Kamel, S., El-Gendy, A. A., Hassan, M. A., El-Sakhawy, M., & Kelnar, I. (2020). Carboxymethyl cellulose-hydrogel embedded with modified magnetite nanoparticles and porous carbon: Effective environmental adsorbent. *Carbohydrate Polymers*, 242(April). <https://doi.org/10.1016/j.carbpol.2020.116402>
- Kanikireddy, V., Varaprasad, K., Jayaramudu, T., Karthikeyan, C., & Sadiku, R. (2020). Carboxymethyl cellulose-based materials for infection control and wound healing: A review. *International Journal of Biological Macromolecules*, 164, 963–975. <https://doi.org/10.1016/j.ijbiomac.2020.07.160>

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- Lee, K. I., Lin, J. W., Su, C. C., Fang, K. M., Yang, C. Y., Kuo, C. Y., ... Chen, Y. W. (2020). Silica nanoparticles induce caspase-dependent apoptosis through reactive oxygen species-activated endoplasmic reticulum stress pathway in neuronal cells. *Toxicology in Vitro*, 63(August 2019), 104739. <https://doi.org/10.1016/j.tiv.2019.104739>
- Lin, P., Liu, L., He, G., Zhang, T., Yang, M., Cai, J., ... Tao, S. (2020). Preparation and properties of carboxymethyl chitosan/oxidized hydroxyethyl cellulose hydrogel. *International Journal of Biological Macromolecules*, 162(November 2020), 1692–1698. <https://doi.org/10.1016/j.ijbiomac.2020.07.282>
- Mahmoodi, N. M., Khorramfar, S., & Najafi, F. (2011). Amine-functionalized silica nanoparticle: Preparation, characterization and anionic dye removal ability. *Desalination*, 279(1–3), 61–68. <https://doi.org/10.1016/j.desal.2011.05.059>
- Mahmoud, M. E., Abdou, A. E. H., Sobhy, M. E., & Fekry, N. A. (2017). Solid–solid crosslinking of carboxymethyl cellulose nanolayer on titanium oxide nanoparticles as a novel biocomposite for efficient removal of toxic heavy metals from water. *International Journal of Biological Macromolecules*, 105(December 2017), 1269–1278. <https://doi.org/10.1016/j.ijbiomac.2017.07.156>
- Mapkar, J. A., Iyer, G., & Coleman, M. R. (2009). Functionalization of carbon nanofibers with elastomeric block copolymer using carbodiimide chemistry. *Applied Surface Science*, 255(9), 4806–4813. <https://doi.org/10.1016/j.apsusc.2008.11.068>
- Pourrajab, R., Noghrehabadi, A., Hajidavalloo, E., & Behbahani, M. (2020). Investigation of thermal conductivity of a new hybrid nanofluids based on mesoporous silica modified with copper nanoparticles: Synthesis, characterization and experimental study. *Journal of Molecular Liquids*, 300(February 2020), 112337. <https://doi.org/10.1016/j.molliq.2019.112337>
- Rao, Z., Ge, H., Liu, L., Zhu, C., Min, L., Liu, M., ... Li, D. (2018). Carboxymethyl cellulose modified graphene oxide as pH-sensitive drug delivery system. *International Journal of Biological Macromolecules*, 107(PartA), 1184–1192. <https://doi.org/10.1016/j.ijbiomac.2017.09.096>
- Sepulveda, J., Villegas, C., Torres, A., Vargas, E., Rodriguez, F., Baltazar, S., ... Galotto, M. J. (2020). Effect of functionalized silica nanoparticles on the mass transfer process in active PLA nanocomposite films obtained by supercritical impregnation for sustainable food packaging. *Journal of Supercritical Fluids*, 161(July), 104844. <https://doi.org/10.1016/j.supflu.2020.104844>
- Shahbazi, M., Ahmadi, S. J., Seif, A., & Rajabzadeh, G. (2016). Carboxymethyl cellulose film modification through surface photo-crosslinking and chemical crosslinking for food packaging applications. *Food Hydrocolloids*, 61(December), 378–389. <https://doi.org/10.1016/j.foodhyd.2016.04.021>
- Tang, J., Li, Y., Song, Y., Wu, X., Yu, G., & Tam, K. C. (2020). Carbodiimide coupling versus click chemistry for nanoparticle surface functionalization: A comparative study for the encapsulation of sodium cholate by cellulose nanocrystals modified with β -cyclodextrin. *Carbohydrate Polymers*, 244(May), 116512. <https://doi.org/10.1016/j.carbpol.2020.116512>
- Zhang, C., Yang, X., Li, Y., Qiao, C., Wang, S., Wang, X., ... Li, T. (2020). Enhancement of a zwitterionic chitosan derivative on mechanical properties and antibacterial activity of carboxymethyl cellulose-based films. *International Journal of Biological Macromolecules*, 159(September), 1197–1205. <https://doi.org/10.1016/j.ijbiomac.2020.05.080>
- Zhang, Z., Zhu, Y., Dai, R., Zhang, Y., Wang, H., & Li, J. (2018). Enhanced photocytotoxicity induced by a platinum diimine complex employing amine-functionalized magnetite-silica nanocomposites as delivery vehicles. *Photodiagnosis and Photodynamic Therapy*, 23(June), 50–54. <https://doi.org/10.1016/j.pdpdt.2018.06.002>
- Zhong, Y., Wang, J., Yuan, Z., Wang, Y., Xi, Z., Li, L., ... Guo, X. (2019). A mussel-inspired carboxymethyl cellulose hydrogel with enhanced adhesiveness through enzymatic crosslinking. *Colloids and Surfaces B: Biointerfaces*, 179(December 2018), 462–469. <https://doi.org/10.1016/j.colsurfb.2019.03.044>

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Zhu, X., Bao, L., Wei, Y., Ma, J., & Kong, Y. (2016). Removal of toxic indigo blue with integrated biomaterials of sodium carboxymethyl cellulose and chitosan. *International Journal of Biological Macromolecules*, 91(October), 409–415. <https://doi.org/10.1016/j.ijbiomac.2016.05.097>