

Technological factors influencing on production of pharmaceutical-grade carboxymethyl cellulose (CMC) from cotton cellulose

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Received: 6 December 2023; Accepted for publication: 15 August 2024

Abstract. The effects of sodium hydroxide (NaOH) concentration, molar ratios of monochloroacetic acid (MCA) to anhydroglucose unit (AGU), molar ratios of NaOH to MCA, ethanol concentration, and volume on carboxymethyl cellulose (CMC) production were investigated. The results demonstrated that CMC with an average substitution degree of 0.9267 was obtained using 50 % (w/v) NaOH, a MCA/AGU molar ratio of 1.3, and a NaOH/MCA molar ratio of 3. The optimal washing process for achieving pharmaceutical-grade carboxymethyl cellulose involved a series of five washes with 60 mL of 80 % v/v ethanol, resulting in impurity residue consisting of sodium chloride (NaCl) and sodium glycolate (HNa) at 0.23 % and 0.19 %, respectively. This process represented the least amount of solvent required to attain pharmacopoeial standards for CMC purity, while also minimizing the number of washes needed to preserve the quality of the CMC product. These results offered a practical method for preparing high-purity CMC for use in the pharmaceutical industry.

Keywords: Carboxymethyl cellulose, cotton cellulose, pharmaceutical grade.

Classification numbers: 1.1.2, 1.4.2.

1. INTRODUCTION

Carboxymethyl cellulose (CMC) is one of the most important cellulose derivatives due to its excellent physicochemical properties and wide range of applications. In pharmaceutical formulations, CMC is commonly used as a binder, thickener, stabilizer, and emulsifier in tablets, capsules, creams, and gels because of its biocompatibility and water solubility [1]. CMC is usually utilized in the form of sodium carboxymethyl cellulose (Na-CMC), which exhibits superior solubility and storage stability.

CMC is synthesized through two main steps: alkalization and carboxymethylation. During alkalization, cellulose is treated with sodium hydroxide (NaOH) to produce alkaline cellulose, an intermediate with enhanced reactivity. This process disrupts the crystalline structure of cellulose and increases its accessibility for subsequent chemical modification [2, 3]. The alkalization of cellulose with NaOH is typically carried out at 35 °C for 1 h. The concentration of NaOH is a critical parameter because it significantly influences the degree of

substitution (DS), solubility, and viscosity of the resulting CMC. Previous studies have reported that higher NaOH concentrations generally increase the DS of CMC [4, 5].

Following alkalization, alkaline cellulose reacts with monochloroacetic acid (MCA) to introduce carboxymethyl groups onto the cellulose backbone. Carboxymethylation is typically carried out at 60–65 °C, and increasing the reaction temperature within this range has been shown to enhance the DS of CMC [6–8]. The molar ratio of MCA to anhydroglucose unit (AGU) is another important factor. Although increasing the MCA/AGU ratio initially improves DS, further increases often result in a decline due to side reactions between MCA and NaOH, which reduce the efficiency of substitution [6, 9]. Therefore, optimization of both the MCA/AGU and NaOH/MCA ratios is essential to maximize product quality and yield.

The choice of solvent also plays a crucial role in CMC synthesis. Ethanol and isopropanol are the solvents most commonly used for carboxymethylation. Although no study has conclusively established the superiority of one solvent over the other, many reports indicate that isopropanol generally produces CMC with higher DS values under comparable conditions [8, 10]. This effect is attributed to phase separation in the reaction medium, which enhances cellulose exposure to alkali while reducing side reactions between MCA and NaOH [11, 12]. In addition, isopropanol offers advantages for future industrial-scale production and economic feasibility.

The quality of the starting cellulose material strongly affects the properties of the final CMC product. Cotton is an attractive cellulose source in Viet Nam because it is inexpensive, readily available, and contains a high proportion of cellulose [13]. High-purity cotton cellulose contributes to a more consistent synthesis process and facilitates the production of CMC with desirable physicochemical properties. Several studies have demonstrated the successful synthesis of high-quality CMC from cotton-derived cellulose [14–16].

For pharmaceutical applications, achieving a suitable DS alone is insufficient. Pharmaceutical-grade CMC must also meet strict purity requirements. According to pharmacopeial standards, CMC should have a DS between 0.7 and 1.2 and a purity exceeding 99.5 % [1]. The major impurities generated during synthesis are sodium glycolate (HNa) and sodium chloride (NaCl), both of which originate from reaction by-products. For example, the European Pharmacopoeia specifies maximum limits of 0.25 % for NaCl and 0.4 % for HNa in sodium carboxymethyl cellulose [1]. Therefore, purification is a critical step in CMC production.

Purification is typically performed by washing the synthesized CMC with ethanol, in which CMC is insoluble while the impurities are soluble. Consequently, the ethanol concentration and washing volume can significantly affect impurity removal and final product purity [2,4,5]. Despite the importance of this step, limited information is available regarding the optimization of purification conditions for pharmaceutical-grade CMC production.

Therefore, the aim of this study was to synthesize pharmaceutical-grade CMC with a degree of substitution between 0.9 and 1.0 while meeting pharmacopeial requirements for impurity levels ($\%NaCl \leq 0.25\%$ and $\%HNa \leq 0.4\%$). To achieve this objective, the effects of NaOH concentration, MCA/AGU ratio, NaOH/MCA ratio, and the concentration and volume of ethanol used during purification were systematically investigated.

2. MATERIALS AND METHODS

2.1. Materials

Cotton sourced from Buon Don, Dak Lak (Viet Nam), with an average fiber length of approximately 20 mm and a moisture content of about 4 %, was utilized in this study. The cellulose content was found to be around 95 % by dry weight, leading to its classification as predominantly composed of cellulose. Subsequently, the cotton underwent a cleaning process, followed by pulverization, and was then dried at a temperature of 80 °C until a constant mass was achieved. Ultimately, the processed cotton was stored in moisture-absorbing containers. After treatment, the average length of the cotton fiber was around 1.5 mm, making it suitable for use in subsequent experiments.

In this study, sodium hydroxide (NaOH) 99.9 % (Xilong Scientific Co., Ltd, China), isopropanol (IPA) 99.7 % (Xilong Scientific Co., Ltd, China), monochloroacetic acid (MCA) 99.7 % (Acros Organics, America), glacial acetic acid 99.9 % (Xilong Scientific Co., Ltd, China), ethanol 96 % (Xilong Scientific Co., Ltd, China), silver nitrate (AgNO₃) 99 % (ThermoFisher Scientific, America), sodium chloride (NaCl) 99 % (Xilong Scientific Co., Ltd, China), hydrogen peroxide (H₂O₂) 30 % (Xilong Scientific Co., Ltd, China), potassium chromate (K₂CrO₄) 98.5 % (Merck & Co., Inc., Germany), hydrochloric acid (HCl) 36 % (Xilong Scientific Co., Ltd, China), sulfuric acid (H₂SO₄) 98 % (Merck & Co., Inc., Germany), glycolic acid 99 % (ThermoFisher Scientific, America), 2,7-dihydroxynaphthalene 99.9 % (Acros Organics, America), acetone 99 % (Xilong Scientific Co., Ltd, China) were used.

2.2. Method to investigate factors affecting the quality of CMC

Initially, a preliminary survey was conducted to determine the most suitable NaOH concentration by varying its concentration (i.e., 20 %, 25 %, 30 %, 40 %, 50 %, 60 % w/v) while maintaining MCA/AGU = 1.3 (mol/mol) and NaOH/MCA = 3 (mol/mol). Subsequently, the results from this survey were used to investigate the effect of different MCA/AGU ratios (i.e., 1, 1.1, 1.3, 1.5, mol/mol) on the synthesis of CMC. Next, the optimal NaOH/MCA molar ratio was determined by exploring the effect of different ratios (i.e., 2.5, 3, 3.5, 4) while taking into account the results from the previous two surveys. In the final step, CMC was subjected to washing with varying concentrations (70 %, 75 %, and 80 % v/v) of EtOH to determine the most efficient and cost-effective concentration for achieving maximum cleanliness. The survey experiments were conducted with three repetitions, and the data presented in the paper represent the average results of those experiments.

Three grams of cotton cellulose were introduced into 65 mL of isopropanol with continuous stirring for 30 minutes. Following this process, the mixture was slowly dripped with a NaOH solution, and further stirred for 1 hour at 37 °C. After this initial phase, the reaction flask received an MCA solution (MCA dissolved in IPA), and stirring continued for an additional 30 minutes. Subsequently, the temperature was raised to a range of 60-65 °C, allowing the carboxymethylation reaction to proceed for 90 minutes. After the reaction, neutralization was achieved using acetic acid. The resulting solution underwent filtration through a Buchner funnel to eliminate any solid residue. The obtained solid was subjected to agitation with EtOH multiple times until the absence of a white precipitate was confirmed, as assessed through testing with 0.1 N AgNO₃ solution. The final product was dried at 60 °C until a constant weight was achieved, followed by storage in a polyethylene bag at room temperature.

2.3. Methods for Quality Assessment of CMC

The determination of the CMC quality basically followed the guidelines provided by the American Society for Testing and Materials (ASTM) D1439-22 [17].

2.3.1. Determining the degree of substitution (DS)

The degree of substitution (DS) of carboxymethylcellulose (CMC) was determined by acidification and back-titration. Briefly, 1.0 g of CMC was dispersed in 20 mL of 96% ethanol, followed by the addition of 1.5 mL HNO₃. The mixture was stirred, heated to boiling for 5 min, and further stirred for 15 min. The precipitate was collected by filtration, washed with preheated 80% ethanol until acid-free, and dried at 105 °C for 3 h. The dried sample was weighed and transferred to a flask containing 100 mL water and 25 mL of 0.5 N NaOH. After complete dissolution, the mixture was boiled for 15–30 min. The excess NaOH was then titrated with 0.5 N HCl using phenolphthalein as the indicator. The DS value was calculated from the amount of alkali consumed by the carboxymethyl groups. The degree of substitution is calculated as follows:

$$A = \frac{BC-DE}{F} \quad (1)$$

$$G = \frac{0.162A}{1-0.0584A} \quad (2)$$

Where: A = milliequivalents of acid consumed per gram of sample; B = NaOH solution added, mL; C = normality of the HCl; D = HCl required for titration of excess NaOH, mL; E = normality of the HCl; F = acid carboxymethylcellulose used, g; G = degree of substitution; 162 = gram molecular mass of the anhydroglucose unit of cellulose, and 58.4 = net increase in molecular mass of anhydroglucose unit for each carboxymethyl group substituted.

2.3.2. Determining residues of sodium chloride (NaCl)

The NaCl residue in CMC was determined using Mohr's method. Briefly, 1.0 g of sample was dispersed in 23 mL water and 2 mL of 30% H₂O₂, then heated in a steam bath with occasional stirring until a nonviscous solution was obtained. After cooling, 2–3 drops of 5% K₂CrO₄ indicator were added. The solution was titrated with standardized 0.01 N AgNO₃ until a persistent brick-red color of Ag₂CrO₄ appeared. The titration was performed in triplicate, and the average value was used for calculation. The residues of NaCl are calculated as follows:

$$\%NaCl = H \times E \times 58.4 \quad (3)$$

where: H = normality of the standardized AgNO₃; E = AgNO₃ solution consumed, mL; 58.4 = gram molecular mass of sodium chloride NaCl.

2.3.3. Determining residues of sodium glycolate (HNa)

The glycolic acid content was determined according to the ASTM method using a calibration curve of absorbance versus glycolic acid concentration. Briefly, 0.5 g of sample was dissolved in 5 mL acetic acid and 5 mL water. Carboxymethyl cellulose was precipitated with 50 mL acetone and 1 g NaCl, then removed by filtration. The filtrate and washings were collected in a 100 mL volumetric flask and diluted to volume with acetone. A blank solution was prepared similarly without the sample. Aliquots (2 mL) of the sample and blank solutions were transferred into separate 25 mL volumetric flasks, followed by the addition of 20 mL of 2,7-dihydroxynaphthalene reagent. After heating in a water bath for 20 min, the solutions were

diluted to volume with H₂SO₄. Absorbance was measured at 540 nm against the blank, and the glycolic acid content was calculated from the calibration curve.

2.3.4. Calculation of CMC yield [9]

The yield of CMC was calculated by the gravimetric method. To calculate the yield, the net weight of dried CMC (in grams) was divided by dried weight of cellulose (in grams):

$$\text{Yield of CMC (\%)} = \frac{\text{Weight of dried CMC (g)}}{\text{Dried mass of cellulose (g)}} \times 100 \quad (4)$$

2.3.5. Determining the moisture content [17]

To determine the moisture content of the sample, approximately 1 gram of the sample was weighed to the nearest 0.001 gram in a tared and covered weighing bottle. The cover was removed, and the bottle was placed in an oven at 105 °C for 2 hours. After drying, the bottle was cooled in a desiccator, the cover was replaced, and the bottle was weighed. This drying and weighing process was repeated every 30 minutes until the mass loss did not exceed 5 milligrams in 30 minutes. The moisture content was then calculated by comparing the initial and final weights of the sample.

The percentage of moisture (M) is calculated as follows:

$$M = \left(\frac{A}{B}\right) \times 100 \quad (5)$$

Where: A = Mass loss from heating, g; B = Sample used, g.

3. RESULTS AND DISCUSSION

3.1. Investigating some factors affecting DS of CMC

3.1.1. Effect of NaOH concentration on DS of CMC

Figure 1 displays the effect of varying NaOH concentration on the DS of CMC, under conditions where the MCA/AGU ratio was 1.3, and the NaOH/MCA ratio was 3.

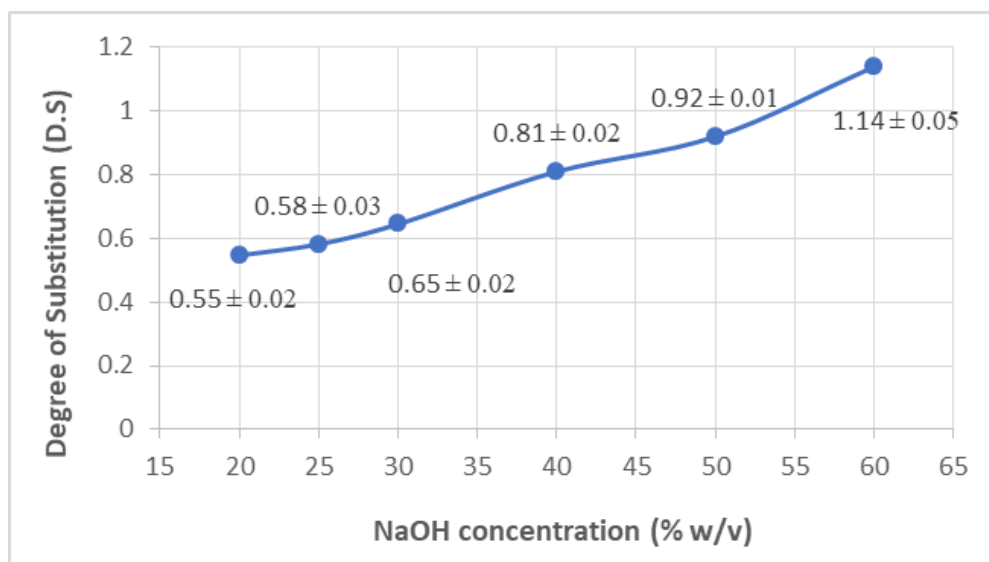


Figure 1. Changes in DS with different NaOH concentrations.

Upon examining the data table, it was evident that the DS values increased as the NaOH concentration increased from 20 % to 60 %, which was in accordance with previously published research [5, 6]. This was attributed to the increase in the concentration of hydroxide ions (OH⁻) in the reaction mixture. These OH⁻ ions served to break the glycosidic bonds between the glucose units in the cellulose molecule, making it more susceptible to the carboxymethylation reaction. Furthermore, another plausible explanation was derived from the observation that, at a constant NaOH/AGU ratio, an increase in NaOH concentration leads to a reduction in water content in the solution. Water served as the primary medium for side reactions between NaOH and MCA, therefore diminishing the water content resulted in a decreased occurrence of side reactions.

However, the main focus of this study was to synthesize CMC with a DS between 0.9 and 1. As a result, a 50 % NaOH concentration was chosen for the upcoming survey. It should be noted that preparing a 60 % NaOH solution was quite challenging due to the limited solubility of NaOH in water. Furthermore, purifying CMC products with a degree exceeding 1 proved to be difficult. This was resulted from the water absorption of high DS CMC during the ethanol-water washing step.

3.1.2. Effect of molar ratio MCA/AGU on DS of CMC

For the second investigation, our aim was to determine the optimal molar ratio of MCA to AGU. We employed a 50 % NaOH solution and a NaOH/MCA ratio of 3 (mol/mol). The results of this investigation are presented in Figure 2.

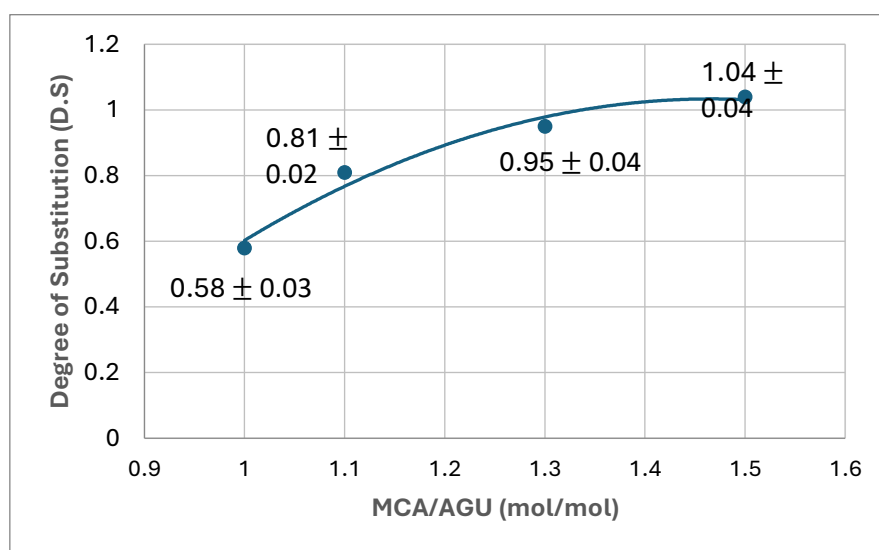


Figure 2. Changes in DS with different MCA/AGU molar ratios.

As the amount of MCA used in the reaction increased, the consequent DS of CMC also increased. This result was similar to published research [6]. This is attributed to the fact that an increase in MCA quantity resulted in more carboxymethyl groups being introduced onto the cellulose, thereby raising the degree of substitution in the resulting CMC product. However, contrary findings were presented in the study [8], in which the degree of substitution (DS) exhibited a continuous and pronounced decrease as the MCA/AGU ratio increased from 1 to 1.4. This discrepancy could be attributed to the divergent choice of reaction solvents. While this study chose anhydrous isopropanol (99.7 %) as the solvent, the study [8] utilized 80 % ethanol.

Solvents with higher water content provided favorable conditions for the occurrence of side reactions leading to the degradation of MCA, resulting in a diminishing DS with increasing MCA concentrations. In contrast, the current study employed anhydrous isopropanol, inducing a distinct phase separation when water was introduced. This stratification maximizes cellulose exposure to the etherification agent, enhancing substitution efficiency.

Based on the initial goal set out in the introduction and the difficulties in handling CMC with a DS > 1, the optimized molar ratio MCA/AGU was chosen as 1.3/1 (mol/mol).

3.1.3. Effect of NaOH/MCA molar ratio on DS of CMC

The third survey focused on examining the impact of the NaOH/MCA molar ratio. The outcomes of this investigation are shown in Figure 3.

Initially, as the molar ratio of NaOH/MCA was raised, there was a marked increase in DS, but then it started to decline gradually. This trend illuminated the fact that a lower ratio results in fewer hydroxide ions in the reaction solution, which in turn reduces the number of broken glycosidic bonds. However, if the ratio became too high, there was an excessive amount of hydroxide ions, which promoted the unwanted side effect of MCA hydrolysis, leading to a decrease in the effectiveness of the carboxymethylation reaction.

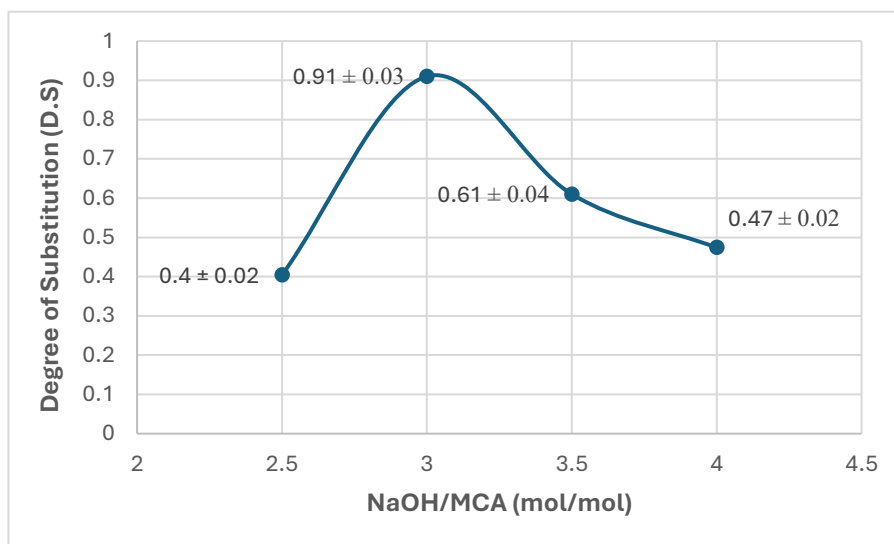


Figure 3. Changes in DS with different NaOH/MCA molar ratios.

3.2. Investigating the effect of washing solvent on CMC purity

3.2.1. Effect of ethanol concentration on CMC quantity

As previously indicated, we employed ethanol as the washing solvent. Table 1 displays the results of the investigation into the impact of varying ethanol concentrations on the quantity of the final product. All of the washed products had DS greater than 0.9 and were the products of a reaction that utilized 3.00 g of cellulose, 50 % NaOH, MCA/AGU ratio of 1.3 (mol/mol), and a NaOH/MCA ratio of 3 (mol/mol).

Under identical reaction conditions and equivalent starting material, the increase in ethanol concentration resulted in a higher yield of CMC. At the ethanol concentration of 80 % v/v, the highest yield of carboxymethyl cellulose (CMC) was obtained, specifically at 136.1 %.

Table 1. Quantity of CMC with various concentrations of ethanol.

CMC's yield	DS	%EtOH (v/v)	Washing times	Volume/time (mL)
98.1 % (± 0.52 %)	0.93 (± 0.02)	70	3	100
108.0 % (± 0.44 %)	0.91 (± 0.03)	75	3	100
136.1 % (± 0.48 %)	0.95 (± 0.01)	80	3	100

In the course of washing the product, it was observed that when using ethanol concentrations of 70 % and 75 %, the filtrate became turbid, indicating that some of the CMC had dissolved into the water during the washing process. This result suggested that CMC has absorbed some of the water in the washing solvent, leading to product loss.

3.2.2. Effect of washing times and washing volume on CMC purity

The primary impurities analyzed in the residues were sodium chloride and sodium glycolate. The level of sodium chloride residue was determined using Mohr's titration, whereas the residue of sodium glycolate was evaluated using the calibration curve method recommended by ASTM [17]. A calibration curve was established by correlating the absorbance values with glycolic acid concentration, as demonstrated in Figure 4.

Using the methods mentioned for analyzing residues, we examined the impurity residues based on the washing time and the volume of the washing solvent. The results of these investigations are illustrated in Table 2.

The results showed that using 80 % (v/v) ethanol for washing five times, each time with 60 mL, yielded NaCl and HNa residues of 0.23 % and 0.19 %, respectively. According to the European Pharmacopoeia standards, NaCl residue in CMC must be below 0.25 % and HNa must be below 0.4 % to meet the specifications [1]. Therefore, using 80 % (v/v) ethanol for washing the product five times, each time with 60 mL, was considered an appropriate washing method in this study.

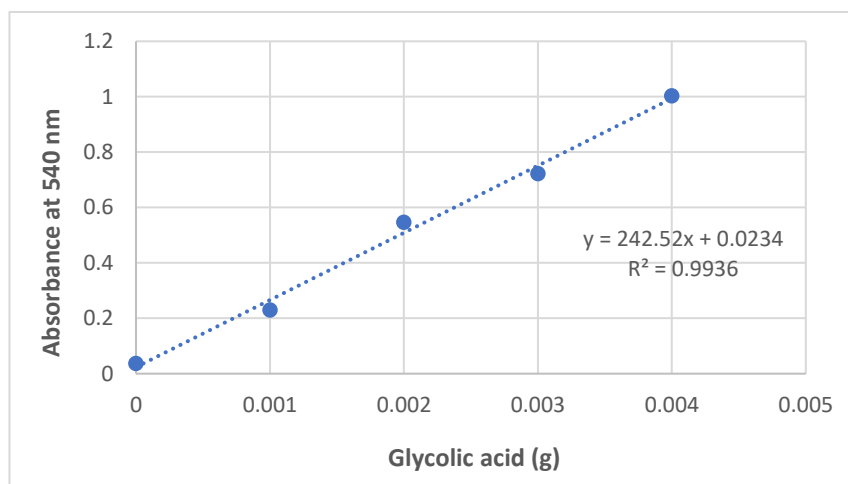


Figure 4. Calibration curve for colorimetric determination of glycolic acid with 2,7-dihydroxy naphthalene reagent.

Table 2. Impurity residues in CMC after multiple washes.

No.	%EtOH (v/v)	Washing times	Volume/time (mL)	%NaCl	%HNa
1	80	3	100	5.11 % (± 0.05 %)	4.62 % (± 0.03 %)
2	80	4	100	2.03 % (± 0.02 %)	1.5 % (± 0.03 %)
3	80	5	100	0.62 % (± 0.01 %)	0.41 % (± 0.03 %)
4	80	5	50	0.97 % (± 0.03 %)	0.45 % (± 0.03 %)
5	80	6	50	0.25 % (± 0.02 %)	0.23 % (± 0.02 %)
6	80	5	60	0.23 % (± 0.02 %)	0.19 % (± 0.03 %)

Moreover, in experiments 3 and 4, despite reducing the solvent volume used for each wash by half, there was no significant difference in the purity of the product. This indicated that the number of washes played a more significant role in washing performance compared to the volume of the solvent used. However, it was also important to note that excessive washing was not beneficial, as demonstrated in experiments 5 and 6. Despite experiment 6 utilizing a smaller washing volume compared to experiment 5, the resulting products still exhibited higher quality and met the required purity standards outlined in the pharmacopoeia.

Compared to the CMC quality reported in the study [18], it is worthy to note that the pH of both resulting CMC solutions remained within the neutral range, and all impurities were below 0.5 %. However, the DS of the CMC obtained in this study appeared to be relatively higher and met the requirements specified in the European Pharmacopoeia 2005.

4. CONCLUSIONS

The synthesis of CMC, with its degree of substitution and purity, conformed to the 2005 European pharmacopoeial standards. The reaction conditions included a NaOH concentration of 50 %, an MCA/AGU ratio of 1.3 (mol/mol), and a NaOH/MCA ratio of 3 (mol/mol), resulting in a degree of substitution in the range of 0.91-0.95. The CMC produced was spongy, and upon dissolution, the cellulose fibers were no longer visible, having an ivory-white color and a neutral pH of 7.

Ethanol with a concentration of 80 % (v/v) is a suitable solvent for washing CMC with a DS greater than 0.9, as it minimizes the amount of CMC lost due to water solubility. However, the effectiveness of the washing process carried out by the experimenter also played a vital role in limiting the CMC dissolution in water.

To achieve the required purity level of CMC, with a CMC's yield of 136.1 % and 80 % ethanol as the washing solvent, a minimum of 5 washes, each with 60 mL, is necessary. This implies that the minimum solvent volume required is 75 times the weight of the product. However, the number of washes has a more significant impact than the volume of solvent in achieving the desired purity.

CRedit authorship contribution statement. Nguyen Thu Tra: Experimentation, Writing - original draft. Nguyen Thi Viet Thanh: Supervision, Writing - review editing. Ta Hong Duc: Supervision, Writing - review editing.

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

REFERENCES

1. Rowe R. C., Sheskey P. J., Owen S. C. – Handbook of pharmaceutical excipients, 5th edn, Pharmaceutical Press, London (2005).
2. Yeasmin Mst. S., Mondal Md. I. H. – Synthesis of highly substituted carboxymethyl cellulose depending on cellulose particle size. *Int. J. Biol. Macromol.*, **80** (2015) 725–731. <https://doi.org/10.1016/j.ijbiomac.2015.07.040>.
3. Ciolacu D., Popa V. I. – Structural changes of cellulose determined by dissolution in aqueous alkali solution. *Cellul. Chem. Technol.*, **39** (2005) 179–188.
4. Shui T., Feng S., Chen G., et al. – Synthesis of sodium carboxymethyl cellulose using bleached crude cellulose fractionated from cornstalk. *Biomass Bioenergy*, **105** (2017) 51–58. <https://doi.org/10.1016/j.biombioe.2017.06.016>.
5. Panchan N., Wattanapan P., Sungsinchai S., et al. – Optimization of synthesis conditions for carboxymethyl cellulose from pineapple leaf waste using microwave-assisted heating and its application as a food thickener. *BioResources*, **16** (2021) 7684–7701. <https://doi.org/10.15376/16.4.7684-7701>.
6. Jia F., Liu H., Zhang G. – Preparation of carboxymethyl cellulose from corncob. *Procedia Environ. Sci.*, **31** (2016) 98–102. <https://doi.org/10.1016/j.proenv.2016.02.013>.
7. Celikçi N., Ziba C. A., Dolaz M. – Synthesis and characterization of carboxymethyl cellulose (CMC) from different waste sources containing cellulose and investigation of its use in the construction industry. *Cellul. Chem. Technol.*, **56** (2021) 55–68. <https://doi.org/10.35812/cellulosechemtechnol.2022.56.05>.
8. Yanli W., Wen Yuan G., Xia L. – Carboxymethyl Chinese yam starch: synthesis, characterization, and influence of reaction parameters. *Carbohydr. Res.*, **344** (2009) 1764–1769. <https://doi.org/10.1016/j.carres.2009.06.014>.
9. Nguyen T. D. P., Le N. T., Vu T. M., et al. – Synthesis and characterization of carboxymethyl cellulose with high degree substitution from Vietnamese pineapple leaf waste. *Vietnam J. Sci. Technol. Eng.*, **64** (2022) 13–18. [https://doi.org/10.31276/vjste.64\(3\).13-18](https://doi.org/10.31276/vjste.64(3).13-18).
10. Singh R. K., Singh A. K. – Optimization of reaction conditions for preparing carboxymethyl cellulose from corn cobic agricultural waste. *Waste Biomass Valorization*, **4** (2013) 129–137. <https://doi.org/10.1007/s12649-012-9123-9>.
11. Yokota H. – The mechanism of cellulose alkalization in the isopropyl alcohol-water-sodium hydroxide-cellulose system. *J. Appl. Polym. Sci.*, **30** (1985) 263–277. <https://doi.org/10.1002/app.1985.070300121>.
12. Stigsson V., Kloow G., Germgård U. – The influence of the solvent system used during manufacturing of CMC. *Cellulose*, **13** (2006) 705–712. <https://doi.org/10.1007/s10570-006-9083-y>.
13. Gordon S., Hsieh Y.-L. – Cotton: Science and technology, Woodhead Publishing Limited, United Kingdom (2007). <https://doi.org/10.1533/9781845692483>.
14. Haleem N., Arshad M., Shahid M., Tahir M. A. – Synthesis of carboxymethyl cellulose from waste of cotton ginning industry. *Carbohydr. Polym.*, **113** (2014) 249–255. <https://doi.org/10.1016/j.carbpol.2014.07.023>.
15. Rahaman Md. S., Nahar S. S., Islam J. M. M., et al. – Utilization of waste textile cotton by synthesizing sodium carboxymethyl cellulose: an approach to minimize textile solid waste. *Adv. Polym. Technol.*, **2022** (2022) 1–10. <https://doi.org/10.1155/2022/4255409>.
16. Abdullaevich Y. S., Ergashovich Y. K., Abdukhalilovich S. A., Shavkat o'g'li G. I. – Synthesis and characterization of sodium-carboxymethylcellulose from cotton, powder, microcrystalline and nanocellulose. *Polym. Eng. Sci.*, **62** (2021) 677–686. <https://doi.org/10.1002/pen.25874>.
17. ASTM D1439-22 – Standard test methods for sodium carboxymethylcellulose, ASTM International (2022). <https://doi.org/10.1520/d1439-22>.
18. Yuldoshov S., Sarymsakov K. – Purified carboxymethyl cellulose for the pharmaceutical industry. *Int. J. Adv. Sci. Technol.*, **29** (2020) 4733–4737.