

# Synthesis and Characterization of Hybrid Alginate/Cellulose Aerogels as Drug Delivery Carrier

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## ABSTRACT

Technology of material development on drug delivery system has expanded vastly nowadays. The potential of alginate and carboxymethyl cellulose (CMC) as drug delivery carrier is presented. The alginate and CMC was prepared as hybrid hydrogels via sol-gel method and dried by supercritical CO<sub>2</sub> and at ambient conditions. Their mechanical strength was physically observed by their shrinkage percentage. Different concentration of alginate and CMC were synthesized to determine the effect of material variation composition on the physical and chemical characteristics. Physical and chemical properties of the hybrid aerogels were investigated by FTIR and TGA analysis. Results demonstrated that drying the hydrogels by supercritical CO<sub>2</sub> produced alginate/CMC aerogels with smaller shrinkage percentage i.e. 12.5% in comparison to ambient drying that extremely shrank the hydrogel as high as 45.4%. for 3 wt% alginate/1 wt% CMC. This work suggests that the hybrid alginate/CMC aerogels dried by supercritical CO<sub>2</sub> has a great potential to be applied as drug delivery carrier due to its mechanical strength and good thermal stability at high temperature.

**Keywords:** Sodium alginate (Na-Alg), supercritical CO<sub>2</sub>, aerogels, carboxymethyl cellulose (CMC), drug delivery carrier

## 1. INTRODUCTION

Aerogel is an extraordinary class of porous solids with complex interconnectivity and branched shape of several nanometers. It may be synthesized in different designs, colors, and structure, ranging from monolithic to nanoparticles. Aerogels are composed of 99.8% of air that makes the substance has a nearly invisible look [1]. In principle, aerogels are made via a sol-gel method that produce wet gels comprises of pores filled-liquids (commonly alcohol). The liquid in the wet gels is then extracted by supercritical fluids, leaving the pores of the gels filled with air and producing a solid porous structure [1]. Numerous biopolymers have been studied to fabricate as the most suitable materials for drugs and delivery applications such as lignin, starch, pectin, cellulose and alginate. Recently, hybrid biopolymer aerogels such as starch, pectin and κ-carrageenan have gained interest for multiple applications in life science [2][3][4]. The method includes mixing with a second component and crosslinking in presence of crosslinker agent.

Over a decade, alginate has been considered as an attractive polysaccharide for aerogels-based materials in wide range of applications especially as for drug delivery carrier [5], [6] as it is environmentally friendly, cheap and has been regarded as safe for oral administration [7]. Alginate is naturally and abundantly derived from brown seaweed. This biopolymer is composed of straight, unbranched

polysaccharides with acid debris of 1,4-linked-β-D-mannuronic acid and α-L-gluronic acid leftover. It is one of the most used biopolymers used in the development of new materials in delivery systems, due to its interesting properties such as biodegradability, biocompatibility, simple shape, and strength to form gels simply in the presence of metal cations [8].

Cellulose is the most abundant, economical and easily accessible carbohydrate polymer which normally can be extracted from plants. This biopolymer has been extensively studied for drugs delivery and biomedical applications as drugs carrier or coating materials because of its low toxicity, biodegradability, low cost and stability [9][10]. Sodium carboxymethyl cellulose (CMC) is a water soluble ionic cellulose ether derivate from carboxymethylation of the hydroxyl of cellulose backbone [11]. CMC is considered as affordable, environmentally friendly, and could lessen the possibility for toxicity when they being used as coating substances. However, pure CMC without any co-materials has showed poor stability and mechanical strength due to its original structure. Therefore, it is anticipated that the addition of one or two other biopolymers to the CMC is anticipated may enhance the carrier or storage characteristics of the aerogels in drug delivery system (DDS). Such aerogels made from a blend of more than one biopolymer are called hybrid aerogels. The interesting properties of alginate and cellulose encourage the development of new carrier for drug delivery system.

This work presents a synthesis of hybrid alginate/cellulose aerogels dried by supercritical CO<sub>2</sub> as extracting solvent for drug delivery system are presented. Supercritical drying of aerogels using CO<sub>2</sub> at its above critical pressure and temperature has been accepted by scientists as the most reliable technique to produce highly porous solid that could retain the original size of the gel without collapsing the three-dimensional structure. At supercritical condition, CO<sub>2</sub> and liquids (commonly alcohol i.e. ethanol) in the gel are miscible. This behavior of the drying could minimize the force on the pores, thus reducing the gel ruptures [12]. In this work, hybrid alginate/cellulose aerogels were synthesized via sol-gel method and dried by supercritical CO<sub>2</sub> and air drying at ambient conditions. Effect of different composition of alginate and CMC were studied and their physical and chemical properties were investigated.

## 2. METHODOLOGY

Alginic acid sodium salt from brown algae and glucono- $\delta$ -lactone (GDL) were purchased from Sigma Aldrich. Calcium carbonate (CaCO<sub>3</sub>) Bendosen AR and denatured ethanol HMBG were purchased from local supplier, meanwhile carboxymethyl cellulose (CMC) were supplied by Waris Nove Sdn Bhd.

### 2.1 Preparation of hybrid alginate/CMC alcogels

Different mixture concentration of alginate and CMC hydrogels were prepared via an internal gelation process. A measured weight of sodium alginate and CMC were dissolved in distilled water separately and stirred vigorously before were combined to obtained final hybrid solution. Later, 2 wt% calcium carbonate (CaCO<sub>3</sub>) was added to the hybrid alginate/CMC solution. The ion Ca<sup>2+</sup> divalent cations from CaCO<sub>3</sub> acts as crosslinker to form alginate gel. To permit the solution to turn into a gel, 2 wt% of glucono- $\delta$ -lactone (GDL) was added to free the Ca<sup>2+</sup> and thus decrease the pH of the solution. The complete hybrid mixture was poured into the mold, then was covered with parafilm to avoid contamination and was kept in refrigerator for 18h at temperature 4°C to completely form the hydrogel [13]. Prior to the supercritical drying, water content in the gels need to be replaced with alcohol. This is because the presence of water during the supercritical extraction can lead to the shrinkage of the gels. Therefore, the hybrid (alginate/CMC) hydrogels was sequentially submerged in ethanol-water mixture ranging from 30, 50, 70 and 90% v/v and two times using absolute ethanol to enhance the removal of water from the hydrogels. At this point, the gels are called as alcogels and ready for drying process.

## 2.2 Drying of alcogels

### 2.2.1 Supercritical drying of alcogels

Drying of the synthesized hybrid alginate/CMC alcogels was performed using supercritical CO<sub>2</sub> at 120±5bar and 40°C. At first, the alcogels were placed in drying compartment and the temperature was set to 40°C. Once the desired temperature achieved, CO<sub>2</sub> was pressurized into the high-pressure column at a rate of 4 bar/min until reaching the desired pressure [4]. A repeated circular flow of CO<sub>2</sub> started for about 5h with collection of ethanol in every 1h of the extraction time. After completed the 5h, the supercritical CO<sub>2</sub> was slowly depressurized at a rate of 2 bar/min to avoid sudden shrinkage and can caused gels ruptured. The gels produced from the supercritical drying is called as aerogels. For each combination of alginate and CMC formulation, the drying process was conducted in triplicate.

### 2.2.2 Air drying of alcogels

Alcogels of hybrid alginate/CMC were placed on a petri dish and covered with aluminum foil for air drying to take place. They were left for air dry for 24h at room temperature. The weight of the alcogels were measured until a constant weight was obtained when it was assumed all the liquid has been vaporized from the gels to produced xerogels. The drying of samples was replicated three times for each parameter of the formulation of hybrid alginate/CMC.

## 2.3 Characterization analysis

Textural properties of the hybrid aerogels were characterized by scanning electron microscopy (SEM) analysis using JEOL JSM 820 model Bruker Quantax 2000 with magnification at high resolution images at voltage of 2-4kV. The samples were splattered-coated with a gold layer. The synthesized hybrid aerogels were qualitatively characterized by FTIR (Bruker Platinum-ATR) equipped with software of OPUS Optik GmbH in the range from 400 to 4400 cm<sup>-1</sup> of wavelength. Thermal gravimetric analysis (TGA) was used to determine the thermal characteristics of the hybrid aerogels were carried out from 20 to 600 °C at rate of 10°C/min using a TGA Mettler Toledo SAE system.

## 3. RESULTS AND DISCUSSION

### 3.1 Effect of drying process on hybrid alginate/CMC aerogels

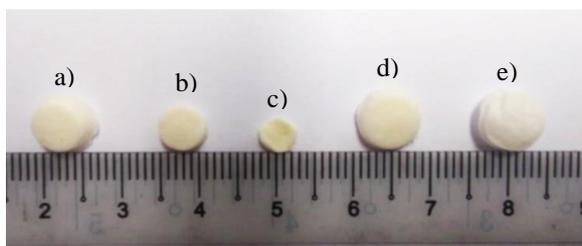
From Table 1, it can be seen that the shrinkage of the hybrid alginate/CMC dried at ambient condition resulted to the highest percentage in comparison to the gel shrink dried by supercritical CO<sub>2</sub>. The unique properties of CO<sub>2</sub> that has near-zero surface tension at supercritical condition reduce

the force acting on the mesopores of the gel. As a result, the shrinkage of the gels is minimized. On the other hand, for drying at ambient pressure, solvent evaporates and cause the liquid-vapor phase present on the structure of the gel. This situation resulted to the decreases the radius of curvature of liquid-vapor interfaces, and has exerted pressure on the gel structure [14].

**Table 1:** Shrinkage percentage of hybrid alginate/CMC dried by supercritical CO<sub>2</sub> and at ambient condition.

Alginate/CMC concentration (wt%)	Volume shrinkage (%)	
	Supercritical CO <sub>2</sub>	Ambient Drying
1/1	20.3	40.5
1/2	15.5	18.1
1/3	60.3	78
2/1	18.4	36.7
3/1	12.5	45.4

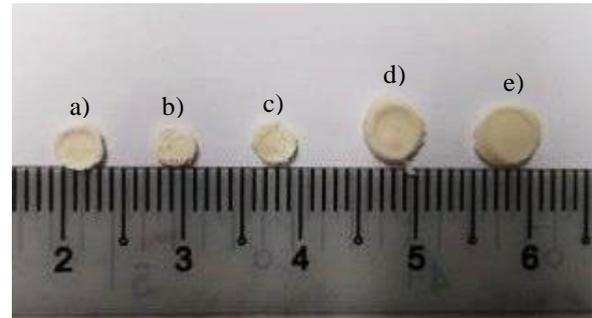
However, among all the aerogels dried by supercritical CO<sub>2</sub>, the variation of the aerogel's shrinkage was dependent on the composition of the alginate and CMC. This can be seen from the Figure 3 that showed the dried hybrid alginate/CMC aerogels at different alginate/CMC concentration. Increase the composition of CMC from 1 to 3 wt% with constant 1 wt% alginate caused largest shrinkage of the aerogels. From Table 1, the 1 wt% alginate+3 wt% CMC aerogels displayed as the largest shrinkage i.e. 60.3% in comparison to the aerogels composed of 2 wt% alginate and 1 wt% CMC. On the other hand, the 3 wt% alginate+1 wt% CMC that has higher content of alginate showed a lower shrinkage in comparison to other composition of alginate/CMC. This indicates that higher concentration of alginate makes the aerogels more stable and compact. Veronovski et al. (2012) also demonstrated that when the alginate concentration was increased, the gels appeared to be compact due to more cross-linked formed during the gelation.



**Figure 1:** Supercritical drying of blank hybrid alginate/ cellulose aerogel: a) 1wt%alginate+1wt% CMC, b) 1wt % alginate+2wt% CMC, c) 1wt % alginate+3wt% CMC, d) 2wt % alginate+1wt % CMC, e) 3wt % alginate+1wt % CMC.

On the other hand, when the alcohogels were dried at ambient pressure (Figure 2), gels with 1 wt% alginate exhibited as the most shrank product in comparison to the gel that composed of 2 and 3 wt% alginate content. In this case, it is observed that the increase of CMC

concentration with alginate less than 1wt% resulted to poor mechanical strength of the gel.

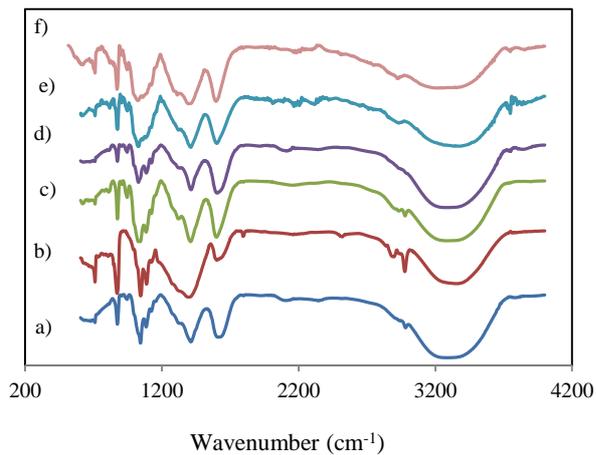


**Figure 2:** Air drying of blank hybrid alginate/ cellulose aerogel: a) 1wt % alginate+1wt % CMC, b) 1wt % alginate+2wt % CMC, c) 1wt % alginate+3wt % CMC, d) 2wt % alginate+1wt % CMC, e) 3wt % alginate+1wt % CMC.

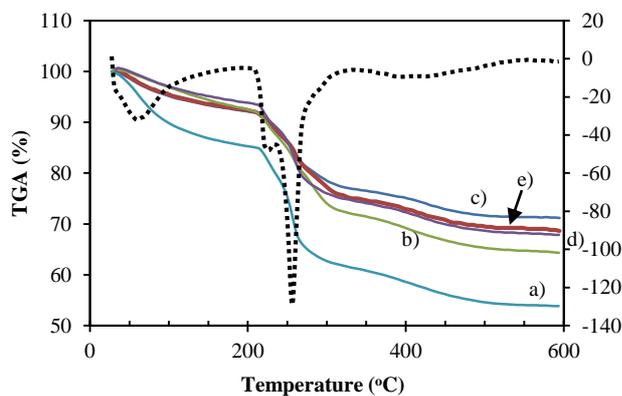
### 3.2 Physical and chemical characteristics

FTIR analysis was used in this experiment to study the component present in the hybrid alginate/CMC aerogel and to understand the behavior as well as their interaction if present. As shown in Figure 3, the absorption peaks of the alginate correspond to the similar band of the CMC mainly at 3400 cm<sup>-1</sup>, 1600 cm<sup>-1</sup> and 1400 cm<sup>-1</sup>. The raw CMC exhibited a broad and strong absorption at ~3368 cm<sup>-1</sup> wavelengths, that corresponds to the -OH bonding. This peak was also appeared in the hybrid aerogels at the similar absorption band. However, the most broad and intense peak of -OH at 3310 showed in the 1 wt% alginate/1 wt% CMC indicating the enhanced hydrogen interaction between alginate and CMC. In addition, it also may due to more water present in the gel that probably was not properly removed during the solvent exchange with ethanol. The properties of CMC that could retain high water [15] can be the cause that the shrinkage of the 1 wt% alginate/1 wt% CMC and justify the gel was more damaged during the drying.

Comparing the spectra between the raw CMC and the synthesized hybrid aerogels, it can be seen that most of the significant absorption bands of the raw CMC were displayed, indicating the present of CMC compounds. The similar characteristics of 3 wt% alginate/1 wt% CMC with the raw CMC indicating possibly the alginate at higher than 2 wt% has poor chemical interaction with CMC. Several other characteristics absorption bands also observed such as at 2188 cm<sup>-1</sup> (C≡C stretch), 1602.75 cm<sup>-1</sup> (C=C stretch), 1403.47 cm<sup>-1</sup> (-C-H stretch), 914.51 cm<sup>-1</sup> (=C-H stretch), 1015.97 cm<sup>-1</sup> (C-O stretch), and 872.62 cm<sup>-1</sup> (=C-H stretch).



**Figure 3:** FTIR spectra of hybrid alginate/ cellulose aerogels: a) 1 wt% alginate+1 wt% CMC, b) 1 wt% alginate+2 wt% CMC, c) 1 wt% alginate+3 wt% CMC, d) 2 wt%alginate+1 wt% CMC, e) 3 wt% alginate+1 wt% CMC, f) raw CMC.

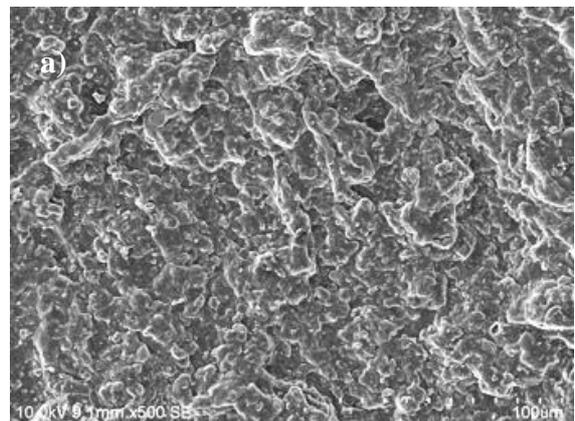


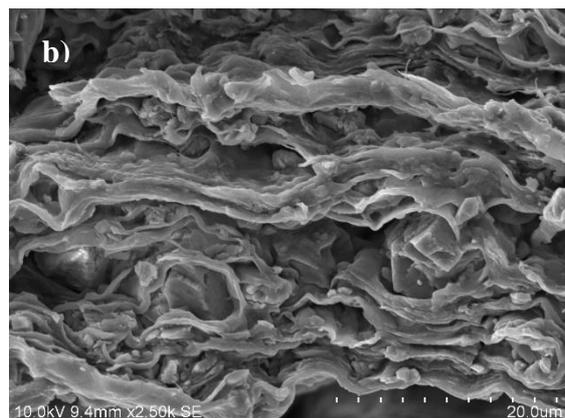
**Figure 4:** TGA thermogram of hybrid alginate/CMC aerogels: a) 3 wt% alginate+1 wt% CMC, b) 1 wt% alginate+3 wt% CMC, c) 1 wt% alginate+1 wt% CMC, d) 2 wt%alginate+1 wt% CMC, e) 1 wt% alginate+2 wt% CMC.

Thermal stability of the hybrid alginate/CMC aerogels was characterized by TGA analysis. The analysis was carried out at a heating rate of 10 °C/ min and temperature range of 20 to 600 °C. Figure 4 shows the TGA thermogram hybrid alginate/CMC aerogels formed using supercritical drying. It is observed that for 1 wt% alginate+1 wt% CMC, the thermal degradation of blank hybrid alginate/ cellulose aerogel starts at temperature interval of 30.55 °C to 125.15 °C, due to the loss of components such as water, low molecular weight solvents, or gas desorption [16]. A sharp reduction from 210 to 280 could be attributed to the oxidation of hydroxyl group (-OH) from alginate and CMC compounds. Furthermore, as temperature increased from 300 to 540 °C onset of thermal (inert gas) or thermo-

oxidative (certain content of O<sub>2</sub>) decomposition and carbonization of hydrocarbonated compounds occurred by pyrolysis that has no volatiles formation related. All the hybrid alginate/CMC aerogels exhibited a similar pattern of their thermal stability from 100 until 500 °C, which corresponds to the loss of water, hydroxyl group and decomposition of carboxyl group [17] towards the end of the analysis. However, the 3 wt% alginate/1 wt% CMC lose ~55% of their weight when temperature reached 600 °C whilst the weight loss of other concentration blends of alginate/CMC was in the range of 75-65%. This probably indicates that the alginate/CMC aerogels containing higher than 2 wt% of alginate might loses more weight by pyrolysis than CMC. The decomposition temperature of the hybrid alginate/CMC aerogels was found approximately increased in comparison to the blank alginate aerogels (i.e. ~250 °C) which ranging from 257 to 260 °C. The present of phase interaction between the both biopolymers and had improved the hybrid compounds thermal stability.

The textural properties of the hybrid 3 wt% alginate/ 1 wt% CMC aerogels at magnification of 10k is presented in Figure 5. As it can be seen in Figure 5a, the surface of the aerogels appears as compact and show small part of cavities. The cavities were maybe derived from the CMC dispersion that possibly occur during the mixing and gelation process making hydrogels. However, the porous structure of the alginate is not clearly observed, which is could be due to deposition of CMC on the mesopores of the alginate structure. On the cross-sectional view (Figure 5b), the layers structure are results from the crosslinking of the alginate biopolymer during the gelation. The ununiform layers maybe were disrupted due to the presence of CMC that also participated in the crosslinking process.





**Figure 5:** SEM image of textural of hybrid alginate/CMC aerogels dried by supercritical CO<sub>2</sub>; 3 wt% alginate/1 wt% CMC, a) surface view, b) cross-sectional view.

#### 4. CONCLUSION

Hybrid alginate/CMC aerogels at different concentration were synthesized and dried by supercritical CO<sub>2</sub> and at ambient pressure. Results demonstrated that increasing the alginate and CMC content decreased thermal stability of the hybrid aerogels when the temperature was higher than 200 °C. Higher mechanical strength of hybrid alginate/CMC aerogels dried by supercritical CO<sub>2</sub> were found in comparison to the gels dried at ambient condition making it as more promising to be applied as drugs carrier compared to the xerogels that dried at ambient pressure. The synthesis and characterization of hybrid alginate/cellulose aerogels could embark as the most promising candidate for drug delivery system and biomedical applications.

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