Synthesis and Characterization of β-Cylodextrin/Alginate Aerogel Dried by Ambient Drying

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Abstract— Aerogel is an attractive candidate for the drug delivery system in order to increase dissolved compounds solubility because of its excellent features with large surface area and high pore volume. These properties can only be obtained when the materials are dried by supercritical CO_2 ($SCCO_2$) to remove liquids present in solid pores. However, this method is so power-intensive and dangerous that it is difficult to practice and sell. Therefore it is very important to synthesize aerogels at a reasonable cost using an ambient pressure drying technique. Even though aerogels have a comparatively elevated compression strength, the structural power of aerogels is not great, because it is very brittle owing to its very small tensile strength and because of the quantity of water in its framework of 99%, they break readily when the stress and heavy load pressure applied to it. The aim of this work were to determine the suitable ratio for the formation of aerogel and to study the morphology and properties of β-cyclodextrin (β-CD)/alginate aerogel. Percentage of shrinkage level for aerogel decrease as the amount of B-cyclodextrin increase. β-CD mixed with alginate to form aerogels enhanced the thermal stability and the rate of decomposition. The application of β-cyclodextrin results in more stable aerogel decomposition about 270 to 290^{o}C for each sample except B1 and B2. The surface area of aerogel increase when β-CD introduced to sodium alginate at first but the surface area suddenly decrease when the amount of β-CD increase which also give a results to low porous structure of aerogel. Lastly, the pore volume of each sample increase as the amount of β-CD increase.

Keywords— drying, alginate, aerogels, β-cyclodextrin

I. INTRODUCTION

Throughout recent years, biomaterials have been commonly used for continuous delivery systems to enhance drug safety, effectiveness and consumer enforcement. The efficacy of the drug molecules can be significantly increased by controlling their release and distribution within the body. According to [1] water solubility and dissolution rate are two critical factors that affect the medication process formulation and development and limit their therapeutic applications.

Among biomaterials, aerogels have gained a lot of attention in the field of pharmaceuticals. Due to its low density, high specific surface area, high porosity and other outstanding characteristics, aerogel has a broad variety of applications in catalysts, adsorbents, thermal or noise insulation material, drug carriers and other materials [2]. Aerogel has attracted more and more attention as a drug carrier. However, the two most important factors for drug carriers in the pharmaceutical industry are biocompatibility and biodegradability [3].

In the past research in 1995, drug delivery system was prepared with hydrophilic and hydrophobic silica aerogels. The appropriate aerogels were balanced by drug solution adsorption, then filtered and dried as drug carrier to make loaded aerogels. Although silica aerogels have high particular surfaces and excellent biocompatibility, they are small in pharmaceutical applications due to bad biodegradability. To fix these issues, aerogels based on polysaccharides were first suggested for drug carriers in 1995 [4]. Due to its low toxicity, reproduction and good biological performance, aerogel polysaccharides, such as sodium alginate [5] and chitosan [6] are used as a drug carrier.

An alginate is described as a natural polysaccharide biopolymer extracted from brown algae. It includes α-L-guluronic acid and β-D-mannuronic acid (M) residues that are linearly linked to 1,4-glycosidic connection [7]. It is used as a gelling agent, a stabilizer for colloids and a suspender. In various fields such as biomedical, pharmaceutical, absorption due to biodegradable, biocompatible, non-toxic, low cost and stable, natural biopolymer has been widely used. Alginate aerogel characterized by the combination of unique aerogel characteristics and particularly high surface polysaccharides, open porosity, good compatibility and biodegradable [8].

Aerogel is a synthetic ultra-light porous material produced from the gel where the liquid part of the gel has been substituted by gas. Aerogel can be made from various chemical compounds and is manufactured by removing gel liquefaction components by supercritical drying. In recent years, intensive research around the world has been linked to high pressure supercritical fluid technology, and the goal of providing various biodegradable aerogels with supercritical fluids has been accomplished [9].

In addition, supercritical fluid technology has many benefits compared to standard procedures. Capillary stress and associated drying shrinkage can be avoid by using this

method. However, this method is so power-intensive and dangerous that it is difficult to practice and sell. Therefore it is very important to synthesize aerogels at a reasonable cost using an ambient pressure drying technique [10].

This work focuses on producing β-cyclodextrin/alginate aerogels using sol-gel method and dried by ambient drying to be used as delivery of drug carrier. To the best of our knowledge, it is very limited to date to use biopolymer as a carrier for herbal delivery. One of the innovative techniques for improving the solubility and bioavailability of herbs in the pharmaceutical industry is the development of herbal or medicinal plant carrier. In this study, β-cyclodextrin was mixed using an internal setting method with sodium alginate and dried with ambient drying to form aerogel.

Although the compression strength of aerogels is comparatively high, the main issues related to aerogels is the structural strength because it is very small tensile strength makes it very fragile and due to 99% volume of air in its structure make them easily break when the stress and heavy load pressure applied to it. β-cyclodextrin was mixed with alginate to form aerogels to improve the structural strength of aerogels, the solubility and bioavailability of poorly soluble drugs or compounds. Hydrogel is formed by cross-linking of solution of alginate and β-cyclodextrin derivatives with counter ions such as Ca^{2+} in this method, and the hydrogel is dried to form aerogel by ambient drying.

Cyclic oligosaccharide in β-cyclodextrin have seven (α-1,4)-linked α-D- glucopy-including inner hydrophobic cavity toroidal molecules and external hydrophilic surfaces. β-cyclodextrin can improve drug molecules' solubility, stability, safety and bioavailability which known as the most common application in pharmaceutical [11]. In aqueous solution, through bringing a drug molecule or some molecular lipophilic molecules into the central cavity, β-cyclodextrin may create a complex of inclusion with many drugs and no covalent connections are established or broken during complex forming.

B-cyclodextrin has been an attractive building block for multiple drug delivery systems owing to its desirable toxicological profile, its inherent capacity to preserve and shield some or all of the medication molecules from the external setting [12]. In particular, it showed that β-cyclodextrin derivatives were able to interact electrostatically as non-specific adsorption with Ca^{2+} ions. Ca^{2+} ion can therefore be used as a bridge ion between components that have been negatively charged and compounds of β-cyclodextrin [13]

II. METHODOLOGY

a. Materials

Sodium alginic acid, calcium carbonate ($CaCO_3$), glucono-δ-lactone (GDL), β-cyclodextrin and ethanol were purchased from Sigma.

b. Preparation of β-cyclodextrin/alginate hydrogels

Figure 1 below shows the method on how the β-cyclodextrin/alginate aerogels were prepared. The alginate sodium salt was dissolved in distilled water to obtain the weightage of 1.5 and 3% w/w followed by addition of $CaCO_3$ and β-cyclodextrin to the solution and stirred it until it completely dissolved. Next, glucono-δ-lactone (GDL) is then introduced to the 400 rpm stirring method for 2 to 3 hours to decrease the solution's pH and to initiate the gelation. The hydrogels are then transferred into molds and stored in refrigerator (4ºC) until they are completely gelled. Lastly, the aerogels were taken out from the molds and transferred to petri dish with B1, S1, S2, S3, B2, S4, S5, and S6 labelled.

Due to the low water solubility, the hydrogels had to be turned into alcohols before drying. Soaking directly in a bath with pure ethanol or other organic solvents, however, would result in important irreversible shrinking. In order to prevent this drawback, a gradual exchange of solvents was carried out. Gels were subsequently immersed in mixtures of ethanol-water at concentrations of 30, 50, 70, 90 and twice with 100% of ethanol for 24 hours. In the initial alcogels, soaking in 100 wt% ethanol is done repeatedly to guarantee more than 98 wt% s quality of solvent and to extract water and impurities. Then the hydrogels were dried to become alcogels by using ambient drying.

Table below shows the sample label and composition of each material in β-cyclodextrin/alginate aerogels;

Table 1: Sample label and composition of each material in β-cyclodextrin/alginate aerogels

Label	Sodium alginate (wt %)	β-cyclodextrin (wt %)
B1		-
S1		0.1
S2	1.5	0.5
S3		1.0
B2		-
S4		0.1
S5	3.0	0.5
S6		1.0

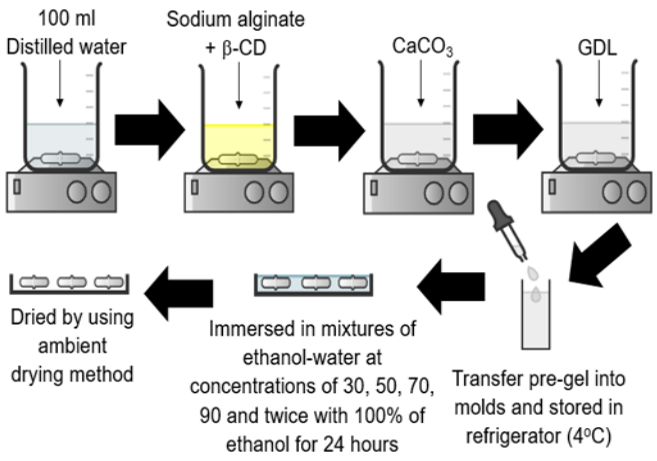


Figure 1: Preparation of β-cyclodextrin/alginate aerogels

c. Morphology and structure characterization

i. Nitrogen adsorption-desorption analysis

Gas adsorption measurements are widely used to define different solid materials' surface area and pore size distributions. The adsorption observed at the gas / solid boundary is also an important element of many fundamental and implemented studies on the design and behavior of good structures. Therefore, the particular surface regions, complete pore volumes and pore diameters of the alginate's spherical core and membrane aerogel specimens were determined, namely by nitrogen physisorption at −196ºC using a Micrometrics ASAP 2020MP tool. Each sample was first degassed under vacuum conditions at 70ºC for 660 min until a stable pressure of 10 mm Hg was obtained. By assuming 0.162nm^2/molecule as the N_2 molecular area, the BET equation was used to determine the surface area. The surface area was calculated on the basis of the Brunauer, Emmett and Teller (BET) method, meanwhile the pore diameter was calculated and its distribution from the isotherms of desorption.

ii. Differential scanning calorimetry (DSC)

Differential calorimetry (DSC) was conducted at a frequency of 10ºC / min from 20 to 600ºC using DSC 822e Mettler Toledo SAE to determine alginate thermal stability and residue decomposition.

iii. Scanning electron microscopy (SEM)

A Sirion 400 NC scanning electron microscope has been used to determine the surface morphology of multi-membrane spherical aerogels. The samples were gold coated and scanned at a voltage of 2–4 kV acceleration.

iv. Thermogravimetric analysis (TGA)

Using a TGA Mettler Toledo SAE method, thermal gravime tric analysis (TGA) is used to assess the thermal properties o f aerogels and was conducted at a level of 10ºC/min from 20ºC to 600ºC.

i. RESULTS AND DISCUSSION

a. Shrinking level before and after ambient drying

There were several analysis have been done to all the samples. Figure 2 and Figure 3 below shows the physical condition of the sample before and after ambient drying process.

Figure 2: Size of 20 cents

Figure 3: Size of aerogel before drying

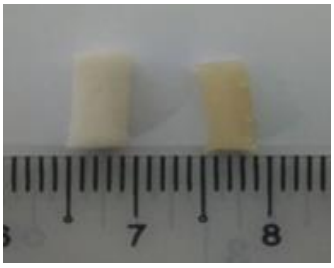


Figure 4: Length of aerogel

Figure 5: Width of aerogel

From Figure 2, the diameter of 20 cents is 4 cm with 4 cm length and width which can be related with Figure 3 which is the size of aerogel sample before ambient drying process. After ambient drying process have been done, the length of aerogel change to 1.9 cm length and 0.4 cm width as shown in Figure 4 and Figure 5 above.

The reduced of size happened because of the shrinkage effect from the drying process which also effect the weight of each sample as shown in Table 1. In addition, drying of aerogel by using the ambient pressure always causes the aerogel to shrink compared to other drying method but ambient drying method is the cheapest method instead of using supercritical drying which is very high cost [14].

Instead of using a ruler in order know the size of aerogel before and after drying process which also consider the shrinkage effect, the reduced of mass in each samples also one of the technique to know how many grams the aerogel loss its weight as the effect from the drying process. By using equation below, the percentage of shrinkage was identified.

$$\text{Percentage of shrinkage}(\%) = \left(\frac{w_2 - w_1}{w_2}\right) \times 100\%$$

Where W_2 and W_1 is the mass of aerogels before ambient drying and mass of aerogels after ambient drying respectively. The results of shrinkage of aerogel can be seen from the Table 1 below;

Table 2: The percentage of shrinkage level of aerogel

No	Label	Weight of sample (g)		Percentage of shrinkage (%)
		Before	After	
1	B1	69.6786	15.7031	77.46353
2	S1	64.8197	14.8360	77.11190
3	S2	73.5695	16.8849	77.04905
4	S3	68.5473	16.0679	76.55940
5	B2	67.7000	16.0395	76.30798
6	S4	69.0572	16.1545	76.60707
7	S5	69.8736	16.5835	76.26643
8	S6	68.5851	16.7907	75.51844

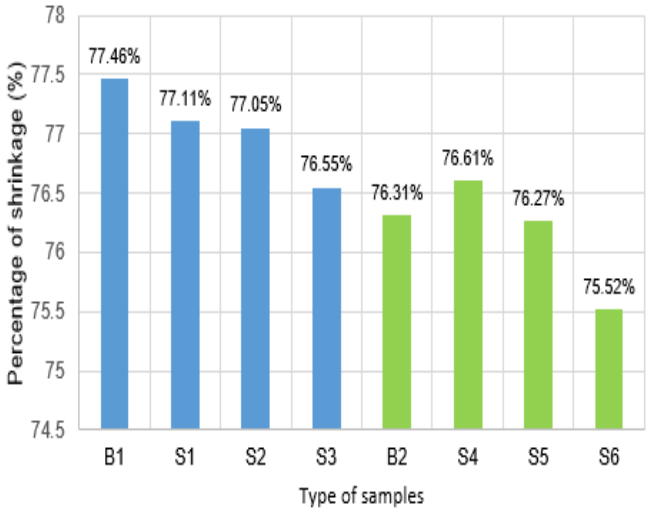


Figure 6: Graph percentage of shrinkage for each samples

Table 2 above show the percentage of shrinkage level of aerogel. From the calculation, it can be see that in a range of 75-77% of shrinkage for each sample happened. From the bar graph plotted in Figure 6, for sample with 1.5% of alginate, the shrinkage level decrease from Sample 1 until Sample 3 due to the increasing percentage of β-CD during the aerogel preparation. This condition also happened for sample with 3% alginate with increasing percentage of β-CD to Sample 4, Sample 5 and Sample 6 with 0.1%, 0.5% and 1.0% respectively. Then, Blank 1 and Blank 2 with 1.5% and 3% of alginate respectively also prepared without any addition of β-CD and the results showed that this sample shrink more than the other sample with the same composition of alginate. This is because as predicted from an aerogel, the aerogels were very thin, had a clearly translucent surface and were relatively fragile [15]. In order to overcome this problem, β-CD is used to reduce the brittleness of alginate aerogels [16].

a. Color changes of aerogels.

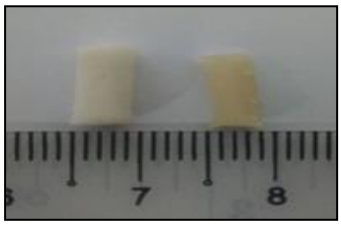


Figure 7: Different color of aerogels for composition of 1.5% and 3% sodium alginate

Based on Figure 7 above, the color of aerogel with 1.5% of alginate was more to white color compared to the aerogel with 3.0% which the color is more to slightly yellowish-brown color. This difference occurs because the percentage of sodium alginate added into the distilled water is not same. As the percentage of sodium alginate increase, the color of the aerogel also becomes more to yellowish-brown color compared to 1.5% of aerogel. Besides, increasing the amount of sodium alginate makes the solvent more viscous. This can be proven during the experiment was conducted. Weight of alginate will give an effect to the viscosity [17]. The weight of the molecules defines whether the sodium alginate viscosity is low or high. A low molecular weight is low in viscosity, while a high molecular weight is high in viscosity [18]. Adding 3% of sodium alginate into 100mL of distilled water make the solution harder to stir compared to 1.5% of sodium alginate.

b. Differential scanning calorimetry (DSC) analysis

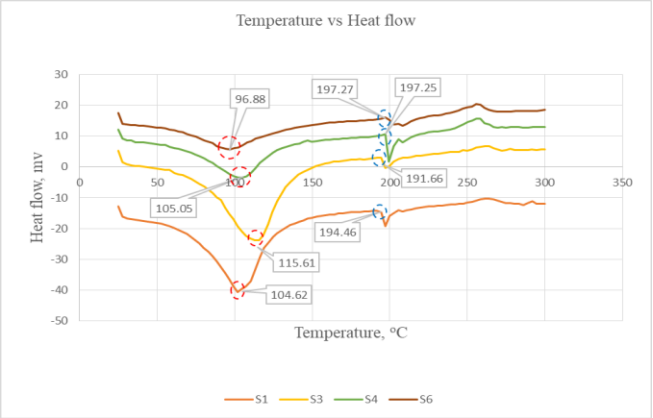


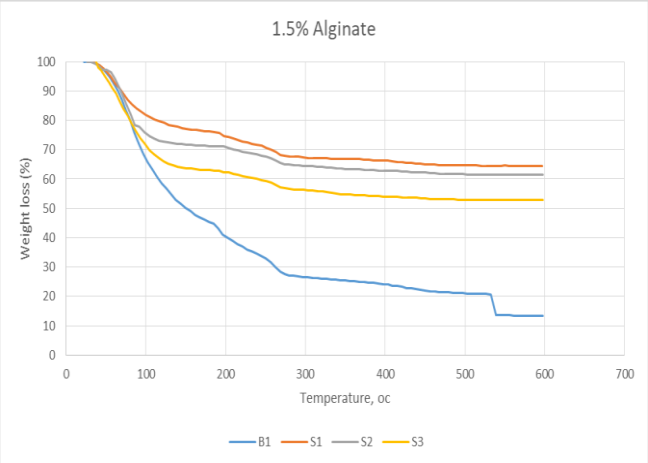
Figure 8: Alginate aerogel thermal stability and residual decomposition by DSC analysis

DSC testing can be used to measure interconnected thermodynamic profiles. The temperature and enthalpy in biopolymer products can also be calculated using DSC analysis through endothermic and exothermic processes [19]. DSC can be used to analyze a crystalline polymer's glass transformation and melting. That was related to the specified and demonstrated peak temperature in Figure 8 above. Plasticizers induces a glass transfer temperature change to a lower temperature as shown in some DSC thermograms, thereby increasing polymer rigidity [20]. In a DSC aluminum plate, each film sample weight about 6-9 mg were placed in the aluminum plate. Each experiment was previously measured by using a blank aluminum plate as a reference. The heating scans were conducted in a nitrogen atmosphere from 25°C to 300°C with 10°C/min heating rate.

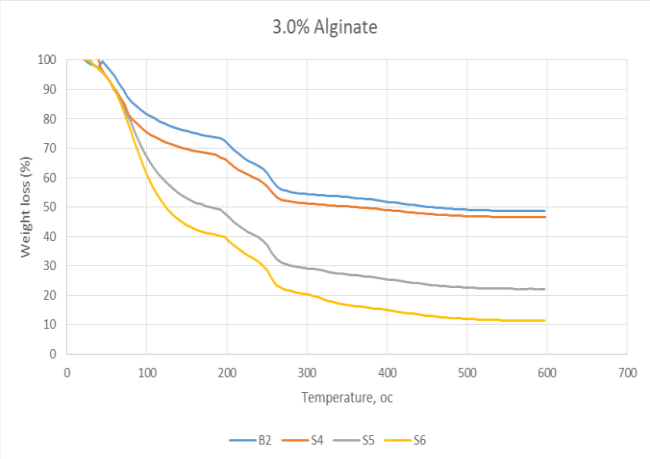
Based on the graph plotted in Figure 8, endothermic occurrences were at the first peak. In Figure 8, it can be observed that the first peak for S1, S3, S4 and S6 were 104.62°C, 115.61°C, 105.05°C and 96.88°C respectively. For S1 and S3 with 1.5% of alginate, the temperature at endothermic peak increase in thermal stability as β-CD increase meanwhile vice versa to S4 and S6 due to the collapse of pore structure. From the results of endothermic peak, it can be conclude that the inclusion of β-cyclodextrin to alginate increased the AG/β-CD aerogel's thermal stability. The interaction of alginate and β-cyclodextrin stabilizes the aerogel system against eruption and therefore demand a higher temperature for composite aerogel. Theoretically, it also proved that cyclodextrin-formed supramolecular complexes are commonly used in nutrition, medicine and agricultural. A special cone-shaped cavity barrel configuration is used to encapsulate guest molecules that can significantly improve guest molecules' solubility, thermal stability, bioavailability and antioxidant capacity [21].

The AG/β-CD aerogel's endothermic band value is attribute to the water release from the biopolymer aerogel for 1.5% and 3% of ALG/β-CD aerogel in the range of 104-115ºC and 96-105ºC respectively. The subsequent activity is linked to the melting of systemic biopolymer chain. An exothermic reaction occur as the temperature increased which lead to decomposition of aerogel. The exothermic reaction occur at 194.46ºC and 191.66ºC for S1 and S3 respectively for sample with 1.5% of sodium alginate. Meanwhile, for sample with 3% of sodium alginate shows that the exothermic appeared S4 and S6 at 197.12ºC and 197.27ºC. The finding was apparently different from the findings recorded by [22] where the alginate was observed to be decomposed at 330-450ºC. In conclude, the combination of β-cyclodextrin with sodium alginate enhanced the AG/β-CD aerogel thermal efficiency.

c. Thermogravimetric analysis (TGA)



(a)



(b)

Figure 9(a) and 9(b): Comparison of ALG/BCD aerogels at different composition with alginate aerogel without β-CD for 1.5% and 3%

The thermogravimetric analysis (TGA) has been carried out with different component ratio on different samples. Using TGA analysis, the effect of β-cylodextrin applied to sodium alginate is studied. The AG/β-CD aerogel biomaterials demonstrated a three-stage decomposition thermal breakdown in the oxidative atmosphere. Initial weight reduction of alginate with introduction of β-cyclodextrin as about 5 to 40% from 30 to 100ºC. Without addition of β-cyclodextrin, the initial weight drop from 20 to 100ºC for about 10% each. It occurrence is in accordance with desorption of heat.

The major weight loss for biopolymer degradation was reported at 200 to 220ºC for biopolymer thermal degradation, accompanied by carbonaceous product decomposition up to 500ºC. Several study have reported the same alginate-based decomposition reaction [23]. Based on Figure 9(a) and Figure 9(b) the application of β-cyclodextrin results in more stable aerogel decomposition about 270 to 290ºC for each sample except B1 and B2. As can be seen from graph plotted at Figure 9(a) and Figure 9(b), the AG/BCD biopolymer curve exist at 260ºC without introducing β-cyclodextrin for B1 and B2 samples. Based on previous study, the blank alginate usually having a decomposition around 250ºC as stated by [23]. In the final stage, as shown in Figure 9(a) and Figure 9(b) above, each sample of aerogel has a normal and fast degradation due to sodium oxide formation between 320 to 500ºC.

d. Brunauer, Emmett and Teller (BET)

Table 3: Brunauer, Emmett and Teller (BET) analysis

No	Label	Surface area (m^2/g)	Pore volume (cm^3/g)	Diameter of ALG/β-CD (nm)
1	B1	2.6730	0.001269	13.6508
2	S1	7.8421	0.002938	14.7639
3	S2	6.2944	0.001381	8.00000
4	S3	4.3579	0.003152	2.85738
5	B2	2.1764	0.000935	16.8891
6	S4	2.7508	0.001655	2.36636
7	S5	3.8178	0.002113	2.18658
8	S6	2.5966	0.001676	2.54333

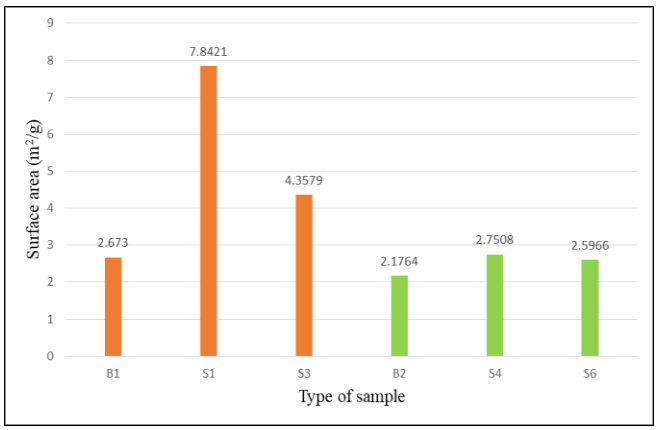


Figure 10: Effect on surface area of aerogels

Alginate's textured surface properties improved with alginate concentration ratio changes from 1.5% to 3%. High alginate content improves aerogel's crosslinking and broad surface area. This is because that the higher concentration of alginates would provide more functional groups of alginate molecules to associate with the calcium crosslinker's agent [24]. Based on Figure 10 above, the surface area of aerogel increase when β-CD introduced to sodium alginate as can be seen at B1 and S1 but the surface area suddenly decrease when the amount of β-CD increase which also give a results to low porous structure of aerogel. Same situation occur for sample with 3% of sodium alginate which increase in surface area when the β-CD added to sodium alginate compared to blank sample. But the surface area of aerogels suddenly collapse as the amount of β-CD added increase which also give results to low porous

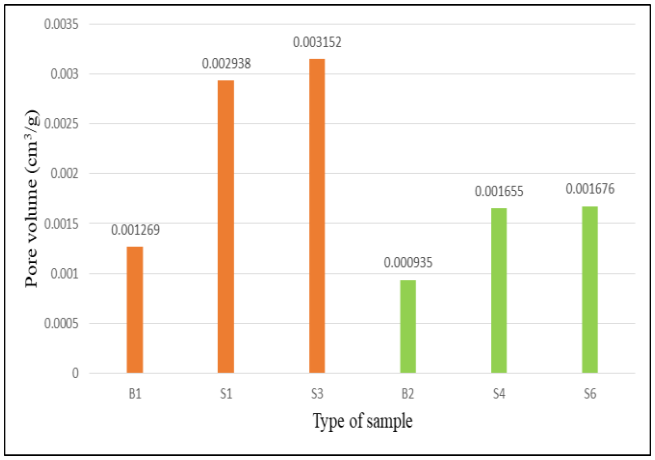


Figure 11: Effect on pore volume of aerogels

Meanwhile, the pore volume of each sample increase as the amount of β-CD increase. From Figure 10 above, the pore volume of aerogel increase when β-CD introduced to sodium alginate as can be seen from the trend of graph at B1, S1 and S3. Same situation occur for sample with 3% of sodium alginate which increase in pore volume when the β-CD added to sodium alginate compared to blank sample. Increased number of pores expressed in a lower volume of shrinkage [25].

ii. CONCLUSION

Aerogel is an attractive candidate for the drug delivery system in order to increase dissolved compounds solubility because of its excellent features with large surface area and high pore volume. By using ambient pressure drying, the shrinkage of aerogel during drying process can be reduced and will give a low density of gels. Even though aerogels have a comparatively elevated compression strength, the structural power of aerogels is not great, because it is very brittle owing to its very small tensile strength and because of the quantity of water in its framework of 99%, they break readily when the stress and heavy load pressure applied to it. The aim of this work were to determine the suitable ratio for the formation of aerogel and to study the morphology and properties of β- cyclodextrin/alginate aerogel were done. From the study shows that combination of β-CD and alginate to form aerogels give affects to the thermal stability and the rate of decomposition. Percentage of shrinkage level for aerogel decrease as the amount of B-cyclodextrin increase. β-CD mixed with alginate to form aerogels enhanced the thermal stability and the rate of decomposition. The application of β-cyclodextrin results in more stable aerogel decomposition about 270 to 290ºC for each sample except B1 and B2. The surface area of aerogel increase when β-CD introduced to sodium alginate at first but the surface area suddenly decrease when the amount of β-CD increase which also give a results to low porous structure of aerogel. Lastly, the pore volume of each sample increase as the amount of β-CD increase.

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