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# SAGO STARCH AND SODIUM ALGINATE AS NATURAL CROSSLINKING FOR CAPSULE ALTERNATIVES

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**ABSTRACT**
Capsule shells are generally made from gelatin. The gelatin that is spread in the world is commonly derived from pigs. This animal is forbidden to be consumed by Muslims. This issue is due to the halal aspect. Sago starch and sodium alginate are halal materials that are capable of gelatinizing. This property made it able to be molded as a capsule. This research aims to determine the formula of sago and sodium alginate as a capsule and the evaluation. Three formulas were made with the ratio of sago and sodium alginate 100%: 0% (formula 1), 50%: 50% (formula 2), and 0%: 100% (formula 3). The capsule was manually molded using a food-grade stainless steel capsule mold. The size of the capsule, weight uniformity, swelling, and disintegration time were determined for a physical evaluation. SLD was used to determine the best formula, and the validation was done using One-sample T-test. The evaluations of the capsule shell were found ranged as follows: the size specifications were 21-22 mm, the body diameter was 6.1-7.2 mm, the cap diameter was 13.6-13.8 mm, weight uniformity was 0.10-0.26 gram, the swelling test was 433-1583%, and the disintegration time was 10.20-14.43 minutes. The best formula based on the SLD of the experiment was formula 3, which are two parameters that met the requirements, i.e., swelling and disintegration time. The sago and sodium alginate were crosslinked, and the capsule was made. However, the performance dislike of gelatin capsules. Continued research shall be done to find the optimum formula and its characteristics for alternative material on halal capsules.

**Keywords:** Capsules; Gelatin; Sago Starch; Sodium Alginate; Simplex Lattice Design

## 1. INTRODUCTION

Capsule is one of the preparations for pharmaceutical application. The use of capsules in the pharmaceutical field is expected as a preparation containing drugs protected by a shell made of solid gelatin intended for oral use (Kemenkes RI, 2014). The primary source of raw materials for gelatin generally comes from animals such as pigs and cows. In addition, those mentioned can also come from poultry and fish as an alternative (Faridah & Susanti, 2018; Maila et al., 2019; Oktaviani et al., 2017; Rizki et al., 2021). In an effort to fulfill halal medicine for the Muslim community, it is necessary to find alternative capsule shell raw materials that are easily available and meet the standards of capsules made of gelatin.

Indonesia is one of the countries whose flora varies, but its use is not optimal. Some examples are starch from certain types of plants and other polymers from plants such as seaweed. One of the polysaccharides that are widely used in various industries, such as the food industry and the pharmaceutical industry, is alginate (Hijriawati & Febrina, 2016).

Alginate is a polysaccharide derived from the cell walls of seaweeds such as Sargassum sp. and Turbinaria sp (Szekalska et al., 2016). Alginate is often applied as a thickener, gelling agent, stabilizer, and emulsifying agent. In addition to the food and pharmaceutical industry, alginate is also used as a thickening agent for textiles, printing, and stamping batik (Mulyani et al., 2018). In addition, other alginate polysaccharides, there are also other polysaccharides, namely starch. Sources of starch are found in various types of plants, one of which is famous is the sago palm. This sago tree or tuber itself is one of the plants with great potential for the industry in Indonesia, especially in the food industry. The utilization of sago trees is still quite limited as an example of the use of sago trees is the leaves as a roof, midribs as glue, and sago stems as a source of carbohydrates (Ciptaningrat, 2020).

A combination of two or more materials during capsule production is commonly done to find the best formula for a capsule with the best physical and chemical properties. The materials will be crosslinked to each other based on their functional groups attached to the material. Crosslinks between alginate and other polymer on capsule production have been reported by a number of researchers (Breger et al., 2015; Simó et al., 2017; Somo et al., 2018). In this study, research was conducted on the use of sago starch and sodium alginate polysaccharide polymers as raw materials for capsule shells as an alternative to gelatin because of the ability of the two raw materials that can carry out the gelatinating process. In addition, it is also to examine the properties of the formed capsule shell.

## 2. METHODS

### 2.1. Tools and Materials

The main ingredient used in this study was food-grade sago starch, food-grade sodium alginate powder obtained from Muda Berkah Jogja. Pharmaceutical-grade glycerin and white vaseline were obtained from PT. BRATACO. The tools used for this research are Mettler Toledo AL204 analytical balance, Memmert water bath, IWAKI CTE33 beaker, IWAKI Pyrex measuring cup, stirring rod, spatula, capsule mold made by the Faculty of Mechanical Engineering, University of Muhammadiyah Yogyakarta, Krisbow KW06-357 caliper, FTIR ALPHA II spectrometer and ERWEKA D-63150 disintegration tester (Type ZT 222).

### 2.2. Capsule Manufacturing

The manufacture of capsule shells uses a modified formula from the standard formula by previous studies (Polnaya et al., 2016). The formula modification is in **Table 1**. The first step in capsule manufacturing was to weigh all ingredients according to the proportions set. Then continue by heating the distilled water for a while in a water bath at 80 °C. After that, add glycerin and continue adding raw materials slowly while stirring until it dissolves and gets the desired viscosity. After that, printed on a capsule mold that has been coated with plastic wrap and smeared with white vaseline.

### 2.3. Capsule Formula Optimization

Simplex Lattice Design (SLD) was used to determine the optimal response of various differences in material composition that total into one part. This technique is carried out with a constant amount of ingredients but varying compositions. The response profile is determined using equation 1 as follows (Bolton & Bon, 2003).

**Table 1.** Modification Formula

| Formulas | A = Sago starch (g) | B = Sodium alginate (g) | Glycerin (mL) | Distilled water (mL) |
|---|---|---|---|---|
| F1 | 10 | 0 | 2 | 88 |
| F2 | 5 | 5 | 2 | 88 |
| F3 | 0 | 10 | 2 | 88 |

$$Y = a(A) + b(B) + ab(A)(B) \quad (1)$$

Where Y is the response or effect produced, a, b, and ab are coefficients obtained or calculated from the experiment. A and B are component levels, with the sum of A + B always having to be one part.

Validation of the SLD equation was done by comparing the theoretical response or prediction generated from the SLD equation with the response produced by the experiment data. One-sample T-test is a statistical analysis test that will be used to test the significance value between the theoretical response value and the average response value of the treatment results (Kraemer et al., 2015).

### 2.4. Quality of Capsule Test

The quality of the capsule was evaluated by determining the weight uniformity, swelling, disintegration time, and morphology of the capsule. The uniformity test was performed by weighing the capsule shell using an analytical balance. Then the results have written and averaged (Suparman et al., 2019). The testing ability of the capsule to absorb water was carried out by a swelling test. The test was carried out with dry capsules weighed first to obtain dry weight (*wo*). The dry capsule was immersed in 50 mL of distilled water for 10 minutes, then weighed after being wiped using dry tissue paper, which then became wet weight data (*wt*). Calculations are made to get the degree of swelling (*Q*) as expressed in equation 2 (Susanti et al., 2020).

$$Q = \frac{wt - wo}{wt}\, x\, 100\% \qquad (2)$$

A disintegration time test was performed to determine how long the capsule disintegrated, ensuring the capsule could release the drug. Six capsules were put in a basket on a disintegration tester. The basket containing the capsules will be lowered 30 times regularly per minute. The water medium used was set at a temperature of 37±2ºC. During the process of up and down the capsule carefully observed, it was confirmed that all capsules to destroyed. The ideal test time requirement for capsule crushing was less than 15 minutes unless otherwise stated (Kemenkes RI, 2014).

Scanning Electron Microscopy (SEM) test was performed to determine the morphology of the capsule. Analysis was carried out by cutting the sample to form a beam and then attached to the specimen holder. The sample was then observed in a specimen chamber and photographed with a particular magnification (Susanti et al., 2020). Fourier Transform Infrared (FTIR) test was performed for crosslinking analysis formed between sago starch and sodium alginate. Sample preparation was done by grinding the sample together with KBr solids. After a homogeneous mixture then, the mixture is molded into pellets. Measurements are made with an FTIR spectrometer (Susanti et al., 2020).

## 3. RESULTS AND DISCUSSION

### 3.1. Manufacture of Capsule Shells

Sago starch as a raw material for capsule shells can be a positive alternative because of its gelatinating properties (Ihsan et al., 2018). Alginate is one part of the polysaccharide that is able to form a gel that cannot melt even by heating (Adicandra & Estiasih, 2016; Herawati et al., 2018). The plasticizer used in making capsule shells is glycerin. Glycerin is able to reduce brittleness and increase the flexibility of the capsule shell (Ihsan et al., 2019; Wulandari, 2016), and the solvent used was distilled water.

Based on the modified formula, a capsule shell was then made, after which the capsule shell was cut for later testing. Before conducting the test, the capsule shell preparation was measured in length and diameter using a caliper. The measurement results of each capsule shell from each formula were then averaged as comparison material with commercial capsules. From the results, it was concluded that the three capsule shell formulas meet the size and length specifications of standard capsules on the market. As for the diameter of the capsule shell, only the cap of the formula three capsule shell meets the specifications. This is because the diameter size of the capsule shell molds is likely to be uneven and does not adjust to the standards on the market. In addition, capsule molding and capsule removal from manual molds can also be a factor causing the resulting diameter not to be up to standard. The capsule that had been made can be seen in **Figure 1**.

### 3.2. Weight Uniformity

Uniformity of the weight of the capsule shell was carried out by weighing the capsule shell on the analytical balance. The average result of uniformity in the weight of the capsule shell for F1 was 0.26 grams, F2 was 0.20 grams, and F3 was 0.10 grams. In the reference journal, it was mentioned for the weight of PT. Capsuleindo Nusantara's maximum weight is 0.10 grams, and the minimum weight is 0.08 grams, while the average weight is 0.09 grams. The average results obtained in the study were then substituted into the SLD equation and obtained in Equation 3. Based on the SLD equation for the weight uniformity test, the predicted weight uniformity of the capsule for predicted different compositions of sago starch and sodium alginate can be seen in **Figure 2**.


**Figure 1**. Morphology of capsule made using sago starch and sodium alginate: (a) 100% sago starch; (b) 50% of sago starch and 50% of sodium alginate and (c) 100% sodium alginate.

$$Y = 0.26\,(A) + 0.10\,(B) + 0.08\,(A)(B) \quad (3)$$

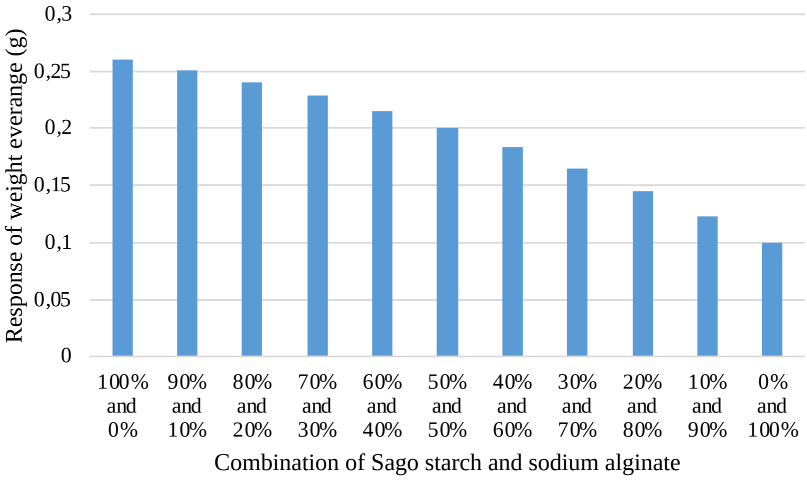


**Figure 2**. Profile of predicted weight average for predicted different compositions of sago starch and sodium alginate based on SLD analysis.

The weight of the capsule shell was influenced by the thickness of the capsule shell where which will be influenced by the capsule shell molding process. Composite printing with an uneven amount of composite or manual manufacturing process can result in unequal thickness of capsule shells (Endriani et al., 2019; Suptijah, Jacoeb, et al., 2012; Suptijah, Suseno, et al., 2012).

### 3.3. Swelling Test

A swelling test was performed to calculate how much the capsule shell was able to absorb water. This test was carried out by weighing a dry capsule, and then the capsule shell was immersed in 50 mL of distilled water for 10 minutes. The soaking time is 10 minutes because at >10 minutes, the capsule shell has begun to crumble. Swelling test research that has been conducted in other studies gets a value of 346.4%.

In this study, the average swelling test results for formula 1 were 453%, formula 2 was 433%, and formula 3 was 1583%. The average results obtained in the study were then substituted into the SLD equation and obtained in equation 4. Based on the SLD equation for the swelling test, the predicted swelling profile of the capsule for predicted different compositions of sago starch and sodium alginate can be seen in **Figure 3**. Several factors, such as the nature of the raw material, the granule's size, the soaking duration, and the pH of the solution, can influence the degree or value of swelling.

$$Y = 453\,(A) + 1583\,(B) - 2340\,(A)(B) \tag{4}$$

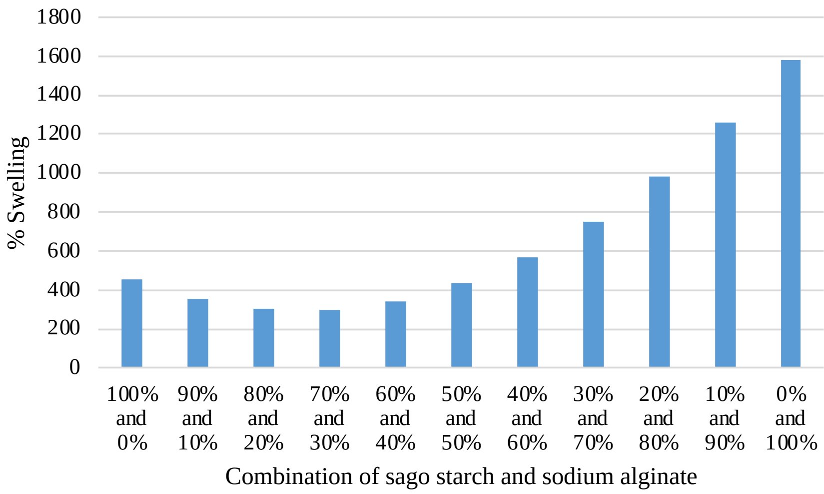


**Figure 3**. Profile of predicted swelling for different compositions of sago starch and sodium alginate based on SLD analysis.

### 3.4. Disintegration Time Test

A wrecked time test was performed to calculate how long it takes for the capsule shell to disintegrate. This test was carried out using six capsules which were immersed into a disintegration tester with a temperature of ±37°C until the capsules were destroyed. The time requirement for destruction in the 5$^{th}$ edition of Indonesian Pharmacopeia is <15 minutes unless otherwise <30 minutes. From the treatment of the study, the average results of the disintegration time test for F1 were 12.08 minutes, F2 was 10.20 minutes, and F3 was 14.43 minutes. The average results obtained in the study were then substituted into the SLD equation and obtained in equation 5. The profile of predicted disintegration time for predicted different compositions of sago starch and sodium alginate based on the SLD equation can be seen in **Figure 4**. The disintegration time of the capsule shell can be affected by the thickness of the capsule shell and the nature of the raw material.

$$Y = 12.08\,(A) + 14.43\,(B) - 12.26\,(A)(B) \tag{5}$$

### 3.5. Formula Optimization

From the SLD equation, the response value is calculated using the following equation 6, where *N* is Normality, *X* is the response of each test, *Xmax* = Maximum desired response, and *Xmin* is Desired minimum response.

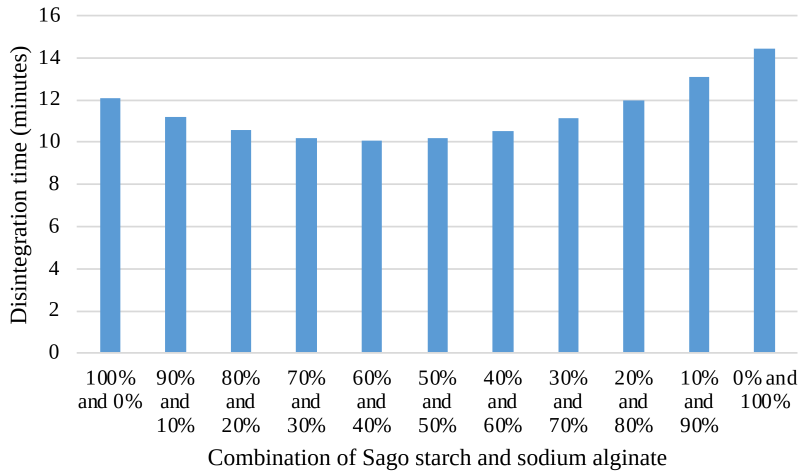


**Figure 4**. Profile of predicted disintegration time for different compositions of sago starch and sodium alginate based on the SLD analysis.

$$Response = N(\frac{X - Xmin}{Xmax - Xmin})\ x\ Weighting \quad (6)$$

The calculation of the total response value then obtained the most optimal response result is the response produced by the formula with a proportion of 100% sodium alginate, which is 0.7. Previous research stated that the determination of the optimum formula was determined by looking at the total response produced. The most optimal formula has the highest response value (Bolton & Bon, 2003). The profile of the predicted total response can be seen in **Figure 5**.

It can be concluded that the use of natural ingredients from plants can be used as an alternative to gelatin ingredients. One example of this material is sodium alginate. In this study, sodium alginate became the raw material for making capsule shells and produced the most optimal response compared to other formulas. Formula using sago starch only and the formula using sago starch and sodium alginate can also produce capsule shells. Still, the response value is less than the capsule made from sodium alginate only when calculated using the SLD method.

The capsule from the results of the Independent-sample T-test obtained, it can be concluded that the optimum capsule shell formula has significantly different properties from commercial capsule shells. The nature of the capsule shell formula is not yet matching with the capsule shell already on the market. Further research needs to be done on other raw material alternatives and make formula modifications to find a more optimal formula with properties that can compensate for commercial capsule shells. The test was conducted to compare the two by statistical test using SPSS software with Independent-sample T-test as in **Table 2**.

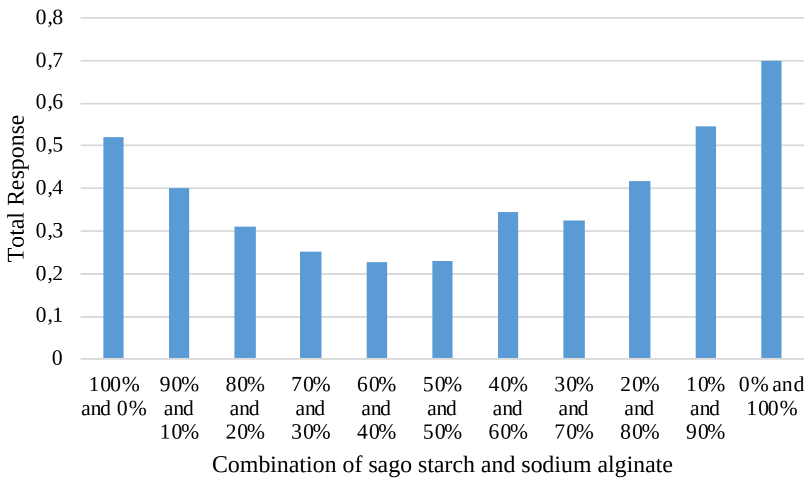


**Figure 5**. The profile of the predicted total response is based on the SLD analysis.

**Table 2.** Test results of the optimum formula of gelatin alternative capsule shells

| Parameters | Formula Optimum | Commercial Shell | Significance | Conclusion |
|---|---|---|---|---|
| Weight Uniformity (g) | 0.100 | 0.110 | 0.346 | Different Meaningless |
| *Swelling* Test (%) | 1583 | 301.067 | 0.000 | Different Meaning |
| Disintegration Time (minutes) | 14.420 | 11.310 | 0.000 | Different Meaning |

### 3.6. SEM Test

The SEM test was performed using an electron microscope. The purpose of the SEM test is to visualize the surface and crosslinking of the capsule shell and observe whether all materials were mixed homogeneously, not separated, and the pores of the resulting film.

**Figure 6a** 300x magnification and 6. b 5000x magnification with a proportion of 100% sago starch obtained homogeneous results, but there are many large and irregular cavity structures in **Figure 6b.** An extensive network of cavities or pores will cause the escalation of cell growth and proliferation of hydrogels and increase drug storage for drug delivery systems (Zhang et al., 2019).

**Figure 6c** 300x magnification and 6.d 1000x magnification with a proportion of 50% sago starch: 50% sodium alginate was obtained surface results that look homogeneous, but there are grains that most likely starch from sago which may be wholly dissolved, so that they are scattered throughout the film and clearly visible then seen from the cross-section there, not two separate phases. The void in **Figure 6d** is not visible when compared to the cavity in **Figure 6b**. This may be due to the mixing of sodium alginate, which increases the bond density between molecules so that no cavity appears. According to research, small cavities or pores in hydrogels will increase the transmission of bioactive molecules and cell migration (Agustin & Padmawijaya, 2016; Nugrahanto et al., 2021).

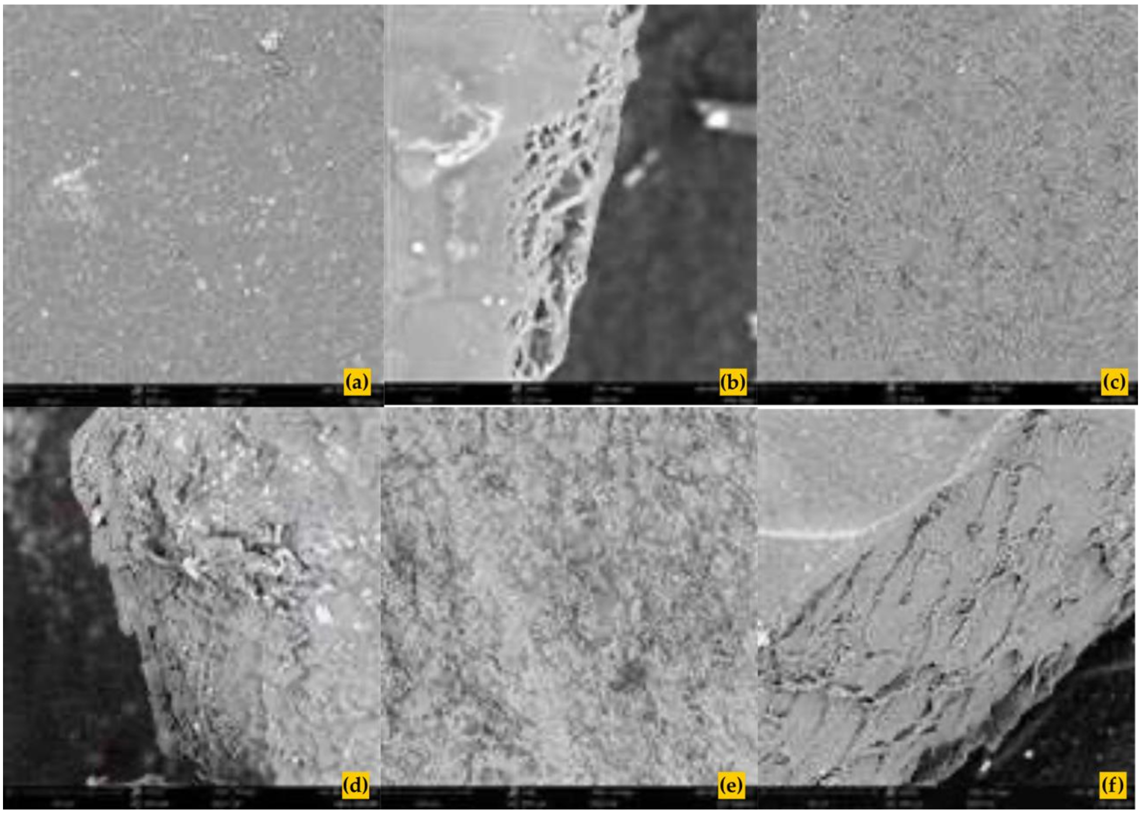


**Figure 6**. SEM Test Results (a) Surface 100% sago starch (b) Cross Section 100% sago starch (c) Surface 50% sago starch: 50% sodium alginate (d) Cross Section 50% sago starch: 50% sodium alginate (e) Surface 100% sodium alginate (f) Cross Section 100% sodium alginate.

**Figure 6e** 300x magnification and 6. f 1000x magnification with 100% sodium alginate component show the result of a film surface that looks homogeneous but rougher. This may be because the film has been damaged due to prolonged exposure to heat due to electron transfer. The cross-section of the film shows the result that there are no cavities in the film.

### 3.7. FTIR Test

FTIR tests were performed using a device called a spectrometer. This test is intended to determine the functional groups present in a sample and inform the structure of an organic compound by looking at its wavenumber. **Figure 7** shows the FTIR chromatogram for 100% sago starch, 50% sago starch and 50% sodium alginate, and 100% sodium alginate.

In the FTIR test, results were obtained for 100% sago starch capsule shells appearing C-C-C, C-C-O, and C-O-C from the cyclic framework of alkanes with O-H coming out of the bending plane at wavenumbers 500-927 $cm^{-1}$. At wavenumbers 950-1204 $cm^{-1}$, there is a strain of C-O derived from the ether of secondary alcohol. The C-H bond appears at wavenumbers 1238-1455 $cm^{-1}$. The C-H bond shrinkage of alkanes appears at wavenumbers 2887-2935 $cm^{-1}$. The O-H strain that forms the intermolecular force appears at wavenumbers 3000-4000 $cm^{-1}$.

The result for a 100% sodium alginate capsule shell is the appearance of wavenumbers 618-719 $cm^{-1}$ indicates C-C-C, C-C-O, and C-O-C of the cyclic framework of alkanes with O-H coming out of the bending plane. At wavenumbers 929-1111 $cm^{-1}$, there is a C-O strain of the ether of the secondary alcohol. The C-H bond appears at wavenumbers 1262-1461 $cm^{-1}$. According to Zahib, the typical absorption of sodium alginate, namely COO- appears at wavenumbers 1616 and 1418, the absence of typical absorption most likely due to the overlap of bands; (Zahib et al., 2021). At wavenumber 1618 $cm^{-1,}$ there is a strain C=C of cyclic alkanes or N-H amine curvature. C-H strain of alkanes at wavenumbers 2849-2952 $cm^{-1}$. At the wave 3000-4000 $cm^{-1,}$ there is an O-H strain that forms intermolecular forces.

Mixing sodium alginate with sago starch produces FTIR tests with C-C-C, C-C-O, and C-O-C from the cyclic framework of alkanes with O-H coming out of the bending plane with a lower wavenumber compared to single sago starch which 577-925 $cm^{-1}$. This is due to the addition of sodium alginate C-O strain appearing at wavenumbers 950-1156 $cm^{-1}$. C-H bonds and playback of alkanes or cyclic alkanes appear at wavenumbers 1327-1415 $cm^{-1}$. C-H strains of alkanes appear at wavenumbers 2887-2935 $cm^{-1}$. O-H forms intermolecular forces because hydrogen bonds appear at wavenumbers 3000-4000 $cm^{-1}$.

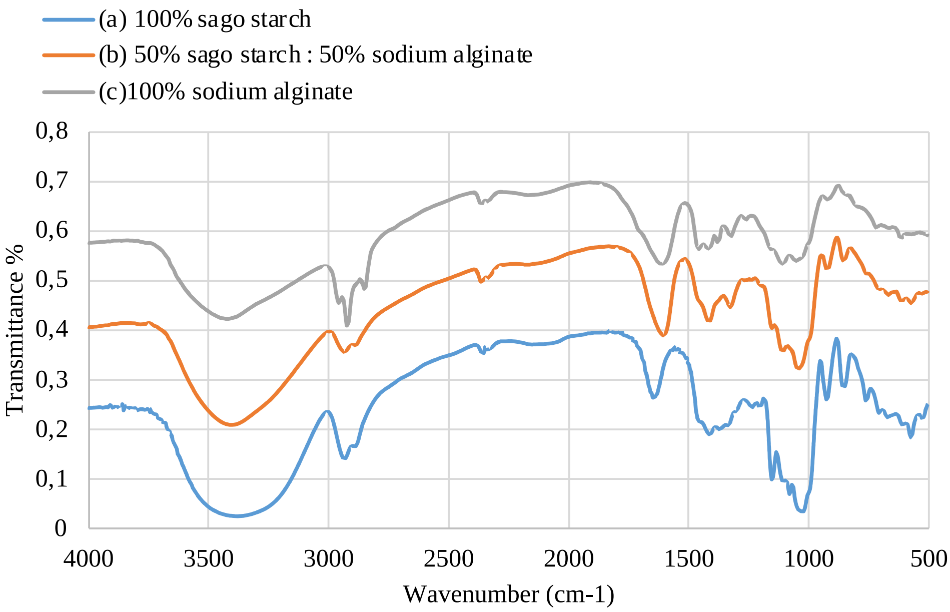


**Figure 7**. FTIR Test Results (a) 100% sago starch (b) 50% sago starch: 50% sodium alginate (c) 100% sodium alginate.

In mixing sodium alginate with sago starch, N-H amine does not appear. This is likely because there are intermolecular bonds in the form of electrostatic interactions, namely the presence of hydrogen bonds so that the N-H functional group bonds become shorter (Derkach et al., 2019).

From the data obtained in the FTIR test, it can be concluded that the mixing of two raw materials will cause a reaction characterized by a shift in wave absorption. The FTIR test results also concluded that there was an electrostatic interaction, namely the presence of hydrogen bonds. With this hydrogen bond, it can also be concluded that there is a physical crosslinking event in accordance with the theory, namely physical crosslinking occurs due to molecular interactions such as ionic and electrostatic. Interactions that occur due to hydrogen bonding, polymerized entanglement, complex stereo formation or crystallization, and hydrophobic or hydrophilic interactions (Hu et al., 2019).

### 3.8. Validation of Simplex *Lattice Design* Equation.

Validation was carried out to ensure that the prediction data obtained from the SLD equation was valid. This is used for further optimization of capsule shell formulas using raw materials of sago starch and sodium alginate. Therefore, a random formula was chosen in this validation, which was 90% sago starch and 10% sodium alginate. The predicted value of the evaluation based on SLD analysis was compared to the experiment data at the same portion of sago starch and sodium alginate. The test was performed to prove the validity of the equation generated from the SLD analysis. The One-sample T-test using SPSS was used to compare theoretical and experimental results. One-sample T-test is a test where the principle aims to test whether the value obtained is significantly different or not from the average of a sample (Kraemer et al., 2015).

The results of the One-sample T-test stated that theoretical and experimental data showed a P value > 0.05 for swelling and disintegration time, which are 0.407 and 0.051, respectively. While for weight specificity, the P value was <0.05, which is 0.000. Thus, based on the results of the One-sample T-test, it can be stated that the predicted value and the experimental value were not significantly different. Then from this research, it is concluded that the Simplex Lattice Design equation was valid when used for the optimization of capsule shell preparation formulas with raw materials of sago starch and sodium alginate.

## 4. CONCLUSION

Based on research that has been done, sago starch and sodium alginate can be used as alternative raw materials for capsule shells to replace gelatin. Crosslinking that occurs is physical crosslinking which is shown by wavelength shifts due to electrostatic reactions. The capsule performance of the crosslink between sago and sodium alginate is not as good as gelatin capsules. The most optimal formula produced in the study was a formula with a composition proportion of 100% sodium alginate, showing the highest response value. SLD can be used to determine the optimum formula for sago and gelatin capsules. The validation test states that the equation generated from SLD was valid because the prediction value was not significantly different from the result of the experimental mean value. Based on these results, further research needs to be carried out in an effort to get the best formula for improving the performance of sago and alginate capsules so that a substitute for gelatin capsules was doubtful of halal.

## 5. ACKNOWLEDGMENT

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## 6. CONFLICT OF INTEREST

All authors declare no conflict of interest.

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