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Research Article

# Optimization of sago starch and sodium alginate crosslink, including calcium chloride as a capsule alternative using the simplex lattice design

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## Abstract

**Background:** Capsule shells are conventionally manufactured using gelatine, primarily sourced from bovine or porcine bones and skins, which presents significant concerns for Muslim consumers. This study seeks to optimize sago starch and sodium alginate crosslinking as viable alternatives to conventional gelatine-derived capsules.

**Methods:** Utilizing calcium chloride ($CaCl_2$) as a crosslinking agent, three formulations were developed: F1 (100% sago starch), F2 (50% sago starch, 50% sodium alginate), and F3 (100% sodium alginate). The Simplex Lattice Design (SLD) was employed to determine the optimal capsule characteristics.

**Results:** Formula F2 showed optimal characteristics with 8.165% weight uniformity deviation, 49.607% water swelling, and a destruction time of 9 minutes, 25 seconds. FTIR confirmed hydroxyl groups with absorption shifts of 1463.6–1389.06 $cm^{-1}$ in F2 and 1476.7–1394.81 $cm^{-1}$ in F3.

**Conclusion:** $CaCl_2$ proved effective for crosslinking sago starch and sodium alginate. SLD identified a 10% starch, 90% alginate ratio as optimal, enhancing capsule uniformity and stability.

## Keywords

calcium chloride, capsule shells, crosslinker, sago starch, sodium alginate

## Introduction

Capsule is a solid preparation consisting of drugs enclosed in soluble hard or soft shells. The existing types comprise hard and soft-shell capsules, whose shells are generally produced using gelatin and occasionally with starch or other suitable materials (Ministry of Health Indonesia 2013). The main source of gelatin is derived from raw materials of bones as well as skins of cattle and pigs, including poultry and fish (Oktaviani et al. 2017; Faridah and Susanti 2018; Liva et al. 2019). Indonesia is among the countries with a majority Muslim population that considers the halal aspect to be crucial (Mu'ti Sazali and Ligte 2019; Vanany et al. 2019). Materials widely used as gelatin alternatives in the pharmaceutical setting are polysaccharides, including sago starch and alginate (Karim and Bhat 2008; Derkach et al. 2020a; Kouhi et al. 2020). Sago starch consists of amylose (±27%) that has a linear structure and amylopectin (±73%) with a branched structure, both representing the soluble and insoluble fractions, respectively. These are polysaccharides composed of anhydrous glucose units connected by α-glycosidic bonds (Ihsan et al. 2018). Meanwhile, alginate is a linear polymer that easily absorbs water and has a high molecular weight along with a straight-chained chemical structure comprising D-mannuronic acid and L-guluronic acid (Xu et al. 2021).

Modifications to gelatin capsule shells include the addition of crosslinker to increase mechanical resistance and reduce membrane solubility in water (Ma and Sahai 2013). During capsule manufacturing, in addition to using starch and alginate materials, crosslinker is added to bridge the formation of bonds between two functional groups (Giri et al. 2012; Song and Wang 2020). Crosslinker influences membrane water swelling rate, which can be minimized, increases the stability, and changes the size of polymer chain density due to the pull decreasing flexibility (Hennink and Van Nostrum 2012). Crosslinkers such as calcium chloride ($CaCl_2$) are distinguished by their covalent and ionic nature, while the addition affects the modification of cohesion between protein chains due to the influence of type, intensity, and distribution on intermolecular interactions. In edible coating formulations, $CaCl_2$ is used as a crosslinking agent, which improves the water resistance, cohesion, hardness, mechanical strength, and barrier properties of materials (Oryan et al. 2018).

The novelty of this research includes optimizing the combination of sago starch and sodium alginate with $CaCl_2$ as a crosslinker using Simplex Lattice Design (SLD) to develop viable alternatives to gelatin capsules. A previous investigation examined the use of sago starch or sodium alginate individually (Harimurti et al. 2023), but the integration of both materials in varying proportions along with $CaCl_2$ has not been comprehensively explored for capsule applications. Therefore, this research aimed to address the gap in the formulation and characterization of non-gelatin capsule shells, focusing on achieving optimal physical properties such as weight uniformity, water swelling degree, and disintegration time. Of this background, the objective of this study is to optimize the formulation of sago starch and sodium alginate using $CaCl_2$ as a crosslinker to produce a capsule shell alternative different from gelatin. Additionally, the ideal formulation will be determined based on critical performance metrics such as capsule weight uniformity, water swelling, and disintegration time through the SLD method.

## Materials and methods

### Material

The raw materials used in this research were food-grade sago and sodium alginate purchased from Muda Berkah Jogja, Special Region of Yogyakarta, Indonesia. Others included pharmaceutical-grade glycerin and white vaseline obtained from Bratachem, as well as analytical-grade $CaCl_2$ sourced from Merck Germany.

### Research method

Crosslink used for capsule shells was produced through steps including the preparation and weighing of all ingredients according to predetermined proportions shown in Table 1.

**Table 1.** Capsule shell formula.

| Formula | Material | | | | |
|---|---|---|---|---|---|
| | Sago starch (g) | Na Alginate (g) | Glycerine (mL) | 2% $CaCl_2$ (mL) | Distilled water (mL) |
| F1 | 10 | 0 | 1 | 1.5 | 50 |
| F2 | 5 | 5 | 1 | 1.5 | 50 |
| F3 | 0 | 10 | 1 | 1.5 | 50 |

Approximately 5 g each of sago starch and sodium alginate raw materials were dissolved in 25 mL distilled water in a glass beaker and stirred until homogeneous. Each resulting solution was mixed in one glass beaker and stirred again until homogeneous, then 1 mL glycerin was added. Subsequently, 1.5 mL of 2% $CaCl_2$ was introduced slowly and mixed until a viscous solution was formed. The viscous solution was covered with aluminum foil and warmed at 70–80 °C in a water bath stirred every 30 minutes for 1 hour. This warmed viscous solution was applied to a stainless-steel capsule mold coated using plastic wrap to ensure easy removal of the produced capsule. The mold was dried for ± 24–48 hours at room temperature, and then capsule shells were removed and trimmed using scissors according to capsule size 00.

The research design was a laboratory experiment to prepare sago starch capsule shells and sodium alginate with a $CaCl_2$ crosslinker. Capsule shells were examined through specification, water swelling, and disintegration time tests. Additionally, the surface morphology was tested with Scanning Electron Microscopy Energy Dispersive X-ray (SEM-EDX), and crosslink formation was evaluated based on the

functional groups analysis using Fourier Transform Infrared Spectroscopy (FTIR). This research was conducted at the Pharmaceutical Research and Technology Laboratory of Universitas Muhammadiyah Yogyakarta, the Integrated Laboratory of Universitas Islam Indonesia, and the Laboratory of PT Glabs Indonesia Utama Bandung, Indonesia.

# Result

## Capsule shell preparation

Capsule shells were prepared through the production of composites, molding, and drying processes. During the production of composites, 5 g each of sago starch and sodium alginate were weighed and dissolved in 25 mL distilled water in a glass beaker, then stirred until homogeneous. Each resulting solution was mixed in one glass beaker, stirred again until homogeneous, and 1 mL glycerin was added. Subsequently, 1 g $CaCl_2$ was dissolved in 50 mL distilled water, from which 1.5 mL $CaCl_2$ solution was transferred into formulas F1, F2, and F3 (Fig. 1).

The mixture was stirred until it thickened before being covered with aluminum foil, followed by heating at 70–80 °C in a water bath stirred every 30 minutes for 1 hour. Heating should be maintained because the solution tends to harden at a very low temperature, while an extremely high temperature will cause melting and the inability to mold. The next step was to mold capsule shells using a capsule molding tool known as a pin bar. Initially, the pin bar was coated with plastic wrap to facilitate easy removal of capsule shells molded through the thick solution distribution on the pin bar, followed by drying for ± 24–48 hours at room temperature. The dried shells were released from the pin bar and cut using scissors according to capsule size 00. F1 could not be formed to resemble capsule shells due to using sago starch only, which failed to thicken properly. The resulting solution was slightly diluted and unable to stick perfectly to the molding tool because sodium alginate was not added as a thickener.

## Capsule shell specifications

The results of capsule shell specifications included length, diameter, and weight parameters presented in Table 2.

The length and diameter were calculated using a caliper, while the weight was measured with an analytical balance, and each of these tests was conducted six times for individual formulas. Capsule molds were sized 00 with the specifications of hard shells referring to PT Kapsulindo or commercial capsule shells. The specification test results for length and diameter measurements corresponded with commercial capsule standards. However, capsule shell weight obtained was different from commercial capsule requirements. Several factors influenced this mismatch because the preparation process was still manual, leading to uneven capsule shells. The molding process and the viscosity of the formulas generated different capsule thickness results.

## Water swelling test results

A swelling test was conducted to determine the ability of capsule shells to absorb water. This was conducted by immersing the capsule in 100 mL distilled water for 15 seconds and replicated in six capsules of each formula, with Table 3 presenting the calculation results.

The average swelling results of F2, F3, and commercial capsules were 49.60%, 54.58%, and 42.26%, respectively. F3 had higher average swelling due to the absorption capacity of the 100% alginate capsule shell produced. The sodium alginate component has anionic groups (hydroxyl and carboxyl) that reduce the tightness of molecular bonds between polymer chains and provide more space for liquid to occupy. This improves the absorption capacity of the film (Choi et al. 2022; Eslami et al. 2023), thereby signifying the reason for capsule shells of F2 possessing a better density than F3.

## Disintegration time test

The disintegration test was conducted to determine the time required for capsule shell preparation to disintegrate. Based on the results presented in Table 4, a good disintegration time was a maximum of 15 minutes. The disintegration time test results were in the specified range, with the other two formulas showing a longer disintegration time compared to F3. This observation was due to the fast or slow destruction time of capsule shells influenced by the formation process. Shells produced in this research had a different weight and thickness from gelatin capsule shells, requiring a longer destruction time (Zilhadia et al. 2022; Naharros-Molinero et al. 2024).


**Figure 1.** Capsule shell characteristics. **a.** Formula F1 (100%:0%) no capsule formed; **b.** Formula F2 (50%:50%) capsule rigid, strong, and smooth; and **c.** Formula F3 (0%:100%) capsule rigid, strong, and rough.

**Table 2.** Capsule shell specifications.

| Formula | Replica | Long (mm) | | | Diameter (mm) | | Weight (g) |
|---|---|---|---|---|---|---|---|
| | | Body | Cap | Entire | Body | Close | |
| **F1** | | | | No capsule shell formed | | | |
| **F2** | 1 | 19.6 | 11.3 | 23.5 | 8.1 | 8.4 | 0.241 |
| | 2 | 20.5 | 11.2 | 23.5 | 8.1 | 8.2 | 0.203 |
| | 3 | 20.2 | 12.0 | 24.0 | 8.1 | 8.3 | 0.266 |
| | 4 | 20.2 | 12,1 | 23.6 | 8.1 | 8.2 | 0.253 |
| | 5 | 19.9 | 12.2 | 24.1 | 8.1 | 8.3 | 0.247 |
| | 6 | 20.1 | 11.6 | 23.9 | 8.1 | 8.2 | 0.255 |
| | **Average** | 20.08 | 11.73 | 23.76 | 8.1 | 8.26 | 0.244 |
| | | | | % Deviation | | | 8.164% |
| **F3** | 1 | 19.5 | 12.5 | 24.4 | 8.1 | 8.6 | 0.416 |
| | 2 | 20.4 | 11.3 | 23.7 | 8.1 | 8.5 | 0.315 |
| | 3 | 20.2 | 11.6 | 24.4 | 8.2 | 8.6 | 0.394 |
| | 4 | 19.7 | 12.5 | 24.5 | 8.1 | 8.5 | 0.618 |
| | 5 | 20.5 | 12.5 | 23.7 | 8.1 | 8.5 | 0.291 |
| | 6 | 19.5 | 11.5 | 24.1 | 8.5 | 8.4 | 0.388 |
| | **Average** | 19.66 | 11.96 | 24.13 | 8.18 | 8.51 | 0.404 |
| | | | | % Deviation | | | 24.174% |
| **Commercial** | | 19.50–20.50 | 11.50–12.50 | 23.30–24.45 | 8.153 ± 0.100 | 8.509 ± 0.100 | 0.12% |

**Table 3.** Water swelling degree results.

| Formula | Original Wight (g) | Swelled Wight (g) | Swelling degree (%) |
|---|---|---|---|
| **F2** | 0.2557 | 0.3752 | 46.73% |
| | 0.2393 | 0.3773 | 57.66% |
| | 0.2991 | 0.4455 | 48.94% |
| | 0.2724 | 0.3943 | 44.75% |
| | 0.2387 | 0.3664 | 53.49% |
| | 0.2444 | 0.3570 | 46.07% |
| | **Average** | | **49.60%** |
| **F3** | 0.4695 | 0.7062 | 50.41% |
| | 0.4179 | 0.6119 | 46.42% |
| | 0.4144 | 0.6841 | 65.08% |
| | 0.4136 | 0.5790 | 39.99% |
| | 0.3881 | 0.6592 | 69.85% |
| | 0.3919 | 0.6105 | 55.77% |
| | **Average** | | **54.58%** |
| **Commercial capsules** | 0.1256 | 0.1786 | 42.88% |
| | 0.1259 | 0.1759 | 39.71% |
| | 0.1208 | 0.1762 | 45.86% |
| | 0.1245 | 0.1816 | 45.86% |
| | 0.1234 | 0.1734 | 40.51% |
| | 0.1224 | 0.1698 | 38.72% |
| | **Average** | | **42.26%** |

**Table 4.** Capsule shell disintegration time test results.

| Formula | Experiments | Disintegration time |
|---|---|---|
| **II** | 1 | 06 minutes 47 seconds |
| | 2 | 08 minutes 30 seconds |
| | 3 | 08 minutes 46 seconds |
| | 4 | 09 minutes 10 seconds |
| | 5 | 10 minutes 30 seconds |
| | 6 | 10 minutes 50 seconds |
| | **Average** | 09 minutes 25 seconds |
| **III** | 1 | 06 minutes 10 seconds |
| | 2 | 07 minutes 25 seconds |
| | 3 | 10 minutes 05 seconds |
| | 4 | 11 minutes 08 second |
| | 5 | 11 minutes 56 seconds |
| | 6 | 12 minutes 05 seconds |
| | **Average** | 10 minutes 08 seconds |

## SEM-EDX test

An SEM test was conducted to observe the morphological structure of capsule shell samples (Fig. 2). The results of SEM characteristics are shown in the morphology (Sundaramurthy and Sundramoorthy 2018) of the 50% alginate: 50% sago starch capsule shells comprised a rough, uneven surface, unfused visible threads, and unevenly distributed constituent materials. Meanwhile, capsule shells of 0% alginate and 100% sago starch had uneven morphology with trapped air bubbles. In comparison, the morphological results of commercial capsules presented less pore distribution.

SEM-EDX is a microscopy test that serves to determine the percentage of elements contained in a sample. This analysis confirms the mixture of components present in the formulas, and the results can be seen in Fig. 3.

Fig. 3a presenting EDX test results shows that capsule shells are dominated by the elements of 63.23% carbon (C), 29.21% oxygen (O), and 4.73% sodium (Na). The raw materials used for the production process are 50% sago starch and 50% sodium alginate, where the constituent ingredients of sago starch are 84.7% carbohydrates with the formula (Cn ($H_2O$) n). Meanwhile, sodium alginate is in the form of a salt compound with the molecular formula ($C_6H_7O_6N_a$)n, and calcium (Ca) present in the F2 preparation is 0.66%. Fig. 3b shows that capsule shells are dominated by 42.59% oxygen, 40.42% carbon, and 8.78% sodium. Furthermore, the material used is 100% sodium alginate with a molecular formula ($C_6H_7O_6Na$)n, and Ca is present at 3.24%. Fig. 3c shows the dominance of 44.66% carbon, 28.84% oxygen, and 25.46% nitrogen (N) in capsule shells, along with a small amount of Ca (0.53%).

Sodium alginate plays a critical role in the crosslinking process due to its unique molecular structure. Comprising D-mannuronic acid (M) and L-guluronic acid (G) units, the proportion and sequence of these blocks influence the crosslinking efficiency with $Ca^{2+}$ ions. The G-blocks exhibit a higher affinity for $Ca^{2+}$, facilitating the formation of strong

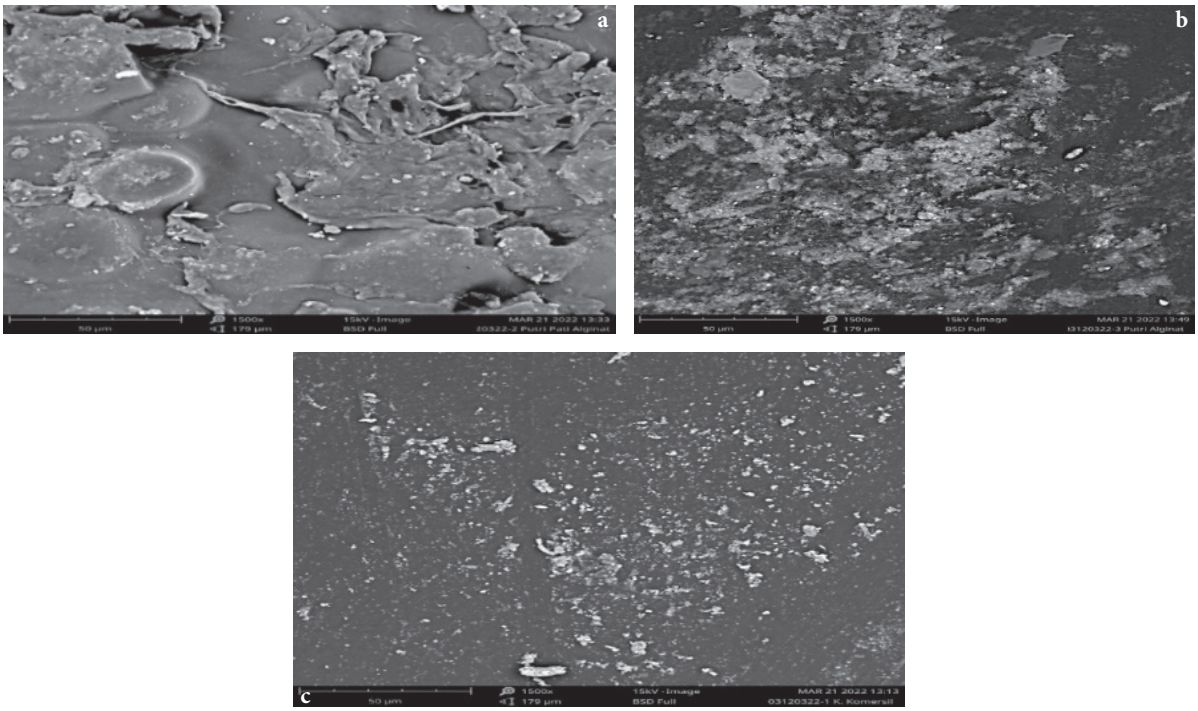


**Figure 2.** SEM test results of capsule morphology with 1500× magnification. **a.** Surface morphology of 50% sago starch: 50% sodium alginate capsule shells (F2); **b.** Surface morphology of 0% sago starch: 100% sodium alginate capsule shells (F3); and **c.** Surface morphology of commercial capsule shells.

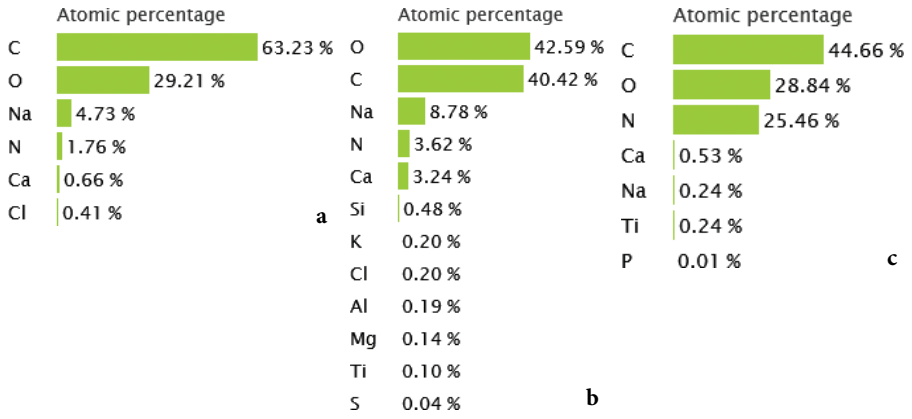


**Figure 3.** Elements contained in capsule shells. **a.** Elements of 50% sago starch: 50% sodium alginate capsule shells; **b.** Elements of 0% sago starch: 100% sodium alginate capsule shells; and **c.** Elements of commercial capsule shells.

ionic bonds that result in enhanced capsule rigidity and reduced solubility. This characteristic explains the superior performance of formulations with a higher alginate content, as evidenced by improved water swelling and disintegration properties. The presence of sodium ions ($Na^+$) in alginate further supports electrostatic interactions during crosslinking, contributing to uniform matrix formation.

## FTIR test

FTIR tests were conducted to determine the functional groups contained in capsule shells by assessing the wave numbers in each formula (Derkach et al. 2020b), including 50% sago starch, 50% alginate, and 100% alginate. This helped to prove crosslink is available in the composites of sago starch and sodium alginate, with Tables 5, 6 presenting FTIR test spectra data.

FTIR test results for the functional groups of capsule shells without $CaCl_2$ crosslinker showed absorption in the hydroxyl group (O-H bending) at 1463.6 $cm^{-1}$ in the 50% sago starch: 50% alginate sample and at 1476. 7 $cm^{-1}$ in the 0% sago starch: 100% alginate. Meanwhile, capsule shells with $CaCl_2$ crosslinker showed the hydroxyl functional group appeared at 1389.06 $cm^{-1}$ absorption in the 50% sago starch: 50% alginate sample and at 1394.81 $cm^{-1}$ in the 0% sago starch: 100% alginate sample. Based on FTIR spectra, there was a peak shift from 1463.6 $cm^{-1}$ to 1389.06 $cm^{-1}$ in 50% sago starch: 50% alginate capsule shells and from 1476.7 $cm^{-1}$ to 1394.81 $cm^{-1}$ in 0% sago starch: 100% alginate. The existence of this peak shift signifies the formation of a new bond in the capsule with the $CaCl_2$ crosslinker. The potential bond hypothesizes that $Ca^{2+}$ attaches to the hydroxyl group of the G-G block (guluronate-guluronate) in alginate to form a gel. (Breger et al. 2015; Derkach et al. 2020b; Sari et al. 2020; Lu et al. 2023).

**Table 5.** Functional groups on capsule shells with $CaCl_2$ crosslinker.

| Wavelength ($cm^{-1}$) | | |
|---|---|---|
| **Sago Starch 50%: Alginate 50%** | **Sago Starch 0%: Alginate 100%** | **Interpretation of Functional Groups** |
| 571.31–644.33 | 584.50–694.00 | C-X (X = *halogen*) |
| 900.10 | 787.04–955.27 | C=C *bending* |
| 1005.32 | 1117.45 | C-O, C-N, C-C *stretching* |
| 1120.11 | 1187.55 | C-O, C-N, C-C *stretching* |
| 1389.06 | 1394.81 | $CH_2$ *wagging band progression*, O-H *bending* |
| 1452.39 | | C-H *bending from alkanes* |
| 1632.64 | 1632.26–1754.84 | C=O *stretching* |
| 1726.13–1834.53 | | C-H *bending* |
| 1888.43–2023.93 | | C-H *bending* |
| 2108.94–2199.09 | | |
| 2334.41 | | C≡C *stretching* |
| 2516.33–2612.80 | | |
| | | S-H *stretching* |
| 2663.50 | | |
| 2772.88–2854.67 | | |
| | | C-H *stretching* |
| | 1822.53 | C ≡ N, Si-H |
| | 1871.83–2042.74 | C-H *bending* |
| | 2126.14–2189.08 | C≡C *stretching* |
| | 2339.40 | |
| | 2492.75–2614.63 | S-H *stretching* |
| | 2716.46 | C-H *stretching* |
| | 2777.40 | *Symmetric* C-H *stretching* |
| 2926.82 | 2937.14 | *Asymmetric* C-H *stretching* |
| 3426.92 | 3444.52 | N-H *stretching* (*non-hydrogen bonded*) |
| | 3574.03 | |
| 3703.60 | 3647.22 | N-H *stretching*, C-H *stretching* |
| 3848.62 | | O-H *and* N-H *stretching*, C-H *stretching* |
| 3907.24 | | |

**Table 6.** Functional groups on capsule shells without $CaCl_2$ crosslinker.

| Wavelength ($cm^{-1}$) | | |
|---|---|---|
| **Sago Starch 50%: Sodium Alginate 50%** | **Starch 0%: Sodium Alginate 100%** | **Interpretation of Functional Groups** |
| 577–925 | 618–719 | C-C-C, C-C-O, *and* C-O-C *cyclic alkane skeletal breathing*, O-H *out-of-plane banding* |
| 950–1156 | 929–1111 | C-O *stretching from ether, secondary alcohols* |
| 1327–1415 | 1262–1461 | C-H *bending and twisting from alkane or cyclic alkane* |
| 1463.6 | 1476.7 | O-H *bending from carboxylic acid groups* |
| | 1618 | C=C *stretching from cyclic alkene or* N-H *bending from amine or* -OH *from adsorbed water* |
| 1606 | | -OH *from adsorbed water* |
| 2887–2935 | 2849–2952 | C-H *stretching from alkanes* |
| 3000–4000 | 3000–4000 | O-H *stretching (forming intermolecular forces)* |

The interaction between calcium ions ($Ca^{2+}$) and alginate predominantly occurs through ionic crosslinking. The carboxylate groups (-$COO^-$) present in the L-guluronic acid blocks of alginate act as coordination sites for $Ca^{2+}$ ions, forming the well-documented "egg-box" structure. This configuration stabilizes the polymer matrix, enhancing mechanical integrity and gelation. FTIR analysis supports this interaction, with notable shifts in the carboxylate-related peaks around 1600–1700 $cm^{-1}$, indicative of $Ca^{2+}$ binding. Additionally, the shifts observed in the hydroxyl group vibrations are likely a secondary effect caused by structural rearrangements due to crosslinking. The hydroxyl groups' altered hydrogen bonding patterns, as evidenced by shifts from 1463.6 $cm^{-1}$ to 1389.06 $cm^{-1}$ in F2 and from 1476.7 $cm^{-1}$ to 1394.81 $cm^{-1}$ in F3, further confirm the formation of a stable crosslinked network. This dual evidence from the FTIR spectra highlights the combined contributions of carboxylate and hydroxyl groups to the capsule shell's structural stability.

## Formula optimization with the SLD method

Formula optimization can be predicted based on the results of sample testing using the SLD method. This was conducted to fulfill the characteristics of a good dosage form as desired (Huisman et al. 1984; Patel et al. 2007; Vaghani et al. 2012; Cherie et al. 2018; Khanam et al. 2018; Indrati et al. 2020), with Table 7 presenting SLD equation results.

**Table 7.** SLD equation results.

| | Equation SLD | Equation |
|---|---|---|
| Capsule weight uniformity | Y = 0 (A) + 26.174 (B) – 0.1955(A) (B) | (1) |
| Water swelling test | Y = 0 (A) + 54.587 (B) – 89.254 (A) (B) | (2) |
| Disintegration time test | Y = 0 (A) + 9.682 (B) – 16.056 (A) (B) | (3) |

The optimum formula range was obtained from the equation using the largest total response based on normalization calculations. In this research, the optimal formula was obtained from the calculations of the response parameters of capsule shell weight uniformity, the water swelling test, and the destruction time test. Subsequently, each parameter was measured to determine the ratios of capsule shell weight uniformity (0.3), water swelling (0.3), and disintegration time (0.4). There were no special provisions in determining the weight of the parameters used, but only based on measuring the weight and size of capsule shells, as well as water swelling and destruction time tests. Capsule shell disintegration time had more significant influence when compared to the parameters of the weight uniformity and water swelling. Fig. 4 is a graph of SLD calculation results, which will be verified by preparing formulas for comparison and validation.

Fig. 4a, representing the graph of the relationship between the % deviation of capsule shell weight uniformity with the composition of sago starch and sodium alginate, shows that higher sodium alginate content leads to higher values of the test parameters. More sodium alginate addition will initiate a greater degree of water swelling (Fig. 4b), while the addition of a higher alginate level tends to extend the disintegration time (Fig. 4c).

### *a. Total response*

Total response is often determined by calculating total response to each test after obtaining the graph data of all parameters. Fig. 5 shows the graph of the relationship between the response and the composition of sago starch and sodium alginate.

The graph shows that the addition of sodium alginate has a higher response than the introduction of sago starch based on the SLD method. This implies that the addition of a higher sodium alginate level will lead to the production of a greater response. Based on the total response, the best formula is 10% starch and 90% alginate with a complete reaction of 0.957 and the inability of alginate addition to increase the total response.

### *b. Validation of SLD equation using one-sample t-test*

The validation test was conducted to ensure that the prediction data obtained from the SLD equation was valid when used for capsule shell formula optimization with sago starch and sodium alginate raw materials. A prediction formula with the proportion of 60% sago starch and 40% sodium alginate was randomly selected for comparison against an accurate sample preparation. The comparison graph of the prediction formula test data with the experimental results is presented in Fig. 6. The difference

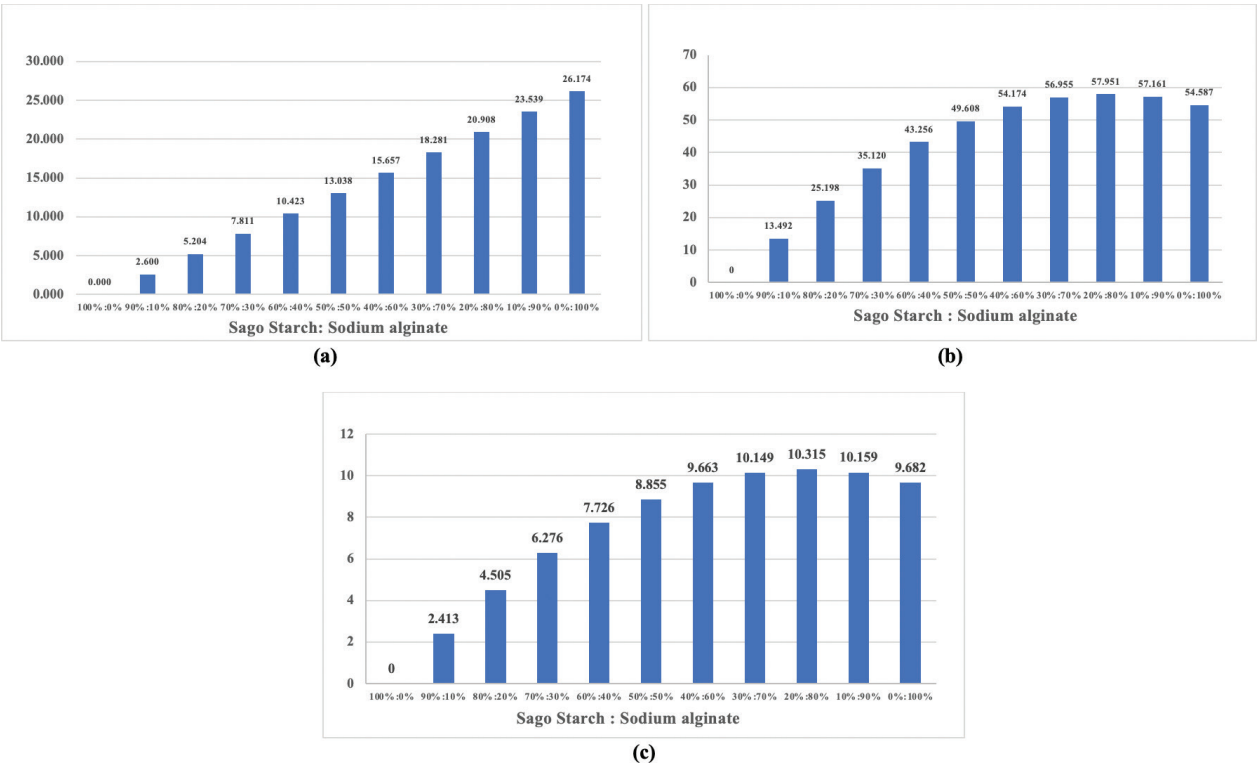


**Figure 4.** Relationship graph of SLD calculation results with sago starch and sodium alginate composition. **a.** Graph of relationship between % deviation of capsule shell weight uniformity with sago starch and sodium alginate composition; **b.** Graph of relationship between degree of % water swelling and composition of sago starch and sodium alginate; and **c.** Graph of relationship between disintegration time and composition of sago starch and sodium alginate.

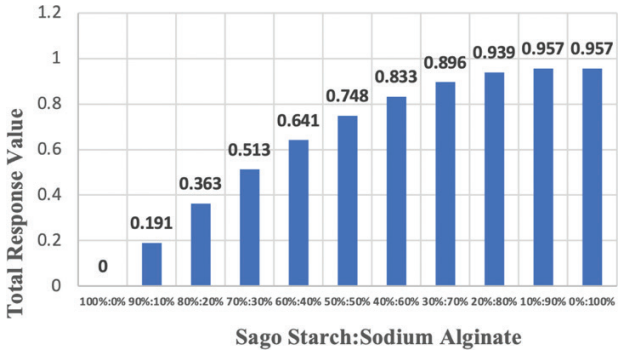


**Figure 5.** Response graph.

in % deviation of weight uniformity, swelling degree, and destruction time of the predicted results when compared with the experimental results of capsule shells was 13.79%, 2.82%, and 6.32%.

The prediction data from different experiments attributed this observed difference to the manufacturing method. A manual method was used to prepare shells in this research with an uneven printing process, thereby generating unequal capsule thickness. Both the prediction data and the experimental results were statistically analyzed using a one-sample t-test. This was used to determine whether the value predicted with the SLD method was significantly different from the average value of the experimental results. The data from the normality analysis of the treatment results conducted using SPSS are presented in Table 8.

The normality results of the two data groups showed a significance value > 0.05, implying that both groups were normally distributed. Subsequently, a one-sample t-test was conducted on these data groups, with Table 9 presenting the obtained results.

**Table 8.** Normality test results.

| Parameters | Significance | Conclusion |
|---|---|---|
| Water Swelling Test | 0.867 | Data is normally distributed |
| Disintegration Time Test | 0.319 | Data is normally distributed |

**Table 9.** One-sample t-test results.

| Parameter | Significant | Conclusion |
|---|---|---|
| Water Swelling Test | 0.180 | Not significantly different |
| Disintegration Time Test | 0.238 | Not significantly different |

One-sample t-test results showed that the values of the two sample groups were > 0.05, with swelling and destruction time tests presenting significance values of 0.180 and 0.238, respectively. These showed a similarity between the predicted and experimental values; hence, the SLD equation would be valid when used to optimize capsule shell formulas comprising sago starch and sodium alginate raw materials with a $CaCl_2$ crosslinker.

## Discussion

The findings from this study demonstrate that a combination of sago starch and sodium alginate, crosslinked with $CaCl_2$, can successfully serve as a non-gelatin alternative for capsule shells. The production method and materials chosen—particularly the use of sago starch and alginate, both polysaccharides—address the demand for halal-compliant materials, meeting the cultural and religious needs of predominantly Muslim populations. Notably, the results show that the $CaCl_2$ crosslinker effectively enhanced the capsule shells' mechanical integrity by creating covalent and ionic bonds, as evidenced by the shift in FTIR spectra, which indicates the formation of a new crosslinked structure.

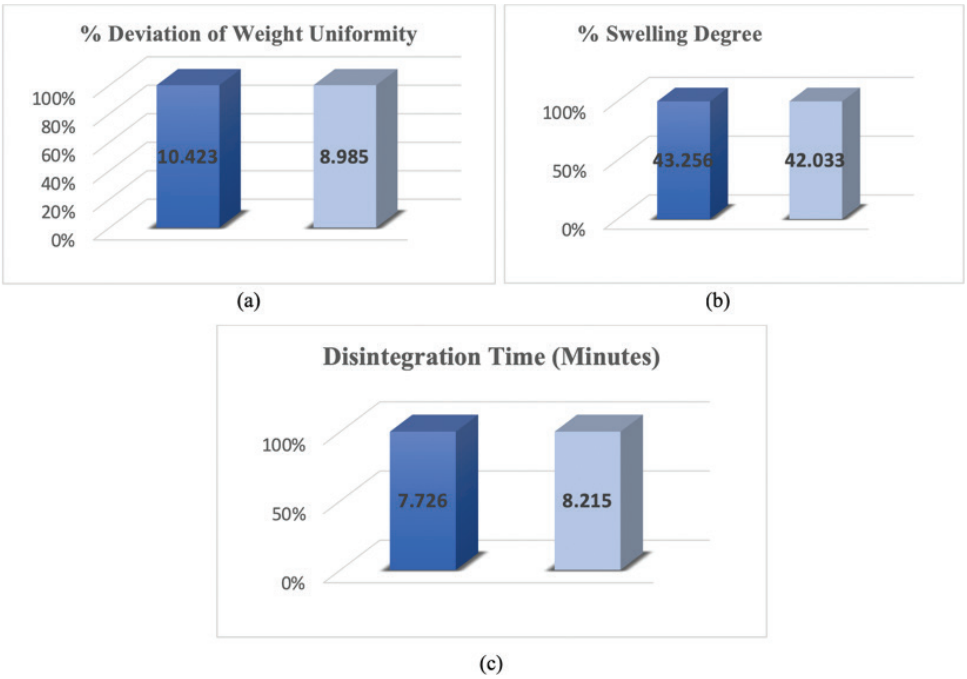


**Figure 6.** Comparison chart of prediction formula test result data with experimental results. **a.** Deviation of predicted and experimental weight uniformity; **b.** Predicted and experimental water swelling degree; and **c.** Predicted and experimental disintegration times.

A primary focus of this study was to optimize the physical characteristics of the capsules, including weight uniformity, water swelling, and disintegration time, through the Simplex Lattice Design (SLD) method. The optimal formulation of 10% sago starch and 90% sodium alginate achieved a balance among these parameters, particularly enhancing water absorption due to the high content of alginate, which is known for its hydrophilic properties. This high alginate content contributed to increased swelling capacity, as observed in the significant water absorption rates. Furthermore, the disintegration test indicated that this formulation had a favorable breakdown time, showing practical viability for use as an oral capsule. The increase in sodium alginate content resulted in higher swelling rates and prolonged disintegration times, a trend consistent with alginate's molecular structure, which enhances water retention due to its hydroxyl and carboxyl groups.

Supporting studies emphasize $CaCl_2$'s role in enhancing mechanical strength and stability in alginate-based matrices. Amiruddin et al. (2023) observed that $CaCl_2$ crosslinking in alginate capsules increases shell rigidity and cohesion, beneficial for pharmaceutical stability and encapsulation applications. Similarly, Prasetyaningrum et al. (2024) demonstrated how $Ca^{2+}$ crosslinking in sodium alginate enhances swelling behaviors and controlled release, aligning with this study's results showing favorable water absorption and disintegration properties. Surface morphology, analyzed through SEM-EDX, revealed that capsules made with higher sago starch content had more porous and uneven surfaces, with visible air pockets, compared to capsules made with sodium alginate, which displayed more uniform morphology. This suggests that sodium alginate contributes to a more cohesive structure, while sago starch, when used in higher proportions, may lead to issues with uniformity due to its granular nature and lower water solubility. These findings are consistent with Kurayama et al. (2012), who found that $CaCl_2$ crosslinking impacts alginate shell uniformity and thickness, supporting the current observations of thicker, more stable capsule shells with higher sodium alginate proportions.

The validation of the SLD model through the one-sample t-test demonstrated that the predicted values for weight uniformity, swelling, and disintegration time were not significantly different from the experimental results, thereby confirming the reliability of the SLD model for predicting optimal formulations. However, it was noted that the manual manufacturing process contributed to some variability in capsule shell thickness, likely impacting uniformity and weight. Future research could improve this method by automating the capsule shell production process, which may yield more consistent results and further enhance the capsule's physical characteristics.

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The findings of this study highlight the feasibility of using sago starch and sodium alginate as halal-compliant materials for pharmaceutical capsules. The 10% sago starch:90% sodium alginate formulation, optimized through the Simplex Lattice Design, offers an effective balance between mechanical stability and disintegration properties. The rapid disintegration time observed in this formulation aligns well with the requirements for oral dosage forms, ensuring efficient drug release. Moreover, the incorporation of $CaCl_2$ as a crosslinking agent enhances the capsule's resistance to environmental factors, such as humidity, making it a promising alternative to conventional gelatin capsules. This study paves the way for further research into automated manufacturing techniques and scaling up the production process to meet industrial demands. While this study establishes the groundwork for gelatin-free capsule formulations, further investigations are warranted to address certain limitations. Automated manufacturing processes should be explored to improve uniformity and reduce deviations in capsule shell thickness. Additionally, long-term stability studies under various storage conditions are necessary to evaluate the capsules' shelf life and resilience. Expanding the scope of crosslinking agents, such as exploring natural alternatives to calcium chloride, may also offer insights into optimizing biocompatibility and reducing environmental impact. These advancements will ensure broader applicability and acceptance of these novel capsule formulations in the pharmaceutical industry.

## Conclusion

In conclusion, this research identified that the mixing of sago starch and sodium alginate with a $CaCl_2$ crosslinker could produce crosslinking as shown in the FTIR test by the appearance of a hydroxyl group band (O-H bending) with a shift in absorption from 1463.6–1389.06 $cm^{-1}$ in F2 and 1476.7–1394.81 $cm^{-1}$ in F3. Based on the results, $CaCl_2$ could be used as a crosslinker for sago starch capsule shells and sodium alginate. Optimal characteristics were observed in F2 with a % deviation of capsule shell weight uniformity of 8.164%, a water swelling degree of 49.60%, and a destruction time of 09 minutes 25 seconds. Using the SLD equation, the optimal formula was found to be 10% sago starch and 90% sodium alginate with a total response value of 0.957.

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# Additional information

## Conflict of interest

The authors have declared that no competing interests exist.

## Ethical statements

The authors declared that no clinical trials were used in the present study.
The authors declared that no experiments on humans or human tissues were performed for the present study.
The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.
The authors declared that no experiments on animals were performed for the present study.
The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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## Author contributions

Sabtanti Harimurti: Supervised the project, provided conceptual guidance, and contributed to study design, methodology, and final manuscript revision; Putri Nur Amalia: Conducted the experiments, performed data analysis, and contributed to the initial manuscript draft; Dyani Primasari Sukamdi: Assisted with experimental procedures and data collection and contributed to data analysis; Hari Widada: Provided insights into the formulation process, contributed to data interpretation, and reviewed manuscript drafts; Sri Nabawiyati Nurul Makiyah: Supported experimental design, assisted in data collection, and contributed to manuscript editing; Tri Wulandari Kesetyaningsih: Contributed to the statistical analysis and assisted in interpreting the results; Muhammad Thesa Ghozali: Assisted with research methodology, contributed to data validation, and provided critical feedback on the manuscript; and Hari Susanti: Contributed to the literature review, data verification, and overall manuscript review.

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## Data availability

All of the data that support the findings of this study are available in the main text.

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