

Development of Wound Dressing Hydrogel Based Combination of Cassava Starch/PVA and Aloe Vera Extract

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Abstract

Wound care involves various methods, including dressing to prevent bacterial infection at the wound site. Typically, these dressings are made from synthetic materials lacking biocompatibility. Many researchers have explored alternative wound dressings derived from natural polymers due to their non-toxic, biocompatible properties and natural degradation, such as starch. However, starch exhibits low mechanical strength, necessitating its combination with other polymers. Additionally, high-quality wound dressings require additional components that can expedite wound healing. Therefore, this study aims to develop a hydrogel-based wound dressing using a combination of cassava starch, polyvinyl alcohol (PVA), and aloe vera extract.

The simplex lattice design (SLD) determined the optimal hydrogel film formula. A comprehensive examination was conducted, encompassing a multitude of parameters; including pH value, swelling index ratio, degradation ratio, and water vapor transmission rate (WVTR). The ideal formula comprised 5% cassava starch, 5% PVA, and 2% aloe vera extract. Characteristics included a swelling ratio of $399.33 \pm 33.13\%$ and WVTR of $816.13 \pm 87.72 \text{ g/m}^2 \text{ day}$, film degradation of $85.93 \pm 0.1\%$ after 14 days, pH of 5.88 ± 0.22 , and tensile strength of $17.92 \pm 12.80 \text{ MPa}$, with a transparent and slightly yellowish appearance. This optimal hydrogel film showed promise as a wound dressing alternative.

Keywords: Wound dressing; Hydrogel; PVA; Cassava starch; Aloe vera.

1. Introduction

Wound dressings are commonly utilized to treat surface wounds and mitigate bacterial infection in the affected area. Essential criteria for wound dressings include biocompatibility and the avoidance of immune responses. However, most conventional wound dressings are synthetic materials with low biocompatibility and limited degradability. Numerous researchers are actively pursuing the development of alternative wound dressings

made from natural polymers. These polymers offer non-toxic, enhanced biocompatibility and facile biodegradability. Among the natural polymers suitable for alternative wound dressing materials are cellulose, chitin, chitosan, and starch [1].

Starch emerges as a promising natural polymer for use in wound dressing materials. Its resemblance to the extracellular matrix suggests compatibility with the body's biological system, minimizing the risk of

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immunological reactions [2]. Additionally, starch boasts biocompatibility, biodegradability, cost-effectiveness, and excellent exudate absorption capacity [2]. However, starch faces challenges such as susceptibility to degradation, low mechanical strength, and a lack of inherent wound-healing properties. Therefore, a synergistic combination of starch with other materials is imperative for developing effective wound dressings. One reinforcing polymer is polyvinyl alcohol (PVA), which features hydroxyl (OH) groups facilitating hydrogen bond formation with starch. PVA further exhibits biodegradability and biocompatibility, thus posing as a promising adjunct material in wound dressing formulations [2].

Incorporating wound healing-accelerating components into wound dressings can significantly improve their effectiveness. Aloe vera extract stands out as a natural ingredient suitable for this purpose. Glucmannan, found in aloe vera extract, has been shown to stimulate fibroblast activity and proliferation [3]. Additionally, aloe vera extract contains compounds such as p-fumaric acid, ascorbic acid, pyrocatechol, and cinnamic acid, known for their antibacterial properties [4]. Furthermore, the mucopolysaccharides present in aloe vera extract help retain moisture in the skin and impart a soothing, cooling effect [4].

Consequently, the development of an alternative wound dressing utilizing a combination of starch, PVA, and aloe vera extract has the potential to be a highly effective wound dressing. This study aims to determine the optimum formula for high-quality hydrogel-based wound dressings. The determination of the optimum formula was based on the simplex lattice design. The optimum formula was determined based on the swelling ratio, the water vapor transmission rate (WVTR), and film degradation.

2. Materials and Methods

2.1. Materials

Polyvinyl alcohol (hydrolyzed, 88%, viscosity 4% = 45 mPa.s) was purchased from Poval (Japan). Aloe vera dry extract powder was purchased from Atina (Indonesia). Cassava starch (cosmetic and pharmaceutical grade) was purchased from a local resource (Indonesia). Potassium chloride, citric acid, and sodium chloride were purchased from Xilong Scientific. Glycerin was purchased from Brataco (Indonesia).

2.2. Preparation of hydrogel film

The preparation of the hydrogel films was conducted using material combinations based on the simplex lattice design method (Table 1). The PVA solution was prepared by dissolving PVA in hot water (70°C) under stirring at 100 rpm. Meanwhile, the cassava starch was dissolved in hot water (90°C), and citric acid was added while stirring at 500 rpm for 10 minutes. The PVA and cassava starch solution were combined at 70°C, stirring at 100 rpm. Glycerol and aloe vera extract were added sequentially to the polymer solution mixture under stirring for 10 minutes for each component. Finally, the solution mixture was poured into a petri dish until the liquid level reached 3 mm and then followed by a drying process using an oven at 40°C for 6 hours. The hydrogel film was washed with distilled water to remove residual citric acid. The washing was performed by immersing the film in 20 mL of water for 15 seconds, repeated 15 times. The film was dried at 40°C for 3 hours using the oven. Finally, hydrogel film was removed from the petri dish and stored in a tightly closed container.

Table 1. Variable component of hydrogel film generated by Simplex lattice design (SLD)

No	Components	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7	Run 8
		Ratio (%)							
1	Cassava starch	7.5	8.75	7.5	10	6.25	10	5	5
2	PVA	2.5	1.25	2.5	0	3.75	0	5	5
3	Citric acid	0.18	0.21	0.18	0.23	0.15	0.23	0.12	0.12
4	Glycerol	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
5	Aloe vera extract	2	2	2	2	2	2	2	2
6	Water	ad 100	ad 100	ad 100	ad 100	ad 100	ad 100	ad 100	ad 100

2.3. Characterization of Hydrogel Film

Physical Properties

The organoleptic properties of the hydrogel films, including color, texture, and odor, were evaluated. Furthermore, the thickness of the hydrogel was measured utilizing a digital thickness gauge (Mitutoyo).

pH Value

The hydrogel film's pH was ascertained using a universal pH indicator solution (Loba Chemie).

Swelling Ratio

The swelling ratio test was carried out: a nonwoven polyester fabric filter (5 μm pore size) was moistened with the test medium and placed in the center of a 9 \times 1.5cm Petri dish. The polyester nonwoven filter was subjected to wetting by applying 8 mL of simulated wound fluid (SWF) or distilled water, with the latter serving as the test medium. The simulation fluid utilized in this study was prepared by dissolving 0.368 grams of calcium chloride and 8.298 grams of sodium chloride in 1 liter of deionized water, as previously described [5].

The dimensions of the hydrogel films were calibrated to approximately 1 \times 1 cm, following which their weight was measured as dry weight (W_0). Subsequently, the hydrogel film was positioned on the polyester nonwoven filter and subjected to an incubation temperature of 37°C. Thereafter, the samples were re-weighed at predetermined time intervals (W_1). The percentage of swelling ratio was calculated using the following equation:

$$\text{Swelling Ratio (\%)} = \frac{(W_1 - W_0)}{W_0} \times 100 \quad (1)$$

W_1 : final weight of hydrogel at the time (mg)

W_0 : dried weight of hydrogel (mg)

Water Vapor Transmission Rate

The hydrogel film was shaped into a circle with a diameter of 2.8 cm and positioned over the mouth of a glass bottle containing 10 mL of distilled water at approximately three-quarters of the hydrogel sample (15). Initially, the bottles containing water were weighed (W_0). Subsequently, the hydrogel film was adhered to the

mouth of each bottle using a PTFE adhesive. The final step entailed incubating the samples at 37°C in a 50% relative humidity environment for 24 hours. The WVTR value was subsequently calculated using the following equation:

$$\text{WVTR (mg/cm}^2 \cdot \text{day)} = \frac{(W_0 - W_1)}{A \times \text{day}} \quad (2)$$

W_0 : initial weight of bottle (mg)

W_1 : weight of bottle after incubation (mg)

A: surface area of mouth glass (cm^2)

Film Degradation Evaluation

The hydrogel films were cut into pieces measuring approximately 1 \times 1 cm and subsequently weighed to determine their initial weight before swelling. A hydrogel film was then positioned on a polyester nonwoven filter, which was then moistened with the test medium (simulated wound fluid) in a Petri dish. The samples were then placed in an incubator set at 37°C. Subsequent weight measurements were obtained at regular intervals, and the maximum weight attained during the swelling process was documented. The percentage of film degradation was then determined using the following equation:

$$\text{Film degradation (\%)} = \frac{(W_0 - W_1)}{W_0} \times 100 \quad (3)$$

W_0 : initial weight of film hydrogel (mg)

W_1 : final weight of film hydrogel (mg)

Tensile Strength Evaluation

The hydrogel sample was meticulously sectioned into rectangular strips, with dimensions precisely calibrated to 2.5 cm in length and 5 cm in width. Subsequently, tensile tests were performed on these strips employing a universal testing machine (RTI-1225, A&D Company, Japan). The testing machine was configured to apply a tensile load of 2.5 kN at a 10 mm/min rate. The resultant value of this test is defined as tensile strength or Young's modulus. The units of measurement for tensile strength test results are N/mm² or MPa [2].

Scanning Electron Microscopy

Morfologi hydrogel film diobservasi dengan menggunakan JSM-6510LA (Japan). The sample was mounted on an aluminum stub with adhesive carbon tape.

3. Results and Discussion

3.1. Preparation of Hydrogel Film

The physical characteristics of the hydrogel film are presented in **Table 2**. The thickness of the hydrogel film was within a range of 0.08–0.5 mm, exhibited a yellowish coloration, was transparent, and had a smooth surface. The optimal wound dressing should generally exhibit a smooth, transparent, flexible surface [6].

Table 2 indicated that the pH value of the hydrogel film in all runs was within the range of 5 to 6. The optimal pH value for a wound dressing was between 5.2 and 6.8, as this range was conducive to wound healing. Suppose the pH value of the wound dressing is higher than the pH value of the wound environment. In that case, the wound-healing process will cease, potentially leading to the development of a chronic wound and an increased susceptibility to infection. The pH value of the wound tissue environment can influence biochemical activity at every stage of wound healing. Therefore, using a wound dressing that can promote wound healing and kill or prevent the growth of bacteria is vital. Wound dressings with a relatively acidic pH can assist in maintaining the acidic pH of the wound tissue, thereby creating optimal conditions for fibroblast activity, which encompasses the processes of migration, proliferation,

and collagen formation. Furthermore, the acidic wound environment can inhibit bacterial growth and enhance antimicrobial activity [7].

Initially, acidosis occurs in the wound tissue due to increased lactic acid and oxygen levels. This condition is necessary to support fibroblast proliferation, cell DNA synthesis, collagen formation, angiogenesis, and macrophage activity. However, chronic wounds have an alkaline environment caused by immune response mechanisms that support bacterial growth, increase proteolytic activity, inhibit fibroblasts, and reduce oxygen supply [8]. Consequently, the wound dressing employed in this study was more appropriate for treating acute wounds resulting from skin lacerations, animal bites, scratches, and surgical incisions.

3.2. Swelling Ratio of Hydrogel Film

The objective of the swelling test was to assess the capacity of the hydrogel film to absorb wound exudate while maintaining a moist environment in the wound without the accumulation of exudate in the wound tissue, thereby facilitating the wound healing process [9]. A suitable wound dressing should exhibit a more than 100% swelling ratio. The results of the swelling ratio test for all hydrogel films conducted in simulated wound fluid and distilled water media can be seen in **Table 3**.

Table 2. Physical parameters of hydrogel films

Run	Cassava starch: PVA ratio (%)	Physical parameters of hydrogel film			
		Thickness	Appearance	Surface texture	pH value
1	(7.5:2.5)	0.10 - 0.45	Transparent Yellowish	Smooth	5.0 ± 0.00
2	(8.75:1.25)	0.10 - 0.35	Transparent Yellowish	Smooth	5.0 ± 0.00
3	(7.5:2.5)	0.08 - 0.5	Transparent Yellowish	Smooth	5.56 ± 0.50
4	(10.0:0)	0.11 - 0.41	Transparent Yellowish	Smooth	5.25 ± 0.30
5	(6.25:3.75)	0.12 - 0.35	Transparent Yellowish	Smooth	5.0 ± 0.00
6	(10.0:0)	0.12 - 0.31	Transparent Yellowish	Smooth	5.0 ± 0.00
7	(5:5)	0.1 - 0.5	Transparent Yellowish	Smooth	5.5 ± 0.00
8	(5:5)	0.1 - 0.6	Transparent Yellowish	Smooth	6.0 ± 0.00

Table 3. Swelling ratio result of hydrogel films (N=3)

Run	Cassava starch: PVA ratio (%)	Swelling ratio (%)	
		Simulated wound fluid	Aquadest
1	(7.5:2.5)	271.17 ± 71.72	331.64 ± 23.89
2	(8.75:1.25)	260.68 ± 41.29	285.16 ± 37.73
3	(7.5:2.5)	129.24 ± 14.34	173.60 ± 16.05
4	(10.0:0)	104.94 ± 7.06	172.18 ± 28.18
5	(6.25:3.75)	68.60 ± 14.85	156.21 ± 4.20
6	(10.0:0)	79.37 ± 3.86	102.71 ± 3.02
7	(5:5)	248.10 ± 46.35	314.67 ± 18.04
8	(5:5)	128.93 ± 17.97	230.80 ± 17.62

The highest swelling ratio was obtained in run 1, which consisted of cassava starch and PVA (7.5:2.5), with a value of $271.17 \pm 71.72\%$. In contrast, run 5 consists of cassava starch and PVA (6.25:3.75), exhibiting the lowest swelling ratio (68.60%) in the simulated wound fluid medium. The two-way ANOVA statistical analysis results demonstrated a statistically significant difference between runs (p -value <0.0001). The data revealed that variations in the combination of cassava starch and PVA in the hydrogel film formula influenced the swelling ratio. Compared to the swelling ratio in distilled water, the swelling ratio of hydrogel film in simulated wound fluid media demonstrated a lower value.

The presence of salt components in the simulated wound fluid was responsible for the observed reduction in the interaction of water molecules with the polymer chain. This phenomenon was attributed to the electrostatic repulsion caused by the salt's ionic charge, which disrupted the hydrogen bonds between the water molecules and the polymer chains [10].

The results of the swelling test in distilled water revealed that run 1 (comprising cassava starch and polyvinyl alcohol at a ratio of 7.5: 2.5) exhibited the highest swelling ratio, at $331.64 \pm 23.89\%$. Conversely, the lowest swelling ratio, at $102.71 \pm 3.02\%$, was obtained by run 6, consisting of cassava starch and polyvinyl alcohol at a ratio of 10:0. A two-way ANOVA revealed a p -value <0.0001 for all runs. In conclusion, the combination of cassava starch and PVA in the formulation affects the swelling ratio of the hydrogel film in distilled water media.

The swelling ability of hydrogel film is controlled by hydrogen bonds between water molecules and polymer chains. Starch and PVA have a high affinity to absorb and retain water from the environment due to the presence of -OH groups in their polymer chains [10]. Starch maintains a balance by absorbing and releasing water molecules from the environment [10].

Conversely, cross-links between polymers can reduce water absorption due to forming a compact three-dimensional structure and reducing free hydroxyl (OH) groups [10]. However, low cross-link density in polymers can increase water absorption capacity and swelling ability [10].

The equation was obtained by the simplex lattice design method for the response of the swelling ratio, as shown below,

$$Y = 90.5377A + 186.899B + 207.183 AB + 1281.38 AB(A-B) \quad (4)$$

Y: swelling ratio (%)

A: cassava starch (g)

B: PVA (g)

According to Equation 4 and **Figure 1**, incorporating cassava starch and PVA into the hydrogel film enhanced its swelling ratio value. The coefficient value of cassava starch was smaller than that of PVA. This suggests that the addition of PVA exerts a more dominant influence on the swelling ratio value of the hydrogel film.

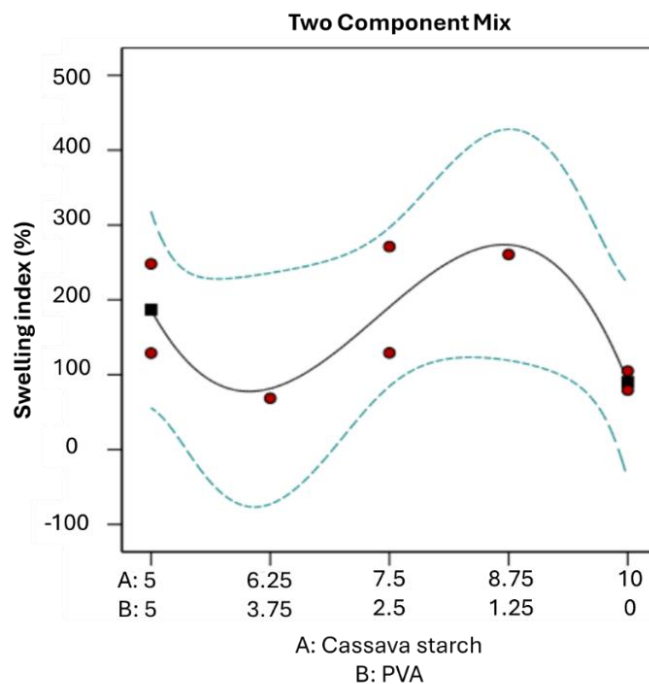


Figure 1. Combination polymer effect on Swelling Ratio response model

3.3. Water Vapor Transmission Rate

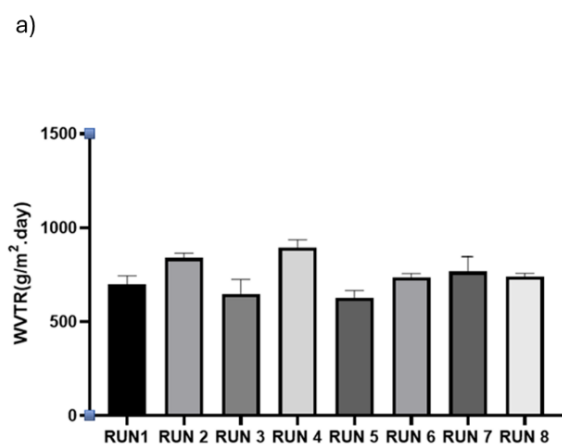
An ideal wound dressing must regulate water loss from the wound to prevent excessive dehydration [11]. A high level of water vapor transmission can result in dehydration of the wound tissue. However, a low level of water vapor transmission can lead to the accumulation of exudate in the wound tissue. Therefore, the ideal

wound dressing must have a higher water vapor transmission rate (WVTR) value than normal skin [11]. The WVTR value of normal skin is approximately 204 g/m².day, and first-degree burns have WVTR values of 279 to 5138 g/m².day [12]. Commercial products generally have WVTR values of 76 g/m².day to 9360 g/m².day [12]. The results of the WVTR test for all runs (Figure 2a) indicated a value of 625.69 ± 40.76 to 839.08 ± 25.90 g/m².day, which were within the range of WVTR values typically observed in commercial products.

The mathematical model obtained from the statistical analysis of WVTR values using simplex lattice design was cubic, while the analysis using ANOVA with a 95% confidence level produced a p-value of 0.1208. This indicated that variations in concentration between cassava starch and PVA in the formula did not affect the WVTR value response. Consequently, the WVTR value cannot be used for the optimization process to obtain the optimum formula. The equation derived from the simplex lattice design method for the WVTR response is as follows:

$$Y = 818.129A + 756.227B - 394.871 AB + 973.048 AB(A-B) \quad (5)$$

Y: WVTR value (%)
A: cassava starch (g)
B: PVA (g)



Referring to Equation 5 and Figure 2b, an increase in the cassava starch to PVA ratio can enhance the hydrogel film's WVTR. Furthermore, the coefficient value for cassava starch was higher than PVA, suggesting that incorporating cassava starch was more influential in increasing the WVTR value response. Conversely, when cassava starch and PVA were combined, the WVTR value decreased. PVA contains more hydroxyl groups than cassava starch, making it more hydrophilic than starch [13]. As a result, when the surface becomes highly hydrophilic, its absorption capacity increases, allowing it to retain water molecules for an extended period, thereby delaying transmission time. In contrast, the hydrophobic surface of the polymer traps water molecules and releases them more quickly [14].

3.4. Degradation of Hydrogel Film

The hydrogel film degradation test aimed to determine the weight loss over a specified period. The hypothesis posited that the hydrogel film would degrade within 14 days. According to Figure 3a, runs 1, 5, 7, and 8 exhibited a degradation value exceeding 90%. Among these, run 1 showed the highest degradation value ($95.88 \pm 1.19\%$), while run 6 demonstrated the lowest value ($55.53 \pm 7.95\%$). A statistically significant difference (p-value=0.0001) was found between the runs using a two-way analysis of variance (ANOVA), indicating that the combination of cassava starch and PVA in the hydrogel film formula affects its degradation.

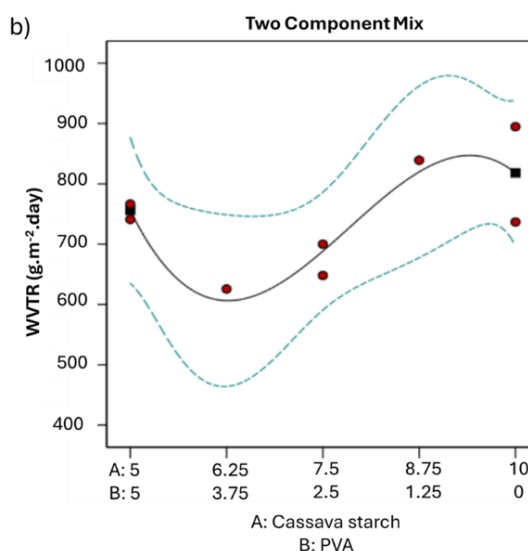


Figure 2. (a) WVTR values of hydrogel films (N=3), (b) Component ratio effect model for hydrogel film WVTR.

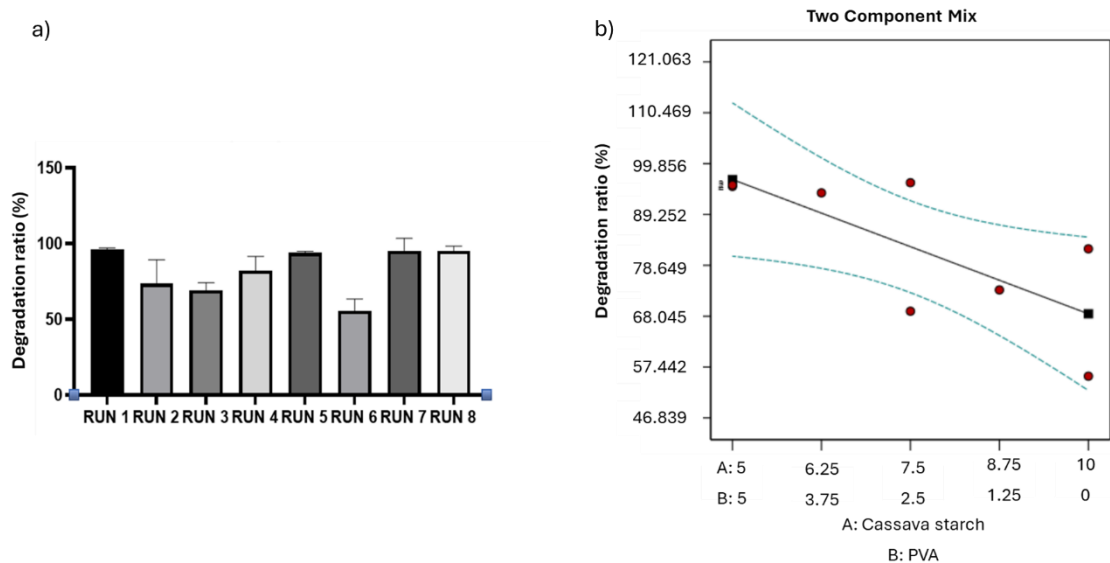


Figure 3. a) Degradation ratio of hydrogel films (N=3), b) Component ratio effect model for hydrogel film degradation.

The mathematical model for the degradation value, generated by the simplex lattice design, was represented as a linear equation. Meanwhile, analysis using the ANOVA method at a 95% confidence level resulted in a p-value of 0.0366, indicating that variations in the concentrations of cassava starch and PVA within the formula significantly affected the degradation value. The equation derived through the simplex lattice design methodology for the degradation value is presented below.

$$Y = 68.546A + 96.5354B \quad (6)$$

Y: degradation ratio (%)

A: cassava starch (g)

B: PVA (g)

Referring to Equation 6 and **Figure 3b**, adding polyvinyl alcohol (PVA) to the formula increased the degradation value of the hydrogel film. This effect can be attributed to the decreased levels of citric acid within the formula, which in turn was caused by the reduced ratio of cassava starch as the PVA ratio increased. Water molecules play a crucial role in facilitating the separation of bonds between polymers. Moreover, the film's resistance to water penetration is influenced by ester bonds within it [2]. Consequently, a higher concentration of citric acid as a cross-linker in the formula can effectively reduce the rate of film degradation [2].

3.5. Optimization of Hydrogel Film Formula-Based Simplex Lattice Design

The determination of the optimal hydrogel film formula was achieved through the implementation of the simplex lattice design method. A comprehensive array informed this process of experimental results. These experimental results encompassed values of the swelling ratio, water vapor transmission rate (WVTR), and film degradation ratio. In order to ascertain the optimal point of the formula, lower and upper limit values were necessary, sourced from the ideal characteristics of hydrogel film-based wound dressing (**Table 4**).

Table 4. Criteria for determining the optimum formula of hydrogel film

Parameter	Goal	Upper limit	Lower limit
Swelling Ratio (%)	<i>in range</i>	400	100
WVTR (mg/cm ² .day)	<i>in range</i>	2500	279
Film degradation ratio (%)	<i>minimize</i>	100	50

As illustrated in **Figure 4**, the maximum attainable desirability value was determined to be 0.931 when the ratio of cassava starch to PVA was set at 5:5%. The final hydrogel film was meticulously prepared and assessed before and after the sterilization treatment, per the recommended formula for hydrogel film fabrication. The characteristics of the optimal hydrogel film are delineated in **Table 5**.

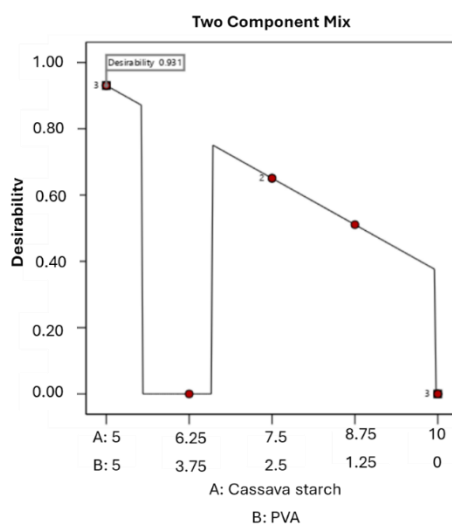


Figure 4. Desirability values of generated optimum formula by SLD

Table 5. Characteristics of the optimal formula hydrogel film before and after sterilization treatment

Parameter	Hydrogel film		Sig. (2. tailed)
	non-sterilized	sterilized	
Swelling Ratio (%)	164.10 ± 23.20	399.33 ± 33.13	<0.0001*
WVTR (mg.cm ⁻² .day)	725.78 ± 19.97	816.13 ± 87.72	0.2666
Film degradation ratio (%)	77.15 ± 0.09	85.93 ± 0.1	0.4903
pH value	6.00 ± 0.00	5.88 ± 0.22	0.5
Tensile Strength (MPa)	12.57 ± 4.42	17.92 ± 12.80	0.5314

Optimal hydrogel film was sterilized by the pressurized steam heat method because this method effectively kills microbes, spores, and viruses [15]. The characteristics of the hydrogel film before and after the sterilization process can be seen in Table 5. The swelling ratio profile of the sterilized hydrogel film produced higher swelling values due to the high temperature used during sterilization. In general, the swelling ratio of starch increases when exposed to higher temperatures [16]. This is due to the weakening of hydrogen bonds between the amylose and amylopectin chains, allowing increased water uptake into the starch [16].

Tensile strength is a crucial indicator of a wound dressing's ability to withstand external mechanical stress. Effective wound dressings must cover the wound area and resist friction without causing damage [17]. The tensile strength of sterile hydrogel film was observed to exceed that of non-sterile hydrogel film, likely due to increased cross-link density induced by the heat and pressure of the sterilization process [18]. Additionally,

incorporating aloe vera extract into the hydrogel film enhanced tensile strength compared to films lacking aloe vera extract (7.65 ± 3.26 MPa). This enhancement was attributed to the glucomannan content in aloe vera extract, which augments the film's tensile strength [19]. Generally, the optimal tensile strength for wound dressings is 1-32 MPa [20]. Therefore, the optimal hydrogel film meets the ideal specifications for use as a wound dressing.

Referring to the SEM image (Figure 5), the morphology of the hydrogel film exhibited irregular nano- and micropores. This structure can facilitate the diffusion of active substances from aloe vera extract into wound tissue, thereby accelerating wound healing. Additionally, pores in the hydrogel film matrix influenced the swelling index capability. These findings indicated that the optimal hydrogel film can be utilized in drug delivery systems that require the capacity to release therapeutic agents [21].

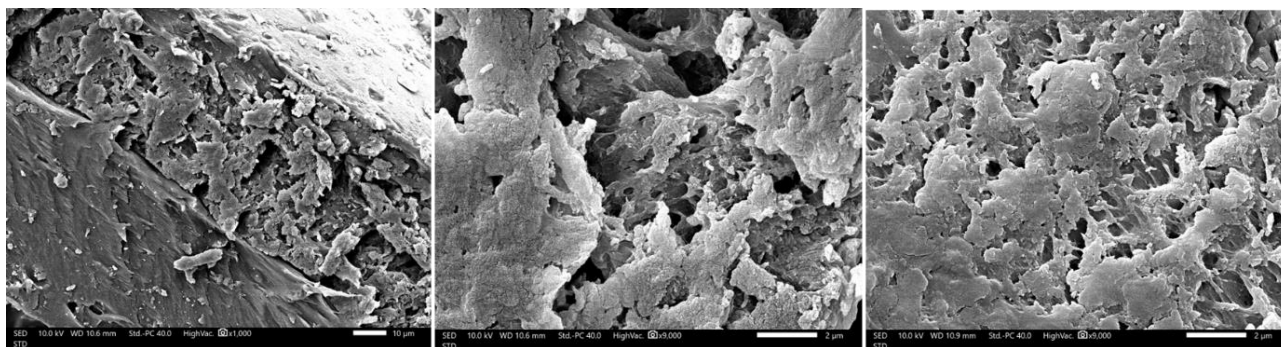


Figure 5. SEM image of cassava starch-PVA based hydrogel film: a) cross-section (scale bar: 10 µm), b) cross-section (scale bar: 2 µm), c) surface (scale bar: 2 µm),

Conclusion

A hydrogel film-based wound dressing with desirable properties was successfully prepared and presented as an alternative wound dressing. The formulation of the hydrogel film that exhibited optimal properties was achieved through the combination of cassava starch at a proportion of 5%, PVA at 5%, and aloe vera extract at 2%. The concentration ratio of cassava starch and PVA significantly influenced several key parameters, including the swelling ratio, the degree of film degradation, and the water vapor transmission rate (WVTR) values. Furthermore, incorporating aloe vera extract into the hydrogel film composition enhanced its mechanical strength, as evidenced by increased tensile strength.

Research involving human participants and/or animals

The authors declare that no human participants and/or animals are involved in this research.

Ethical approval

In this type of study, informed consent is not required.

Conflict of interest

The authors declare no conflict of interest.

Data availability

All data generated or analyzed during this study are included in this published article.

Authors Contributions

Concept – Khadijah Zai (K.Z.), Arini Hastin Dwi Utami (A.H.D.U.); Design – K.Z., A.H.D.U.; Supervision – K.Z.; Resources – K.Z.; Materials – K.Z., A.H.D.U.; Data Collection and/or Processing – A.H.D.U.; Analysis and/or Interpretation – A.H.D.U., K.Z.; Literature Search – A.H.D.U., K.Z.; Writing – A.H.D.U., K.Z.; Critical Reviews – K.Z.

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Using artificial intelligence chatbots

There was no use of artificial intelligence in the making of this article.

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