Indonesian Journal of Pharmaceutical Science and Technology
Journal Homepage : http://jurnal.unpad.ac.id/ijpst/
Research Article

Cellulose Nata de Sago-Hyaluronic Acid Microneedle for Pneumococcal Conjugate Vaccine

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Submitted 21 March 2024; Revised 14 December 2024; Accepted 15 December 2024; Published 28 December 2024

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Abstract

The use of syringe-administered vaccines has increased immunization coverage among children. Still, pneumonia remains the leading cause of death in children under five, accounting for over 70% of fatalities in this age group. To address challenges such as needle phobia, transdermal drug delivery systems offer a promising, minimally invasive alternative for both local and systemic medication administration. This study focuses on developing and evaluating a nata de sago-hyaluronic acid cellulose microneedle formulation for the transdermal delivery of pneumonia vaccines in children. The study consisted of preparing nata de sago, cellulose suspension, microneedle fabrication, and subsequent characterization and effectiveness testing. Results showed that the microneedle reached swelling equilibrium with a swelling degree of 1. Diffusion tests revealed a drug release rate of 1.173% within 90 minutes, penetrating the stratum corneum. Scanning Electron Microscopy (SEM) analysis confirmed an average microneedle length of 763.6 µm and a width of 191.7 µm for Pin 12, demonstrating its suitability for transdermal application. These findings highlight the nata de sago-hyaluronic acid microneedle as a well-designed and effective platform for pneumococcal vaccine delivery, offering a novel solution to improve pediatric immunization and address key challenges in child healthcare.

Keywords: Drug delivery system, Microneedle, Nata de sago, PCV-13 (pneumococcal conjugate vaccine-13)

Microneedle Selulosa Nata de Sago-Asam Hialuronat untuk Penghantaran *Pneumococcal Conjugate Vaccine*

Abstrak

Penggunaan vaksin melalui jarum suntik meningkatkan cakupan imunisasi anak-anak. Di satu sisi, pneumonia masih menjadi penyebab utama kematian pada anak-anak di bawah usia lima tahun, menyumbang lebih dari 70% angka kematian pada kelompok usia ini. Untuk mengatasi fobia jarum suntik, sistem penghantaran obat transdermal menawarkan alternatif yang menjanjikan untuk pemberian obat secara lokal maupun sistemik. *Microneedling* dipilih karena menyediakan metode penghantaran obat yang minimal invasif. Penelitian ini bertujuan untuk mengembangkan dan mengevaluasi formulasi *microneedle* nata de sago-asam hialuronat selulosa untuk pemberian vaksin pneumonia pada anak-anak. Metode yang digunakan meliputi pembuatan nata de sago, suspensi selulosa, fabrikasi *microneedle*, serta pengujian efektivitas dan karakterisasi. Hasil penelitian uji efektivitas *microneedle* diperoleh kesetimbangan dengan nilai derajat *swelling* sebesar 1, uji difusi Franz menunjukkan pelepasan terjadi pada menit ke-90 sebesar 1,173% yang menembus lapisan stratum korneum. Analisis *Scanning Electron Microscopy* (SEM) menunjukkan dimensi *microneedle* dengan panjang rata-rata 763,6 µm dan lebar 191,7 µm pada Pin 12, sesuai untuk aplikasi transdermal. Temuan ini menunjukkan bahwa *microneedle* nata de sago-asam hialuronat efektif dan dirancang dengan baik untuk penghantaran vaksin pneumokokus, sehingga menawarkan solusi inovatif bagi imunisasi anak-anak.

Kata Kunci: Sistem penghantaran obat, *Microneedle*, Nata de sago, PCV-13 (vaksin pneumonia konjugat),

1. Introduction

The development of drug delivery systems is largely driven by the need to address pressing health challenges, particularly in children. Pneumonia, often described by the World Health Organization (WHO) as "the forgotten killer of children," remains the leading cause of death among children under five years old, contributing to over 70% of fatalities in this age group globally. According to WHO, 99% of childhood pneumonia-related deaths occur in developing countries.[1] Indonesia is among the top 10 countries with the highest number of pneumonia-related deaths, second only to diarrhea. In 2019 and early 2020, pneumonia was responsible for 52.7% of childhood deaths in Indonesia, with 466,524 reported cases.[2]

Streptococcus pneumoniae is the most common bacterial cause of pneumonia in children, followed by Haemophilus influenzae type b (Hib) as the second most frequent pathogen. Immunization with the Pneumococcal Conjugate Vaccine (PCV) has proven effective in preventing pneumonia in children. However, the fear and discomfort associated with needle injections often hinder vaccination efforts. To address this challenge, alternative delivery methods that eliminate the need for traditional syringes are essential. Microneedle patches have emerged as a promising solution, offering a pain-free and minimally invasive method for vaccine administration. These microneedles, which penetrate the skin shallowly, provide several advantages, including simplified delivery of active ingredients, reduced risk of microbial infections, and faster post-vaccination recovery compared to conventional needles.[3]

Dissolvable polymer microneedles represent a promising advancement in drug delivery, encapsulating drugs within a biodegradable polymer matrix. Hyaluronic acid, a hydrophilic polymer derived from polysaccharides, enhances skin permeability by modifying the structure of the stratum corneum, thereby improving percutaneous drug absorption.[4] Interestingly, sago liquid waste, a byproduct of processing the traditional Southeast Asian plant sago, contains natural biopolymers such as cellulose. This waste, rich in carbohydrates and proteins, poses a risk of environmental pollution if not managed properly. However, it can be repurposed as a fermentation medium for *Acetobacter xylinum*, which produces Nata de Sago—a natural cellulose suitable for microneedle formulations.[5] Utilizing such locally sourced, sustainable materials offers a dual benefit: reducing environmental waste and advancing innovative drug delivery systems. In Southeast Sulawesi, particularly in Konawe Regency—which accounts for 38.6% of Indonesia's total sago production area—sago waste holds significant potential for sustainable utilization.[6]

This research investigates the formulation of a pneumonia vaccine delivery system using Nata de Sago cellulose combined with hyaluronic acid. This innovative approach, previously unexplored, aims to provide an effective, non-invasive, and sustainable method for delivering the PCV to children. A novel formulation for pneumonia vaccine delivery has been developed, utilizing a microneedle system composed of cellulose from Nata de Sago and hyaluronic acid. The study focuses on polymer-based microneedles, where hyaluronic acid acts as a biodegradable biopolymer. Its properties as a skin permeation enhancer and dissolvable material allow the microneedles to efficiently dissolve upon skin penetration.[7]

This study explores a novel microneedle formulation combining Nata de Sago cellulose and hyaluronic acid for delivering the PCV to children. The objective is to develop and evaluate its effectiveness as a painless, non-irritating, and sustainable alternative to traditional injection methods. By utilizing local natural resources, this research not only promotes sustainable innovation but also addresses the need for child-friendly vaccine delivery systems. The findings provide a foundation for further studies on microneedle technology, highlighting its potential to enhance vaccination experiences by reducing pain and psychological distress in pediatric patients.

2. Methods

2.1. Tools

The tools used in this study included aluminum foil (Total Wrap®), a stirring rod (Pyrex®), analytical balances (Pioneer®), micro needling cartridges (Dr. Pen Cartridge®), microneedle pins (sizes 12, 24, and 42), a porcelain cup, a centrifuge (Corona 6-Hole GL-08®), and various glassware such as Erlenmeyer flasks, beakers, measuring cups (Iwaki®), and test tubes (Iwaki®). Additional equipment included a hotplate stirrer (IKA HS-7), a magnetic stirrer, a portable stove (Sanex), a refrigerator (Sharp), a laminar air flow cabinet (Biobase), and pH litmus paper (Mquant New pH-Indicator®). Accessories such as hansaplast aqua protect adhesive bandages, eppendorf tubes (One Med®), tweezers (GOOI), a mortar and pestle, sieves, plastic wrap, horn spoon, and containers were also utilized. The evaluation for the needle size was conducted using Scanning Electron Microscope (SEM).

2.2. Materials

The materials used in this study included sago wastewater, Nata de Sago, hyaluronic acid (T&T Chemical®), albumin (bovine serum albumin, lyophilized powder®), distilled water (One Med®), vinegar (Dixy®), and Acetobacter xylinum starter culture (Biotechno®). Other materials included benzoyl peroxide (Kimindo®), polyvinyl alcohol/PVA (CCP Albumin Sigma®), polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), sugar (Rose Brand®), sodium hydroxide (NaOH), sulfuric acid (H_2SO_4), and potassium iodide (KI). Additional reagents were sodium thiosulfate pentahydrate, copper sulfate, lead acetate, trisodium phosphate, disodium phosphate, trehalose, urea (food grade, ZA®), soda (Cendrawasih®), and silicone rubber (Kimindo®). Finally, the study utilized PVC-13 vaccine (Prevenar 13®).

2.3. Procedures

2.3.1. Sample Preparation

Sago wastewater samples were collected from a sago flour processing facility in Sampara District, Konawe Regency, Southeast Sulawesi, Indonesia. The samples were initially filtered to remove impurities. All tools used during the process were sterilized through washing and drying. To preserve sterilization, the tools were wrapped in newspaper and secured with rubber bands.

2.3.2. Nata de Sago Preparation

A total of 2 liters of sago wastewater was filtered and boiled. Subsequently, 150 g of sugar and 15 g of urea were added and stirred until the mixture became homogeneous. The solution was allowed to boil again before being cooled. All procedures requiring sterility were performed in a laminar airflow cabinet. After cooling, 5 ml of vinegar was added to the solution and stirred until homogeneous. Then, 250 ml of Acetobacter xylinum culture was introduced, thoroughly mixed, and poured into a tray. The mixture was incubated for 10 days.[5]

2.3.3. Nata de Sago Evaluation Test

- Organoleptic Test

The organoleptic test involved visual observations of color, odor, and texture, following the described method.[8]

- Sucrose Content Test

The sucrose content of Nata de Sago was analyzed using the Luff-Schoorl method. The analysis was conducted in two stages: before and after sucrose inversion.[8]

- Microneedle Mold Fabrication

Silicone rubber (8.55 g) was weighed using an analytical balance and placed into a container. Twenty drops of benzoyl peroxide catalyst were added and stirred until the mixture was homogeneous. The plunger of a microneedling cartridge was removed, and the silicone rubber mixture was poured into the cartridge. The mold was allowed to set for 45 minutes or until completely dry. Once dried, the mold was carefully removed from the cartridge.[9]

- Cellulose Suspension Preparation

A polymer solution was prepared

by dissolving 0.1 g of hydroxypropyl methylcellulose (HPMC) in 5 ml of hot water. Subsequently, 0.1 g of polyvinylpyrrolidone (PVP), 10 g of polyvinyl alcohol (PVA), and 2.6 g of Nata de Sago were added to the solution. The mixture was stirred on a hotplate at 100°C for 90 minutes. Approximately 350 µl of the suspension was poured into the prepared molds and centrifuged for 10 minutes at 1500 rpm. The molds were then allowed to stand at room temperature for 24 hours.[10]

- Vaccine Delivery Mixture Preparation

A vaccine delivery mixture was prepared by combining 0.2 ml of hyaluronic acid, 100 µl of trehalose, 100 µl of albumin, and 0.5 ml of the PCV-13 vaccine. The ingredients were mixed until homogeneous and poured into molds containing 350 µl of the cellulose suspension. The filled molds were stored in a refrigerator for 24 hours.

- Microneedle Patch Manufacturing

A transparent, impermeable plaster (Hansaplast) was used as the base. The microneedles were attached to the plaster pad, which was then placed in packaging. The microneedle patches were stored in a refrigerator to harden and adhere properly.[11]

- Microneedle Formulation

The cellulose Nata de Sago-hyaluronic acid microneedle containing the active pneumonia vaccine was prepared using the solvent casting method. Active and auxiliary ingredients were dissolved in a volatile solvent, such as water or ethanol. The microneedle composition included 0.2 mL of hyaluronic acid, 100 µl of trehalose, 100 µL of albumin, and 0.5 ml of the PCV-13 vaccine. The solution was homogenized and poured into molds. After setting, the microneedles were attached to patches and stored in a refrigerator. The composition of the microneedles is detailed in Table 1.

2.3.4. Microneedle Effectiveness Test

- Swelling Test

The swelling test was performed to assess the hydrophilicity of silicone, particularly its water absorption capacity. The mold containing the suspension and formula was first weighed to record its initial weight. It was then immersed in water for 24 hours. After soaking, the mold was removed, lightly dried, and reweighed. This process of soaking and weighing was repeated every 24 hours for up to 7 days. The degree of swelling was calculated using the weight difference before and after immersion, as shown in the formula:

$$\text{Swelling Degree} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Initial Weight}}$$

- Franz Diffusion Test

To conduct the Franz diffusion test, an ethical clearance letter was obtained as a prerequisite. Following euthanasia, the skin of the mice (excluding the head and feet) was carefully removed using surgical scissors. The excised skin was shaved to remove fur, cleaned with distilled water, and rinsed with a physiological NaCl solution to ensure sterility and usability as a penetration membrane.[13]

The Franz diffusion cell's receiving chamber was filled with 125 ml of methanol. Approximately 250 mg of each gel formulation was evenly applied to the prepared mouse skin, which was then placed on the Franz diffusion device. The diffusion cell was submerged in a water-filled glass vessel equipped with a thermostat and thermometer to maintain a temperature of 37 ± 1°C. A magnetic stirrer was activated to ensure consistent agitation throughout the test. Sampling was performed at intervals

Table 1. Microneedle Formula

No	Material	Total	Use
1	Nata de Sago	350 µl	Microneedle base
2	PCV 13 Vaccine	0.5 ml	Active ingredients
3	Hyaluronic acid	0.2 ml	Microneedle base and enhancer
4	Trehalose	100 µl	Stabilizer
5	Albumin	100 µl	Stabilizer

of 15, 30, 45, 60, 75, and 90 minutes. At each interval, 5 mL of the receiving solution was withdrawn and replaced with an equal volume of methanol to maintain consistent volume. The collected samples were analyzed using a UV spectrophotometer to measure the absorbance of the PCV-13 vaccine at its maximum wavelength.

- Microneedle Characteristic Evaluation Test

The characteristics of the microneedles were evaluated by analyzing their morphology and structure. An optical microscope and a scanning electron microscope (SEM) were employed to examine the microstructure of the microneedles, including their length and width.[14]

3. Results

3.1. Nata de Sago Preparation

Nata de sago was successfully produced through a 10-day fermentation process using sago liquid waste as the substrate and *Acetobacter xylinum* as the starter culture. The addition of the starter culture significantly increased the colony count of *A. xylinum*, promoting the formation of nata de sago. The resulting product was a natural cellulose material characterized by a transparent white sheet with a smooth, slippery surface (Figure 1).

After fermentation, the nata de sago appeared as a solid, agar-like white substance. Bacterial cellulose production was evidenced by the formation of cellulose sheets on the surface of the sago liquid waste medium. This process was driven by the activity of *A. xylinum*, which synthesized cellulose from the sugar content in the medium.

3.2. Sucrose Test Result of Nata de Sago

The sucrose content of nata de sago was analyzed using the Luff-Schoorl method, with the results presented in Tables 2 and 3. The sucrose content before inversion was 1.6%, while the sugar content after inversion was 3.3%. These findings indicate that the nata contains a relatively high sucrose concentration, which is essential for the growth and activity of Acetobacter xylinum. According to SNI 01-4317-1996, the ideal sucrose content for nata is 15%, confirming that the produced nata complies with this standard.[15]

3.3. Results of Making Microneedle Molds

The microneedle molds were fabricated using elastic silicone rubber, chosen for its flexibility and ease of shaping. Silicone rubber molds also dry quickly and are user-friendly. The fabricated molds included pin molds with 12, 24, and 42 pins (Figure 2A). To solidify 8.55 grams of silicone within 45 minutes at room temperature, approximately 20 drops of catalyst (equivalent to about 0.9 ml) were required.

The resulting silicone demonstrated the essential properties for microneedle applications, including heat resistance, electrical conductivity, and superior chemical stability compared to conventional organic rubber. Additionally, the cellulose suspension, prepared using a combination of HPMC, PVA, Nata de Sago, and PVP polymers (Figure 2B). This formulation is non-irritating to the skin, making it suitable for practical use.

3.4. Microneedle Effectiveness Results

Based on the results obtained from the Franz diffusion test, the penetration test of the tpins 12, 24, and 42, it was revealed that pin 24 exhibited the highest release rate at 90 minutes, reaching 1.173%. The penetration test for all three pins was conducted simultaneously at 15, 30, 45, 60, 75, and 90

Figure 1. Nata de Sago cellulose after fermentation by *A. xylinum*

Table 2. Sucrose content of nata de sago before and inversion

	Sample	Blank (ml)	Volume of Titration		Sucrose content (%)
			sample (ml)	AT (Table Number)	
before inversion	Nata de sago (50 ml)	14	13	0.1	1.6
after inversion	50 ml sample nata de sago	25	23	0.2	3.3

minutes. Pin 24 showed a significant increase in sample release at 90 minutes (Table 3), indicating the role of the polymers used (HPMC, PVP, and PVA) in the drug release system of the matrix patch.

3.5. Microneedle characterization results

The results of the microneedle fabrication demonstrate the successful formation of small, conical needles (microneedles) from the template mold (Figure 3a). The needle tips were sharp enough to penetrate the epidermis without causing pain. Based on the morphological observation using SEM, Pin 12 had a length of 763.6 µm and a width of 191.7 µm, pin 24 had a length of 800.4 µm and a width of 190.9 µm, while pin 42 had a length of 777.2 µm and a width of 212.5 µm (Figure 3b). These results confirm the precise fabrication of microneedles suitable for their intended application.

4. Discussion

The resulting silicone molds exhibited desirable characteristics, including excellent heat resistance, electrical conductivity, and chemical stability, as reported in previous research.[16] These properties ensured that the molds maintained their shape during the high-temperature polymer mixing process and the addition of low-temperature vaccines. silicon molecules have a helical structure and low intermolecular forces, resulting in high elasticity and exceptional resistance to extreme temperatures, ranging from -70°C to 200°C.[16] This makes silicon highly resistant to the high temperatures required for mixing the microneedle polymer and the low temperatures involved in vaccine addition, without compromising structural integrity.

Microneedle patches were fabricated using a combination of HPMC, PVA, Nata de Sago, and PVP polymers. The interaction between these polymers did not cause skin irritation, indicating their biocompatibility. In the patch formulation, HPMC acted as a base that bound the nanoemulsion preparation with other polymer components forming the patch. HPMC, a water-insoluble polymer, acted as a crystal barrier to molecular movement, while PVP, a water-soluble polymer, swelled to form a gel-like consistency. This gel-like structure facilitated drug diffusion through natural pores, enhancing the release profile of the active ingredient.[17] The resulting suspension successfully formed needles from the mold with a diameter range of 100 µm.[18]

These dimensions are consistent with the optimal range for microneedles, typically measuring 50-900 µm in length and 1 µm at the tip to ensure effective skin penetration.[19]

Swelling tests were conducted to evaluate the hydrophilicity of the microneedle material. In vitro, drug release studies using

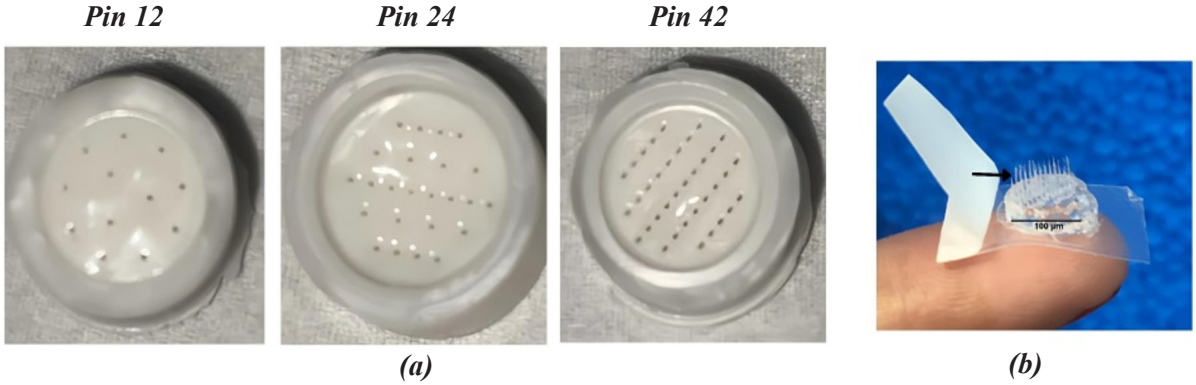

Figure 2. (a) Microneedle mold making results, and (b) Suspension mold results.

Table 3. Sucrose content of nata de sago before and inversion

No	Time (t)	Cumulative Q			% Discharge over time (t)		
		Pin 12	Pin 24	Pin 42	Pin 12	Pin 24	Pin 42
1	15	44.000	1478.667	636.000	0.027%	0.918%	0.395%
2	30	106.667	1532.000	729.333	0.066%	0.952%	0.453%
3	45	177.333	1597.333	873.333	0.110%	0.992%	0.542%
4	60	289.333	1670.667	1042.667	0.180%	1.038%	0.648%
5	75	416.000	1777.333	1233.333	0.258%	1.104%	0.766%
6	90	549.333	1889.333	1438.667	0.341%	1.173%	0.894%

Franz diffusion cells evaluated the drug release profile from the microneedles.[20] The results demonstrated that the developed microneedle patches exhibited controlled drug release, with the release rate influenced by the polymer composition and the size of the microneedle.[21]

This study successfully demonstrated the development of microneedle patches using Nata de Sago as a key component. The patches exhibited desirable properties, including biocompatibility, controlled drug release, and ease of fabrication. These findings suggest that Nata de Sago-based microneedle patches have the potential for biomedical applications, such as vaccine and transdermal drug delivery.

5. Conclusion

The microneedle patches developed using Nata de Sago cellulose and hyaluronic acid demonstrated effective swelling, drug release, and morphological characteristics suitable for transdermal vaccine delivery. Pin 24 exhibited the best release profile, indicating its potential as an ideal microneedle for delivering the PCV-13 vaccine. These findings underscore the feasibility of using sustainable and biocompatible materials for painless and efficient vaccine delivery in children.

Acknowledgements

We would like to extend our sincere gratitude to the Directorate of Learning and Student Affairs, Directorate General of Higher Education, Ministry of Education, Culture,

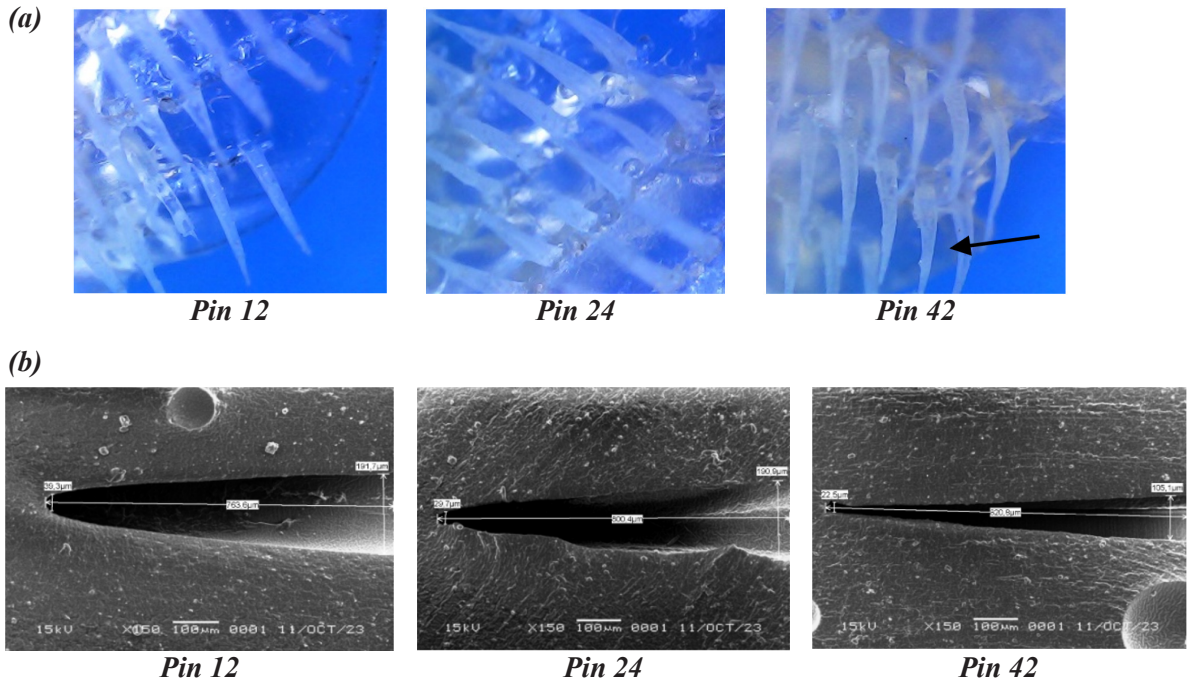

Figure 3. (a) Molding microneedles from Nata de sago and hyaluronic acid observation using an optical microscope; (b) Morphology of Microneedle and its measurement from SEM analysis (magnification = 150×)

Research, and Technology of the Republic of Indonesia, for providing funding for the Student Creativity Program (PKM) in 2023 under contract number 3204/E2/KM.01.00/2023.

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