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Fabrication and Characterization of Injectable Hydrogel Based on Carboxymethylcellulose-Hyaluronic with Variation Hydroxyapatite as a Candidate Regenerative Medicine for Osteoporosis

Fabrikasi dan Karakterisasi Hidrogel Injeksi Berbahan Dasar Carboxymethylcellulose-Asam Hialuronat dengan Variasi Hidroksiapatit Sebagai Kandidat Regenerative Medicine Untuk Osteoporosis

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ABSTRACT

Osteoporosis is a disease can make bones brittle and weak by reducing bone mass and altering bone's microarchitecture. Osteoporosis increases every year, and it is predicted that in 2050, osteoporosis will cause an increase in bone fractures in men by 310% and in women by 240%. Existing treatments for osteoporosis, such as bisphosphonate therapy and tissue transplantation, have several limitations. Hydrogel is a new solution to overcome osteoporosis. In this research, hydrogels are fabricated using three combinations of materials: carboxymethylcellulose (CMC), hyaluronic acid, and hydroxyapatite. In this study, hydrogels were fabricated using a blending method combining CMC, hyaluronic acid, and hydroxyapatite in four formulations: 1:1:0, 1:1:1, 1:1:2, and 1:1:3. The study will identify the optimal hydrogel formulation as a candidate for regenerative medicine in osteoporosis. The XRD results show hydroxyapatite is successfully incorporated into the hydrogels. The fluid affinity test results show that the fabricated hydrogels include 3E, 2E, and 1E. Based on viscosity tests, all fabricated hydrogels fulfill the viscosity requirements for injectable hydrogels, with viscosities ranging from 5 to 200,000 mPa.s. In the stability test, the hydrogels were stable after the freeze-thaw cycle. All of the hydrogels fabricated have an injectability approach 100%. Afterward, the resuspension test showed no change in pH, and formulation 1:1:1 resuspended the least. The SEM results indicate a pore size of 87.06 ± 41.63 µm, and the morphology shows that hydroxyapatite successfully fills the pores. Based on the test results, the 1:1:1 formulation is a strong candidate for regenerative medicine applications in osteoporosis.

Keywords: Injectable Hydrogel, Nanocomposite, Blending Method, Physicochemical Properties, Regenerative Medicine Candidate

ABSTRAK

Osteoporosis adalah kondisi penyakit yang dapat membuat tulang rapuh dan lemah disertai dengan berkurangnya massa tulang serta perubahan mikroarsitektur tulang. Osteoporosis ini meningkat setiap tahunnya dan diprediksi dapat meningkatkan terjadinya patah tulang pada tahun 2050 sebesar 310% pada pria dan 240% pada wanita. Solusi yang ada untuk osteoporosis saat ini berupa terapi bifosfonat dan transplantasi jaringan yang masih memiliki keterbatasan. Hidrogel merupakan solusi terbarukan untuk menangani osteoporosis. Pada penelitian ini hidrogel difabrikasi dengan menggunakan metode pencampuran yang mengombinasikan CMC, asam hialuronat, dan hidroksiapatit sebanyak empat variasi formulasi, yaitu 1:1:0, 1:1:1, 1:1:2, dan 1:1:3. Penelitian ini akan menemukan formulasi hidrogel yang optimal sebagai kandidat regenerative medicine osteoporosis. Hasil XRD menunjukkan hidroksiapatit berhasil terinkorporasi dalam hidrogel. Hasil uji fluid affinity menunjukkan bahwa hidrogel memiliki tipe yang berbeda-beda. Hasil pengujian viscosity menunjukkan seluruh sampel memenuhi viskositas hidrogel yang dapat diinjeksi yaitu 5 sampai 200.000 mPa.s. Uji stability menunjukkan semua sampel bersifat stabil. Seluruh hidrogel yang difabrikasi memiliki tingkat injectability yang mendekati 100%. Hasil uji percolation menunjukkan formulasi hidrogel 1:1:1 memiliki kemampuan slow release. Kemudian, uji resuspension tidak menunjukkan abnormalitas pH dan hidrogel 1:1:1 memiliki kemampuan pembentukan endapan kembali paling lama. Hasil uji SEM menunjukkan ukuran pori sebesar 87,06 ± 41,63 µm dan morfologi menunjukkan hidroksiapatit telah berhasil mengisi pori matriks. Dari keseluruhan hasil pengujian, formulasi 1:1:1 dapat sebagai kandidat regenerative medicine untuk osteoporosis.

***Kata Kunci**: Hidrogel Injeksi, Nanokomposit, Metode Pencampuran, Sifat Fisikokimia, Kandidat Pengobatan Regneratif*

1. INTRODUCTION

Osteoporosis is a severe disease that requires a solution to overcome it. Right now, overcoming osteoporosis can be achieved using conventional methods like tissue transplantation, such as autograft, allograft, and xenograft, which have several limitations, including a limited stock, an increased risk of transmission of disease, and a potential rejection response in the body (Abdul-Monem et al., 2021; Sarita, Rai, et al., 2024). Another solution for osteoporosis is using a scaffold that is fabricated from metal, which also has several limitations, disturbing the structural and functional aspects of bone that can obstruct bone regeneration (Jinugu et al., 2024). Bisphosphonate therapy can also be another solution for osteoporosis, but it still has limitations that can cause side effects (Joenputri, 2020). A new solution to overcome osteoporosis is hydrogels (Abdul-Monem et al., 2021).

Recently, hydrogels have been extensively developed with respect to the variety of material combinations within a single hydrogel and the methods of hydrogel fabrication. Hydrogels can be fabricated from natural polymers, synthetic polymers, or a combination of the two (Bashir et al., 2020). Commonly used polymers include carboxymethylcellulose (CMC), hyaluronic acid (HA), and hydroxyapatite (HAP). CMC is widely used in hydrogels because CMC is a material that has good biocompatibility and biodegradability, and CMC has low toxicity and low immunogenicity (Kaith et al., 2021; Priya et al., 2021; Zhang et al., 2022). On the other hand, hyaluronic acid is commonly used because it can help in tissue regeneration (Amsia, 2021; Zhang et al., 2024). The use of hyaluronic acid is beneficial because the material has biocompatibility, biodegradability, and viscoelasticity that are convenient for medical applications (Chang et al., 2024; Moreira et al., 2024). While hydroxyapatite is also commonly used, especially in hydrogels that are applied in bone, because hydroxyapatite has the same mineral as natural bone (Sari et al., 2020). Hydroxyapatite exhibits good bioactivity, biocompatibility, and osteoconductivity, and is non-toxic and non-inflammatory (Bień et al., 2025; Mondal et al., 2023). Based on the characteristics of these three materials, some studies have combined them into hydrogels for bone regeneration.

The previous study fabricated hydrogels that can increase bone regeneration. However, the researchers sought to maintain the hydrogel's viscosity by combining HA with CMC. HA promotes bone regeneration, and CMC is used to maintain the hydrogel's viscosity (Lin et al., 2022). The previous study combining CMC with

HA has limitations in application. It focuses on dental cells and does not provide pschochemical characterization for the fabricated hydrogels.

Furthermore, another study combining HA and HAP as a hydrogel shows good results, indicating that adding HAP to HA improves mechanical characteristics and can increase cell adhesion and proliferation (Bień et al., 2025). The previous study that combines HA with HAP shows a good result for regeneration in fibroblast cells and has shows psyhochemical characterization (Tan et al., 2022). However, that study doesn't focus on bone regeneration.

This study will combine CMC, HA, and HAP into hydrogels for osteoporosis, as previous studies have not examined this combination. This research will determine the optimal hydrogel fabrication ratio and characterize each variation, enabling identification of the best hydrogel candidate for regenerative medicine in osteoporosis.

2. RESEARCH METHOD

2.1 Materials

CMC, hyaluronic acid (MW = 1,300,000 Da), nano-hydroxyapatite 60 nm (MW = 502.31 Da), glycerol, deionized water, trypan blue dye, NaCl, $CaCl_2$, agar powder, gelatin, phosphate buffer saline (PBS). All material used was technical grade.

2.2 Methods

2.2.1 Preparation for CMC gel

Weigh 4.4 g of CMC and mix it into 20 g of glycerol solution. Next, add deionized water until the total weight of the solution mixture reaches 100 g (Paramadini et al., 2023).

2.2.2 Preparation of 1% HA Solution

1 g of HA was dissolved in deionized water at 50°C using a hotplate stirrer until homogenized (Lin et al., 2022).

2.2.3 Preparation CMC-HA gel

CMC and HA that were prepared before mixing with a ratio of 1:1 using an overhead stirrer at 1100 rpm until homogenized (Paramadini et al., 2023).

2.2.4 Preparation 5% HAP Solution

5 g of HAP was dissolved in deionized water at room temperature using a hotplate stirrer until homogenized (Lin et al., 2022).

2.2.5 Preparation CMC-HA-HAP Hydrogels

HAP solutions were added to the CMC-HA gel; the variation of adding HAP based on the study (Chocholata et al., 2020). **Table 1** shows all of the variation. This step will yield four hydrogel variants.

Table 1. Variation Formulation Hydrogels

No	Hydrogels	Ratio Formulation [CMC: HA : HAP]
1.	CMC-HA-HAP0	1:1:0
2.	CMC-HA-HAP1	1:1:1
3.	CMC-HA-HAP2	1:1:2
4.	CMC-HA-HAP3	1:1:3

2.2.6 X-Ray Diffraction (XRD) Test

The test began with freeze-drying until the hydrogel was dry. After that, each hydrogel was cut into small pieces. Then, each sample piece was tested using XRD in the angle range of 5°- 80° (Sarita, Dayaram, et al., 2024).

2.2.7 Fluid Affinity Test

The first step is to prepare solution A by dissolving 8.29 grams of NaCl and 0.36 grams of CaCl2 in 1 L of distilled water. Then, prepare a 50 mL syringe with the tip cut. Subsequently, prepare the substrate by weighing 2 ± 0.01 g of agar powder in a glass beaker and adding solution A until the total mass is 100 ± 0.02 g. Prepare the agar substrate using a hotplate stirrer at 121 ± 1°C for 20 minutes.

Gelatin powder was added to test solution A at a rate of 65 ± 0.02 g and stirred using a hotplate stirrer at a temperature of 60°C for twelve to eighteen hours. Then, 10 g of the resulting agar or gelatin substrate was placed separately into a 50 ml syringe. Each syringe was weighed and recorded as W1. Next, 10 g of the test sample was added, and the mass of the syringe was recorded as W2. The syringe was then sealed and left at room temperature for 48 hours. After 48 hours, the syringe is weighed and recorded as W3. After weighing, the sample is removed using a plugger, leaving the gelatin or agar substrate. Then, the

syringe mass is weighed again and recorded as W4. From the mass calculation results, W5 can be calculated using the formula:

$$\%W5 = \frac{(W3-W4)-(W2-W1)}{(W2-W1)} \times 100\% \quad (1)$$

W1=syringe with substrate (agar or gelatin); W2=syringe with substrate and sample; W3=syringe with substrate and sample after 48 hours; W4=syringe with substrate after gel removal (Paramadini et al., 2023).

2.2.8 Viscosity Test

This test was conducted using a Brookfield viscometer with spindle number 64 at a speed of 6 rpm at room temperature (Tasqué et al., 2023). Measurement of the viscosity ratio of each hydrogel variation, repeated three times (Paramadini et al., 2023).

2.2.9 Stability Test

This test was conducted in 3 freeze-thaw cycles, in which each sample was frozen or thawed for at least 48 hours. Freezing was performed using a freezer, and thawing was performed at room temperature (Jacob et al., 2025).

2.2.10 Percolation Test

This test was conducted to examine the permeability capacity of the hydrogel by taking 1 ml of the hydrogel using a syringe placed in an upright position. Then, 500 µl of trypan blue dye was poured onto the surface of the hydrogel (Sarita, Dayaram, et al., 2024).

2.2.11 Injectability Test

This test was conducted using a 12 ml syringe and an 18G syringe. The test was repeated five times, and the average injectability percentage of each hydrogel variation was calculated. The injectability percentage of the hydrogel was calculated by measuring the mass of the hydrogel before and after injection, which can be calculated using the following formula (Alonso et al., 2021):

$$\text{Injectability} = \frac{\text{mass hydrogel expelled}}{\text{Total initial mass hydrogel}} \times 100\% \quad (2)$$

2.2.12 Resuspension Test

This test is conducted to examine the ability of a suspension to return to its original form after undergoing sedimentation. This test is conducted in two aspects: the time required to reform the suspension and the pH of the suspension sample solution. This test is performed by adding Phosphate Buffered Saline (PBS) to the suspension and shaking it (Putra et al., 2019).

2.2.13 Scanning Electron Microscope (SEM) Test

The SEM test was conducted by comparing the control hydrogel with the hydrogel with optimal characteristics. This test was conducted to determine the morphology of the surface and the size of the pores formed in the hydrogel (Sarita, Dayaram, et al., 2024).

2.2.14 Statistical Test Data

Data analysis used a one-way ANOVA statistical test with a p-value of less than 0.05, which indicates that there are significant differences between data groups (Jacob et al., 2025).

3. RESULT AND DISCUSSION

3.1 Result Fabrication CMC-HA-HAP Hydrogels

Hydrogel fabrication has been successfully carried out by combining CMC, HA, and HAP with four formulation variations in Table 1. The 1:1:0 formulation (CMC-HA-HAP0) is a hydrogel without hydroxyapatite, showing a homogeneous colloidal gel. On the other hand, hydrogels containing hydroxyapatite, namely formulations 1:1:1 (CMC-HA-HAP1), 1:1:2 (CMC-HA-HAP2), and 1:1:3 (CMC-HA-HAP3), have a suspension-like form due to the presence of HAP precipitation. This precipitation indicates that HAP undergoes agglomeration and low solubility in water, which reduces the mobility of HAP in a solution (Maggi et al., 2024).

3.2 XRD Test

Figure 1 shows the results of the XRD test, where CMC-HA-HAP0 is the control sample in this study, which does not contain hydroxyapatite and demonstrates the absence of peaks in the XRD test. This proves that the CMC-HA-HAP0 sample does not have a crystal structure or has a low crystal structure, so it can be said to have an amorphous structure (Karatas et al., 2024).

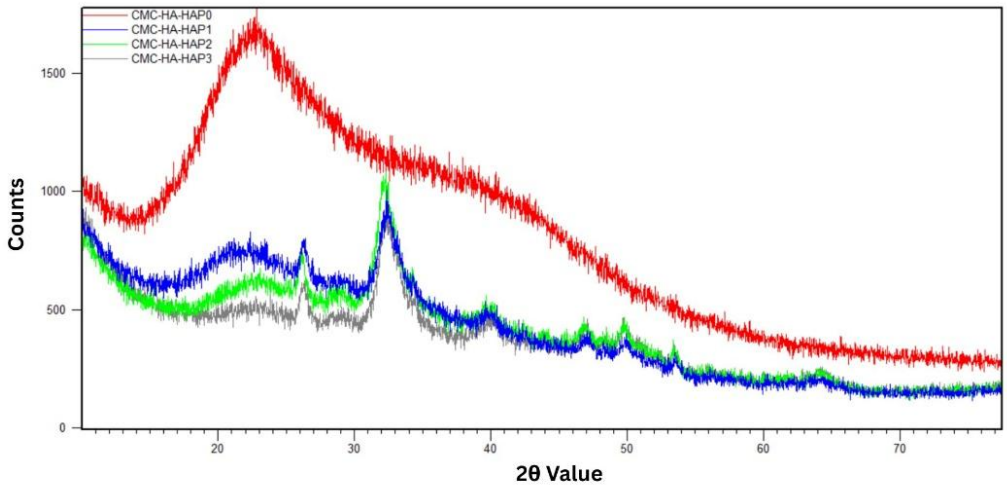

Figure 1. Result X-Ray Diffraction (XRD) Test

The XRD results also show that the CMC-HA-HAP1, CMC-HA-HAP2, and CMC-HA-HAP3 hydrogel samples have successfully incorporated HAP into the hydrogel, as evidenced by the formation of diffraction peaks in 26.0°, 32.1°, 40,1°, 46,8°, 49,7°, and 53,3°. The observed diffraction peaks are near and consistent with JCPDS 090432, indicating that the hydroxyapatite in the hydrogel does not alter the shape or crystal structure of HAP (Karatas et al., 2024; Tan et al., 2022; Zhou et al., 2024). Therefore, HAP in the hydrogel has an effective role in the tissue later on. (Karatas et al., 2024).

3.3 Fluid Affinity Test

A fluid affinity test, performed by BS EN 13726-1:2002 standards, determined the hydrogel type based on its ability to donate or absorb a fluid. The results of the fluid affinity test are shown in **Figure 2**, which depicts the absorption and donation capabilities of each sample, where the test results indicate that as the ratio of hydroxyapatite in the hydrogel increases, the absorption capability of the hydrogel decreases, but this is inversely proportional to its donation capability, which actually increases as the hydroxyapatite increases.

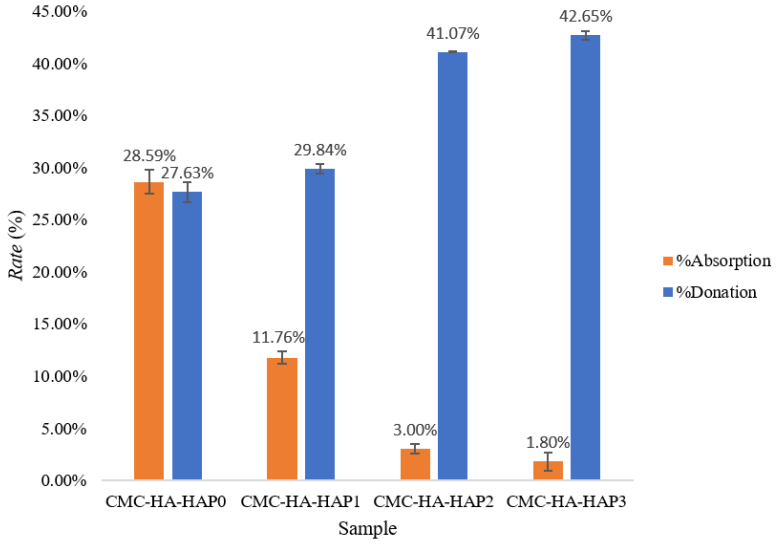

Figure 2. Absorption and Donation Capabilities of Each Hydrogel Variation

Table 2. Types of Hydrogels

No	Hydrogel	Hydrogel Types
1.	CMC-HA-HAP0	3E
2.	CMC-HA-HAP1	2E
3.	CMC-HA-HAP2	1E
4.	CMC-HA-HAP3	1E

The absorption capacity of each sample indicates that the CMC-HA-HAP0 sample, with 28.59%, is a type 3 hydrogel, as its absorption capacity is in the 20-30% range. Then, CMC-HA-HAP1, with an absorption capacity of 11.76%, is classified as hydrogel type 2 because its absorption capacity is in the 10-20% range. For CMC-HA-HAP2 and CMC-HA-HAP3, with absorption capacities of 3% and 1.8%, both hydrogels are type 1, as their absorption capacities are only in the 0-10% range. On the other hand, when considering the donation capacity of all samples, they exceed 25%, indicating that all fabricated hydrogels are type E based on their donation capacity. Therefore, the types of hydrogels fabricated can be summarized in **Table 2**.

The results of the one-way ANOVA on the fluid affinity test data showed a p-value less than 0.05, indicating a significant effect on the variation in the HAP addition ratio in the hydrogel formulation.

Based on the fluid affinity test results, the CMC-HA-HAP1 sample is the optimal formulation. This is because samples in osteoporosis require hydrogels that act as donors so that they can regenerate bone tissue by releasing bioactive substances such as calcium (Chen et al., 2025). Calcium is present in the HAP, which is released when the hydrogel is injected. This bioactive release promotes osteoblast differentiation and regulates the expression of genes related to bone formation (Wang et al., 2025). The CMC-HA-HAP1 sample is better than CMC-HA-HAP2 and CMC-HA-HAP3 because it does not have too high a donation capacity. If the donation capacity is too high, it will cause the hydrogel to have a burst release effect, which can lead to toxic side effects (Klara & Lewandowska-łańcucka, 2022). In addition, the CMC-HA-HAP1 sample is better because it has good absorption properties that support the absorption of nutrients from body fluids, which can aid cell growth. (Annisa et al., 2024).

3.4 Viscosity Test

The viscosity test results shown in **Figure 3** indicate that an increase in the hydroxyapatite solution contained in the hydrogel will decrease the viscosity of the fabricated hydrogel. The viscosity results also show that all samples meet the requirements for viscosity set by US Patent No. US 8,747,899 B2 is in the range of 5 to 200,000 m.Pa.s. The one-way ANOVA results from the viscosity test data have a p-value of less than 0.05, indicating a significant effect or relationship.

3.5 Stability Test

The results of stability testing conducted using the freeze-thaw method for three cycles are shown in **Table 3**. Based on the results, all samples remained stable because they did not change color or odor (Paramadini et al., 2023)

3.6 Percolation Test

Percolation testing was performed qualitatively by observing the movement of trypan blue in the hydrogel samples, the results of which are shown in **Figure 4**. Based on the test results, CMC-HA-HAP1 was the slowest to pass the trypan blue dye compared to the CMC-HA-HAP2 and CMC-HA-HAP3 samples and was not significantly different from the control sample (CMC-HA-HAP0). Therefore, it can be said that CMC-HA-HAP1 has slow-release capabilities suitable for osteoporosis. The slow-release capability of hydrogels will help improve bone tissue regeneration for osteoporosis (Poorirani et al., 2023).

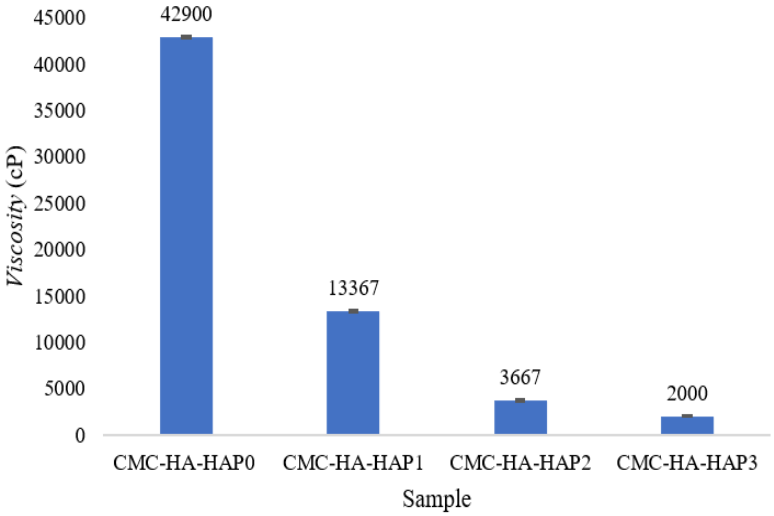

Figure 3. Viscosity of Each Variation Hydrogels

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Table 3. Stability Test Result

Hydrogel	Stability Indicator of Hydrogels	
	No Color Change	No Odor
CMC-HA-HAP0	✓	✓
CMC-HA-HAP1	✓	✓
CMC-HA-HAP2	✓	✓
CMC-HA-HAP3	✓	✓

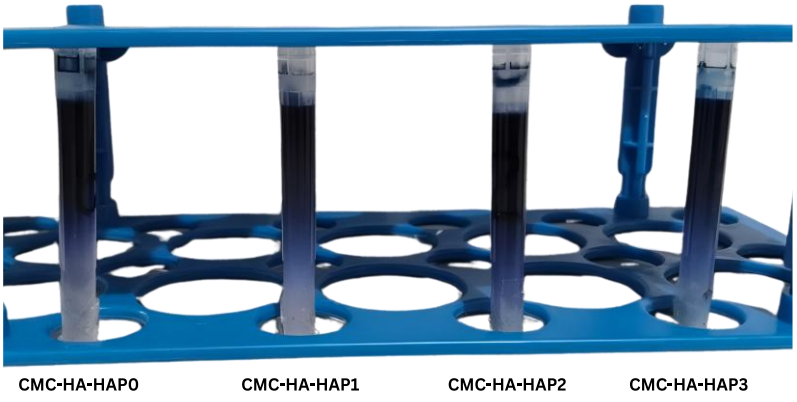

Figure 4. Result of Percolation Test After 6 Days

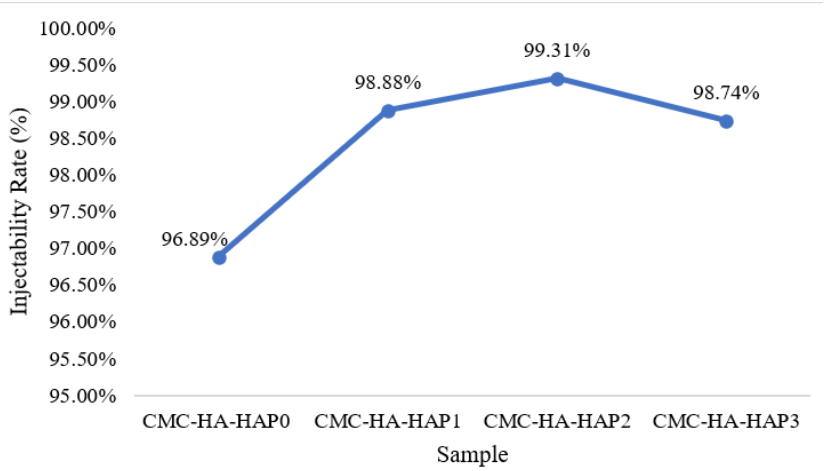

Figure 5. Injectability Rate All Hydrogels

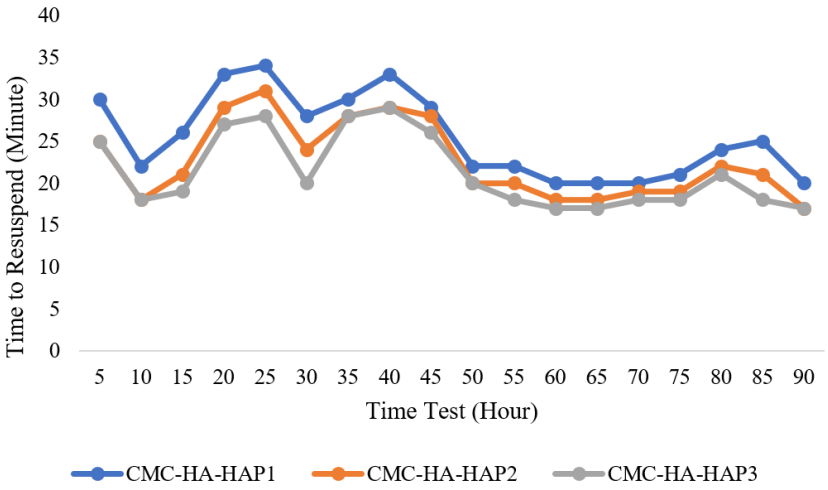

Figure 6. Resuspension Test Based on Time for Resuspend

Table 4. Resuspension Test Result pH

Hydrogel	pH Condition	
	Before Adding PBS	After Adding PBS
CMC-HA-HAP1	7	7
CMC-HA-HAP2	7	7
CMC-HA-HAP3	7	7

3.7 Injectability Test

This injectability test determined how easily the material can be dispensed through a syringe needle. This study adjusted needle selection according to US Patent No. US 8,747,899 B2, namely, 16- to 22-gauge needles for injection. The results of this injectability test are shown in **Figure 5**, which shows that the injectability percentage ranges from 96.89% to 99.31%. The

injectability percentage for all samples was close to 100%, indicating that the mass dispensed was not significantly different from the mass introduced. Therefore, the high injectability percentage indicates that the hydrogel can deliver accurate doses suitable for clinical injection applications (Moreira et al., 2018).

3.8 Resuspension Test

Resuspension testing examined the pH and time required for suspension reforming. The results of resuspension testing for pH are shown in **Table 4**, where all samples containing hydroxyapatite did not experience pH abnormalities after adding PBS.

As shown in **Figure 6**, resuspension testing over time showed that the CMC-HA-HAP1 sample had the slowest resuspension time. The precipitates formed in all hydroxyapatite samples could be resuspended without sticking to the vial.

3.9 SEM Test

The SEM test results are divided into two parts, namely the morphology of the hydrogel and its dispersion energy. The SEM morphology of the hydrogel is shown in **Figure 7**. The test results revealed that the average pore size of the CMC-HA-HAP0 hydrogel was 87.06 ± 41.63 µm, that result show in **Figure 7A**. This pore size is still within the range of 10–500 µm, which can support tissue growth and nutrient supply (Martinez-garcia et al., 2022; Sarita, Dayaram, et al., 2024). CMC-HA-HAP0 hydrogel is considered a matrix in which hydroxyapatite is filled into the pores formed in the matrix. Hydroxyapatite as a filler has been successfully incorporated, as evidenced by the morphology of the filled pores shown in **Figure 7B**. On the other hand, the dispersion energy is shown in **Figure 8**. **Figure 8A** depicts that in CMC-HA-HAP0 contains some atoms like oxygen, carbon, nitrogen, and sodium. On the other hand, for CMC-HA-HAP1, that show in **Figure 8B** have same result as CMC-HA-HAP0, but there are some new atom show, like calcium and phosphorus. That Ca and P are from hydroxyapatite, which can indicate successful incorporation of hydroxyapatite in matrix CMC-HA.

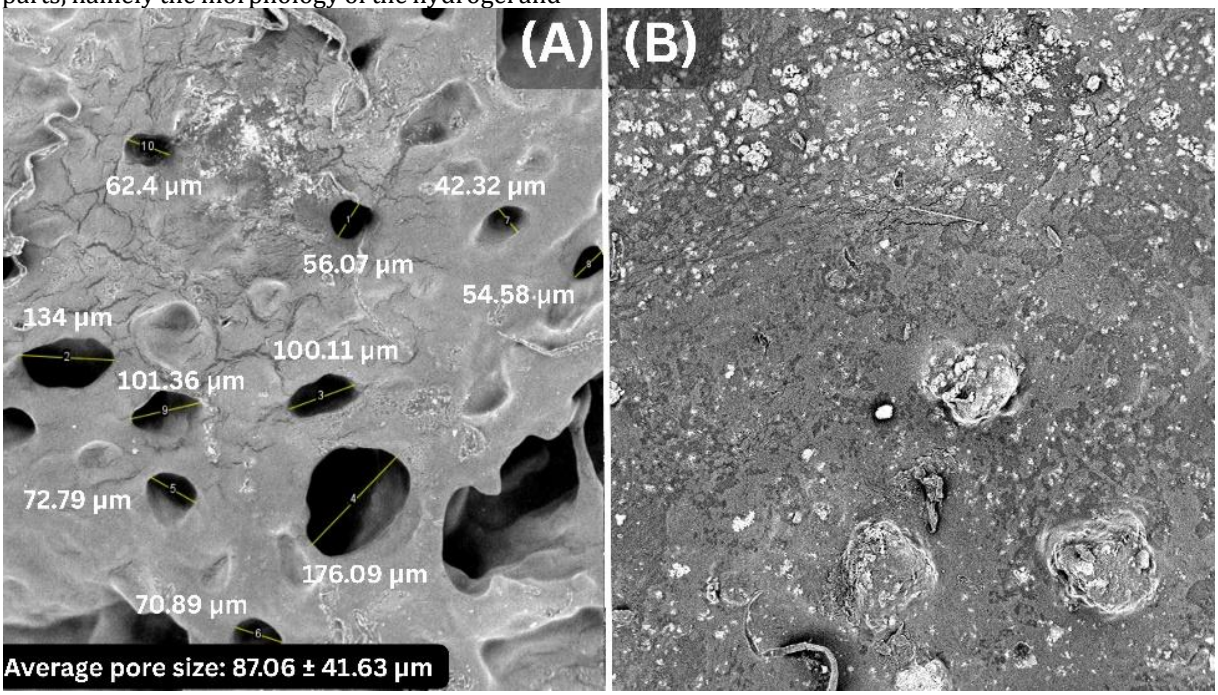

Figure 7. Morphology Result from SEM with Magnification 265× (A) CMC-HA-HAP0 (B) CMC-HA-HAP1

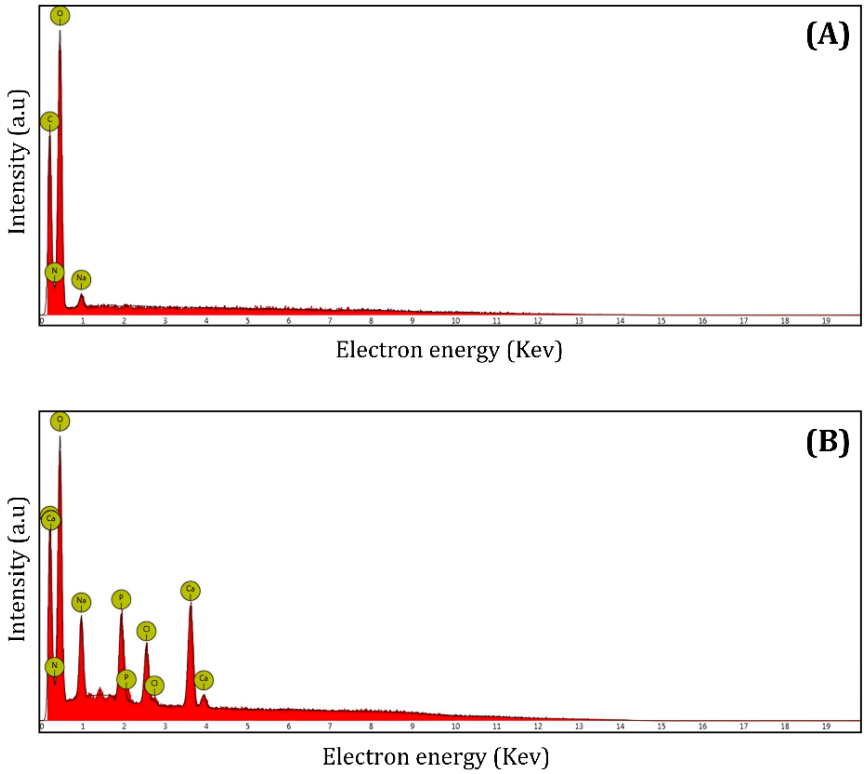

Figure 8. Energy Dispersive (A) CMC-HA-HAP0 (B) CMC-HA-HAP1

4. CONCLUSION

The XRD test results show that hydroxyapatite has been successfully incorporated into the hydrogel, as evidenced by the formation of diffraction peaks. The results of the fluid affinity test show that the hydrogel has types 3E, 2E, and 1E. The results of the viscosity test show that all samples have viscosities in the range of 5 to 200,000 mPa.s, consistent with the viscosity of injectable hydrogels. All fabricated hydrogels were stable after freeze-thaw cycles. The injectability rate was close to 100%, making it suitable for injection. CMC-HA-HAP1 passed trypan blue the slowest, indicating slow release capability. Furthermore, the resuspension test showed no pH abnormalities, and CMC-HA-HAP1 had the longest recrystallization time. The pore size based on SEM test results was 87.06 ± 41.63 µm, and the morphology of CMC-HA-HAP1 showed that hydroxyapatite had successfully filled the pores formed in the hydrogel. Based on the overall test results, the 1:1:1 (CMC-HA-HAP1) formulation shows characteristics suitable for a regenerative medicine candidate in osteoporosis.

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