Egypt. J. Chem. **Vol. 67**, No. 2 pp. 205 - 213 (2024)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Synthesis and Characterization of Hydrogel Alginate/Poly (N-Vinyl -2-Pyrrolidone) with Double Ionic Cross-Bonded for Drug Delivery and Antibacterial Agent

Kartini Afriani *, Sulaiman Suhartini , Gina Maulia

[a]*Department of Analytical Chemistry, Polytechnic of AKA Bogor, Jalan Pangeran Sogiri No. 283, Bogor 16154, Indonesia*

Abstract

Alginate (Alg), as a biopolymer, has suitable characteristics for drug delivery systems, quickly forming a gel with polyvalent cations and compatible with another polymer like poly (N-vinyl-2-pyrrolidone) (PVP). In this study, the synthesis of Alg/PVP hydrogels with calcium and strontium ion crosslinkers has been carried out and characterized by Fourier Transform Infrared (FTIR) and Scanning Electron Microscope (SEM) and Energy Dispersive X-ray (EDX). The research studies the expansion ratio (swelling), gel percentage, an antibacterial test of the hydrogel, and the application of the hydrogel in drug delivery systems through dissolution tests. The results of the synthesis of Alg/PVP/Ca/Sr hydrogels obtained the development ratio (swelling ratio, Q, %) and gel percentage (%Gel) with Ca^{2+} and Sr^{2+} ions crosslinkers optimum at 70:30 Alg/PVP ratio and 2:3 Ca/Sr ratio, with a Q (%) value of 448.47%±4.19 and a %Gel value of 18.25%±0.05. Hydrogel has antibacterial properties against *Bacillus subtilis* and *Escherichia coli*. Hydrogels can also be used for drug delivery mediums, with dissolution test results for amoxycillin at 46.18% ±1.50 and ibuprofen at 94.83%±0.50.

Keywords: *Alginate;* poly (N-vinyl-2-pyrrolidone)*; hydrogel; antibacterial.*

1. Introduction

Alginate, natural anionic polysaccharide obtained from species of brown algae, is a linear copolymer consisting of two uranic sugars, namely salts of mannuronic acid and guluronic acid. Bond 1→4-D-mannuronic acid (M) and L-guluronic acid (G) join in a block pattern along the chain [1-3], containing the three types of blocks, namely homopolymer M-M blocks and G-G blocks, which are interspersed by heteropolymer blocks of irregular M-G structures. The blocks are arranged in a block wise pattern that determines the chemical and physical properties of the alginate molecule [1]. Alginate has a polyelectrolyte and biopolymer structure, providing favorable properties. The most important ability of alginates is gelation ease in the presence of highly charged or polyvalent cations, especially bivalent cations such as Ca^{2+}. Besides that, alginate is relatively highly soluble in water, large, biocompatible, bio adhesive, biodegradable, non-toxic, relatively non-immunogenic, sufficient transparency, relatively stable, and easy to use. All these properties make alginate widely used in various biomedical and engineering sciences branches. However, alginate has limited stability, influenced by environmental conditions [3]. Previous studies have shown that not only does the chemical structure and molecular size of alginate have an impact on the functional properties of alginate gels, including porosity, swelling behavior, stability, biodegradation, gel strength, gel immunological characteristics, and biocompatibility, but also formation kinetics and gel cation type. Recent years have seen an increasing trend to produce modifications of alginic acid derivatives through different chemical and biochemical techniques [1].

Alginates are developed to manufacture hydrogels through combination with other polymers and are applied for drug delivery, wound dressing, or other pharmaceutical applications. The development of

*Corresponding author e-mail: kartini-a@kemenperin.go.id
Received date 8 May 2023; revised date 10 June 2023; accepted date 16 June 2023
DOI: 10.21608/ejchem.2023.209529.7949

alginate hydrogel as an antibacterial wound dressing medium with various polymers has been carried out, such as alginate/ZnO hydrogel, alginate/gelatin/Poly Vinyl Alcohol (PVA) hydrogel, alginate/chitosan with vitamin E hydrogel, alginate/PVA/PVP, etc. This development is based on physical, chemical, biological, and antibacterial properties as well as its ability to absorb and release the active substances that can assist in the wound healing process [4-7]. Alginates can be crosslinked covalently or ionically. Treenate [8] studied the different effects of Ca^{2+}, Zn^{2+}, and Cu^{2+} ions on the formation of hydroxyethyl acryl-chitosan alginate hydrogel used as a medium for delivering paracetamol. Wu [9] used Ca^{2+} in the blending process of alginate and chitosan as a lysozyme carrier medium. Zia [10] developed an antibacterial burn dressing from alginate and carrageenan through ionic interactions with silver nanoparticles (AgNP). GP & MR [11] grafting of alginate with PEG for wound dressing material using Sr^{2+}. The previous study used one type of cation crosslinker, such as Ca^{2+}, Cu^{2+}, Zn^{2+}, and Sr^{2+}. The combination of two cations or more has yet to be carried out in a recent study. Ca^{2+} and Sr^{2+} are less toxic than Ba^{2+}, then Sr^{2+} has higher chemical stability and stronger mechanical performance when applied in alginate hydrogel [12]. Since Ca^{2+} has less interaction site in alginate than Ba^{2+} and provides more site to physical adsorption, the combination of Ca and Sr is expected to provide hydrogels with higher stability and stronger mechanical properties.

Poly (N-vinyl-2-pyrrolidone) (PVP) is a biocompatible, water-soluble linear, nontoxicity polymer. PVP-based hydrogel has good chemical stability and hydrophilicity. So, it increases polymers' water affinity [11, 13]. Many hydrogels are produced using PVP and applied in the pharmaceutical industry, such as drug delivery systems, wound dressings, and tissue engineering scaffolds [13–19]. The combination of PVP and natural polymer has been used in several studies to improve the ability of the hydrogel to absorb water. Wang & Wang [20] used a mixture of anionic monomers Na-alginate, Na-acrylate, and non-ionic polymers poly(N-vinyl-2-pyrrolidone) to improve hydrogel surface morphology and water absorption ability. Meanwhile, the study by Sadeghi [21] used acrylic acid anionic monomer copolymerized with N-vinyl-2-pyrrolidone (NVP) to increase the ability of superabsorbent hydrogels.

This study synthesized crosslinked alginate hydrogels by combining two cations to increase the hydrogel's ability as a drug delivery medium. Alginate combined with Poly(N-vinyl-2-pyrrolidone) can increase the affinity for water of hydrogel [13, 15, 19]. This paper studied the hydrogel with Ca^{2+} and Sr^{2+} as a crosslinker, the effect of the ratio of alginate/PVP and the various amount of ratio Ca^{2+}/Sr^{2+} on hydrogel's ability to absorb water, the gel fraction, and the ability of hydrogel as drug delivery medium.

2. Experimental

2. 1. Chemicals and Reagents

The materials used include $AgNO_3$, $CaCl_2.5H_2O$, $SrCl_2.6H_2O$, CH_3COOH, potato dextrose agar (PDA) media, nutrient agar (NA) media, nutrient broth media (NB), Phosphate Buffer. All chemical and reagent are from Merck, Germany. Alginate, poly-N-vinyl pyrrolidone (PVP) K 30.000, amoxycillin standard, ketoconazole standard are from Sigma Aldrich, Germany. Amoxycillin (Amosterra, Hosana Jaya Farma, Indonesia), ibuprofen (Proris, Pharos Indonesia), *Escherichia coli* bacteria and *Bacillus subtilis* bacteria (pure isolated strain from the culture collection center of Microbiology Lab of Polytechnic of AKA Bogor, Indonesia), distilled water.

Table 1. The Formulation with variation of Alg/PVP

Sample	Ratio			
	Alg	PVP	Ca^{2+}	Sr^{2+}
I	6	4	2	3
II	7	3	2	3
III	8	2	2	3
IV	9	1	2	3

2. 2. Preparation of Alg/PVP hydrogel

Alginate and PVP with a certain weight ratio (the variation of alginate-PVP refer to Table 1) were weighed and dissolved in distilled water using a stirring hotplate at room temperature. Cross-linkers (the variation of $CaCl_2.5H_2O$ and $SrCl_2.6H_2O$ refer to Table 2), with 5% of total weight, were added to the alginate-PVP mixture and stirred for 1 hour. The product formed was filtered, washed, and dried at 50ºC, and measured the hydrogel product's degree of swelling and cross-linking [19, 22]. The test was carried out with three repetitions.

Table 2. The Formulation with variation of Ca/Sr

Sample	Ratio			
	Alg	PVP	Ca^{2+}	Sr^{2+}
V	7	3	0	0
VI	7	3	1	4
VII	7	3	2	3
VIII	7	3	3	2
IX	7	3	4	1

The degree of swelling was measured by soaking the hydrogel in distilled water for 30 minutes. The weight of the hydrogel and swollen films was determined by an analytical balance. The swelling ratio can be determined by:

$$\%Swelling = [(W_s - W_d)/W_d] \times 100 \quad (1)$$

W_s is the weight of the hydrogel when swollen (g), and W_d is the weight of the dry hydrogel (g) [8, 20-21].

The degree of crosslinking or gel percentage (%Gel) was determined by immersing the hydrogel in 1% acetic acid for 24 hours and then heated at 55ºC until dry. The dry weight before and after immersion was determined by an analytical balance. The percent degree of cross-linking can be determined by:

$$\%Gel = (W_a/W_b) \times 100 \quad (2)$$

W_a is the weight of the hydrogel after immersion (g), and W_d is the weight of the hydrogel before immersion (g) [8, 20-21].

2. 3. Characterization of Alg/PVP/Ca/Sr hydrogel

Initial characterization was carried out using FTIR spectrophotometers (Agilent) in the wavelength region 400-4000 cm-1 to determine the success of the cross-linking process. The samples are coated with gold before surface morphologies characterization with a scanning electron microscope (SEM) and energy dispersive X-ray (EDX) (Jeol JSM 6510 lA), and Uv-visible spectrophotometers (Agilent) for measurement of the percentage of drug release.

2. 4. Antibacterial test with agar disc diffusion method

Amount 0.5 mL of test microbial culture (*Escherichia coli* and *Bacillus subtilis)* was pipetted aseptically into sterile Petri dishes, added NA/PDA medium, which was still liquid (45°C-50°C), homogenized, and allowed to freeze. The disc paper was dipped in Alginate/PVP hydrogel, placed on the surface of the NA/PDA medium aseptically, and incubated at 37°C for 24 hours, then the inhibition zone formed was measured [23]. The antibacterial standards used were amoxicillin and ketoconazole as antifungal standards. The test was carried out with three repetitions.

2. 5. Application of Alg/PVP/Ca/Sr hydrogels in drug delivery systems

Ibuprofen caplets were dissolved in 900 ml of Phosphate Buffer pH 7.4 using the paddle method. Amount of 18 ml aliquots were taken at 15, 30, 45, and 60 minutes and replaced with the same volume, and then 1 ml was diluted into a 50 ml volumetric flask, and the concentration of the drug was released measured by UV-Vis's spectrophotometer at a wavelength of 221 nm [8].

Amoxycillin caplets were dissolved in 900 ml of Phosphate Buffer pH 6.8 using the paddle method. The 18 ml aliquots were taken at 15, 30, 45, and 60 minutes and restored with the same volume. Then diluted, 2 ml into a 50 mL volumetric flask, and the absorbance was measured using a UV-Vis Spectrophotometer at a wavelength of 227 nm [8].

The percentage of drug release (% dissolution) was calculated using the following equation:

$$\%Dissolution = \frac{(A_{sp} \times W_{st} \times Fp_{sp} \times 100\%)}{(R_{st} \times Fp_{st} \times C)} \quad (3)$$

A_{sp} is the sample absorbance, W_{st} is the standard weight, Fp_{sp} is the sample dilution factor, R_{st} is the standard concentration, and Fp_{st} is the standard dilution factor. The test was carried out with three repetitions.

3. Results and discussion

This study's synthesis of alginate-PVP hydrogel used the semi-interpenetrating polymer network (IPN) method. At this stage, the alginate as the main structure of the hydrogel is crosslinked with the ionic crosslinking agent Ca^{2+}, Sr^{2+} in the presence of a linear (non-crosslinked) PVP polymer forming a semi-IPN polymer network. The hydrogel obtained is in a gel which indicates that crosslinking has occurred between the alginate and the crosslinking agent. The hydrogel solution was poured into a printing container and dried in an oven at 60ºC for 48 hours to dry [22] for further characterization. Crosslinking in alginate-PVP hydrogels can occur between –COO- or –OH groups of alginate and metal ions through coordination or partially ionic bonds, Ca^{2+} ions and Sr^{2+} ions forming ionic bonds with –COO- or –OH groups of alginates [2, 8, 11, 12, 24]. Crosslinks are also created

through intermolecular bonds, such as forming hydrogen bonds between polar groups of alginates and PVP. The proposed mechanism reaction describes in Figure 1.

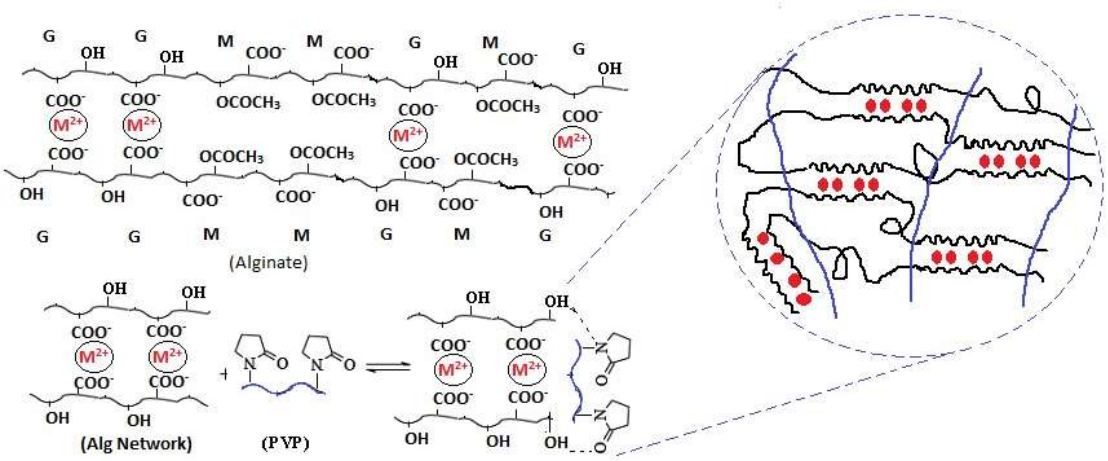

Figure 1. Proposed ionic crosslinking reaction in alginate and intermolecular bond of Alg/PVP

3.1. FTIR Analysis

The alginate absorption peak is found at 3466 cm^{-1}, which showed stretching vibrations of the –OH group and broadening, which indicated the presence of the -COOH group. The 1589 cm^{-1} is a region of asymmetric stretching vibration of the $–COO^-$ group, the 1406 cm^{-1} is peak of symmetric stretching vibration of the $–COO^-$ group, and the 1023 cm^{-1} region indicates the stretching vibration of the C-O group, respectively (Figure 2 (a)). The characteristic spectrum of poly-(N-vinyl-2-pyrrolidone) (PVP) is found at wave number 1636 cm^{-1}, which is the amide carbonyl group's stretching vibration (C=O) and 1274 cm^{-1}, which shows the stretching vibration of the C-N group (Figure 2 (b)). The alginate and PVP peak acquiesce in previous reports [4, 8, 17-20].

The FTIR spectrum of the semi-IPN Alg/PVP hydrogel is shown in Figure 2 (c) and Alg/PVP/Ca/Sr hydrogel film in Figure 2 (d). The spectrum results show the characteristic absorption of the –COOH alginate group with a broad peak found at 3367 cm^{-1} for the Alg/PVP blended hydrogel film and 3345 cm^{-1} for Alg/PVP/Ca/Sr hydrogel film. The widened peak indicates the presence and interaction of the alginate functional group with PVP through hydrogen bonding. The interaction with the crosslinking agent (Ca^{2+}, Sr^{2+}) was characterized by absorption shifts at 1636 and 1420 cm^{-1} in Alg/PVP hydrogel to 1643 and 1438 cm-1 which refer to interaction of Ca^{2+} and Sr^{2+} with -COO- asymmetric and symmetric vibration stretching of Alg in Alg/PVP/Ca/Sr hydrogel film. This result concurs with the previous report [8-9, 19]. Since Ca^{2+} interacts with a slightly G-G block, Sr^{2+} is preferable with G-G and M-G blocks. The remaining metals of calcium and strontium form salt with chlorine as $CaCl_2$ and $SrCl_2$, which are physically absorbed in the alginate chain [12]. The stretching vibration of -C-O- of alginate still occurs at 1025 cm^{-1} in the Alg/PVP hydrogel. Meanwhile, the peak decrease in Alg/PVP/Ca/Sr hydrogel occurs at 1017 cm^{-1}. It indicates the presence of weaker binding between the crosslinker and alginate.

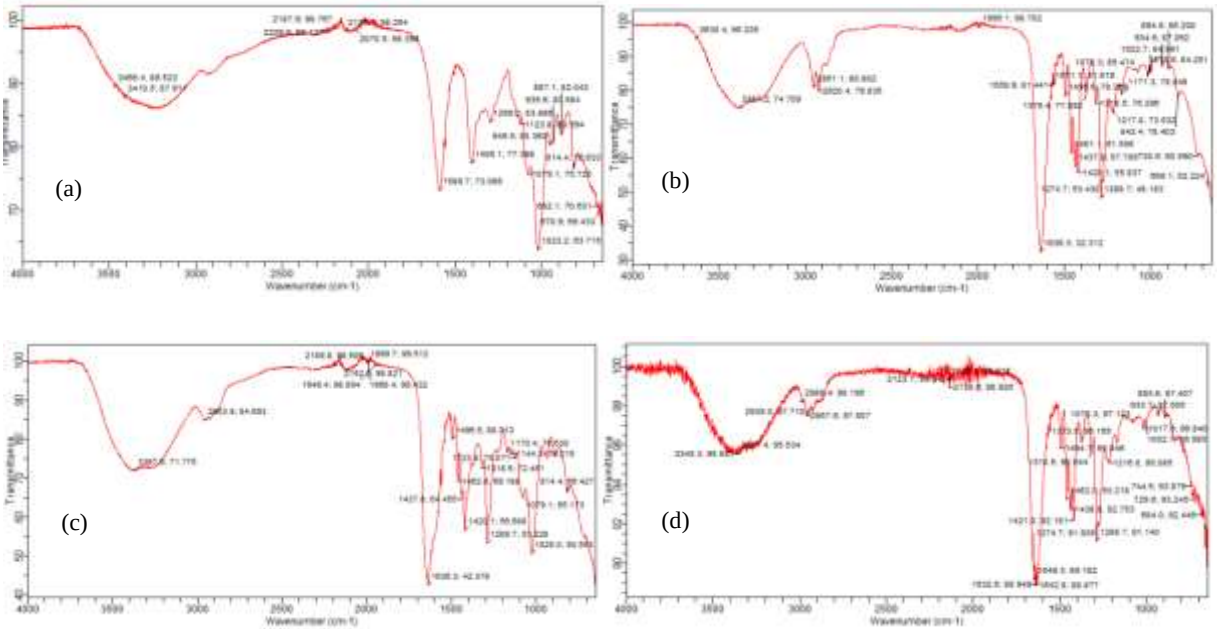

Figure 2. Spectrum FTIR hydrogel film of (a) Alginate; (b) PVP; (c) Alg/PVP hydrogel; (d) Alg/PVP/Ca/Sr hydrogel

3.2. Swelling Ratio (Q, %) and the degree of crosslinking (%Gel)

The hydrogel expansion ratio when adsorbing water (Swelling Ratio, Q, %) and the degree of hydrogel crosslinking (%Gel) are in Figure 3 and 4. The swelling ratio of samples II, III, and IV with different amounts of polymer compiler slightly rose but increased significantly from sample I (Figure 3). Generally, the swelling ratio of each hydrogel sample increases with increasing time (Q10 to Q120); after 120 minutes decrease in the swelling ratio began, and the declining mechanical properties of the hydrogel are showing. The degree of hydrogel crosslinking (%Gel) is gaining with the rise of the Alg/PVP ratio. %Gel value corresponds to the increase in the resulting swelling ratio. With a low %Gel and a higher swelling ratio of sample II, the formulation of hydrogel, in the study of the effect of crosslinker Ca/Sr ratio, uses ratio polymer in sample II.

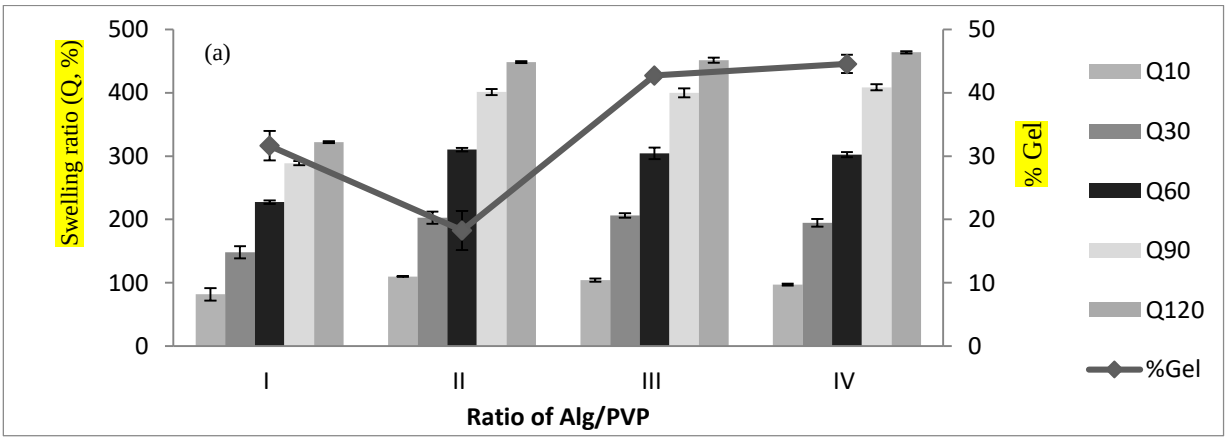

Figure 3. Swelling ratio (Q, %) and gel percentage (%Gel) on various polymer composition ratio

Figure 4 describes the swelling Ratio (Q, %) and Gel Percentage (%Gel) on various crosslinkers. Hydrogel Alg/PVP ionically crosslinked with Ca-Sr, (sample VI, VII, VIII, IX) had better water adsorption ability than non-covalent crosslinked chitosan (sample V, hydrogel blending without crosslinker). The swelling ratio increased through the formation of crosslinks in the hydrogel because the polymer network formed can trap the water or fluids. The gel percentage (%Gel) was relatively large, indicating the formation of relatively strong crosslinks between the functional groups of the polymer. Alg/PVP (sample V) gel percentage value in blending has a relatively low expansion ratio because the network is formed only

from the physical interaction between constituent polymers. The low percentage of %Gel blending Alg/PVP causes the hydrogel to hydrolyze slightly, marked by a decreased swelling ratio in the last 10 minutes of immersed sample in distilled water. The high expansion ratio occurs using a combination of 2 crosslinking ions with the composition of Alg/PVP being 70:30, sample VII, and the crosslinker ratio 2:3 (Figure 4). Thus, the excellent swelling ability can support the hydrogel in absorbing and releasing the active substances incorporated in the hydrogel.

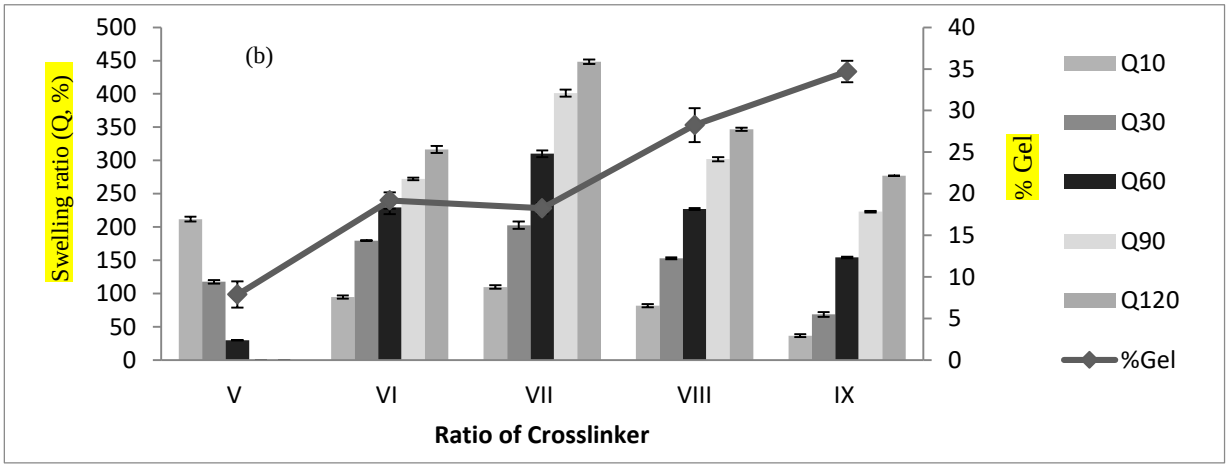

Figure 4. Swelling ratio (Q, %) and gel percentage (%Gel) on various crosslinkers Ca and Sr in the similar polymer composition ratio

3.3. SEM Analysis

The morphology analysis with SEM provides an overview of the hydrogel. The ability of a hydrogel to absorb water is related to the presence of porous spaces in the hydrogel (Risbud M. V. et al. [22]. Porous areas are also present in the bulk polymer network. The porous space allows the absorption of water on the surface, followed by a diffusion process and the entry of water into the centre of the gel or polymer body through capillary forces.

SEM results from Figure 5 show the rough surface of the Alg/PVP/Ca/Sr hydrogel compared to the Alg/PVP blending. The appearance is proportional to the high swelling ratio of the hydrogel. In the EDX analysis, the distribution of Ca and Sr was relatively homogeneous. The rough surface indicates PVP incorporation into the polymer alginate carriage and the cross-linking of the ionic alginate with Ca and Sr.

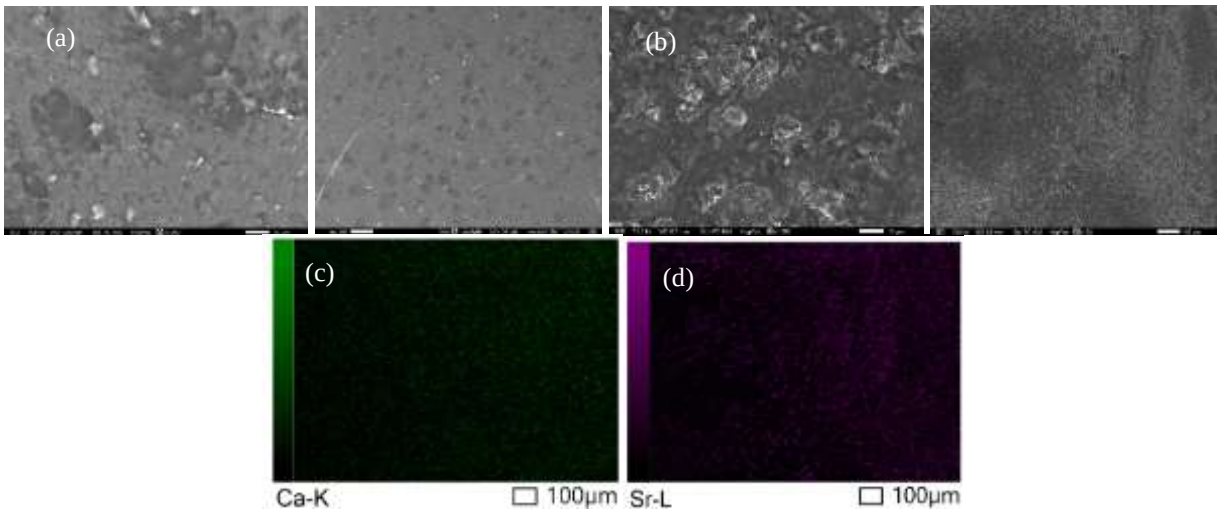

Figure 5. SEM image of hydrogel (a) Alg/PVP, (b) Alg/PVP/Ca/Sr, (c) SEM-EDX-Ca, (d) SEM-EDX-Sr

3.4. Antimicrobial Test of Alginate/PVP/Ca/Sr hydrogel

Observations of the inhibition zones of the antimicrobial test of the Alginate/PVP/Ca/Sr hydrogel can be seen in Figure 6.

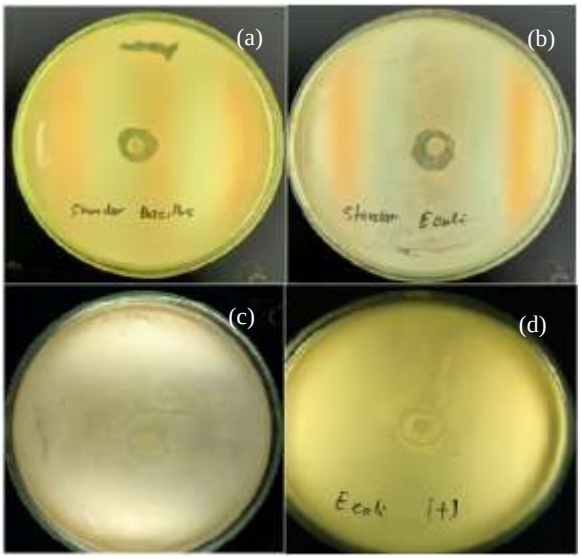

Figure 6. Inhibition zone of (a) standar with *Bacillus substilis*; (b) standar with *Escherichia coli*; (c) sample with *Bacillus subtilis*, and (d) sample with *Escherichia coli*

The Alg/PVP/Ca/Sr hydrogel gave test results as an antibacterial against *Bacillus subtilis* and *Escherichia coli*. The results of the hydrogel test are in line with the research by Pitchaya Treenate and Pathavuth Monvisade [8] and Tiantian Wu et al. [9]. The use of metal ions such as Ca^{2+}, Zn^{2+}, and Al^{3+} as crosslinkers can increase the antibacterial activity of the hydrogels.

Table 3. Antimicrobial Test of Hydrogel Alg/PVP/Ca/Sr

Standard (mm)		Sample VII (mm)*	
E. Coli	*Bacillus*	*E. Coli*	*Bacillus*
0.97±0.06	1.07±0.29	0,97±0.06	0.23±0.12

*inhibition zones in mm

3.5. Application of Alginate/PVP/Ca/Sr hydrogel in drug delivery systems

The dissolution test was carried out at pH 7.4, simulating conditions in the digestive tract. Ibuprofen is the model drug to study the mechanism of drug release from Alg/PVP/Ca/Sr hydrogels. The results of the hydrogel dissolution test can be seen in Figure 7 with rate Std is a standard. At pH 7.4, it gave high ibuprofen dissolution test results on Alg/PVP/Ca/Sr hydrogel. Ibuprofen is poorly soluble in acidic conditions but dissolves well in neutral or alkaline solutions. The carboxylic groups of alginates easily ionize to form carboxylic ion ($-COO^-$) in neutral to basic environment, which produces repulsion force between negative charge of $-COO^-$ and causing chain enlargement/swelling of matrix [25]. At digestive environment, the Alg/PVP/Ca/Sr hydrogel is resulting a more flexible hydrogel so that the release of ibuprofen is relatively fast.

The dissolution test with the amoxycillin compound was carried out at a pH of 6.8, relatively neutral to simulate conditions in the digestive tract. The amoxycillin dissolution test obtained lower % dissolution data than that of ibuprofen, but still can be a medium to release amoxycillin slowly.

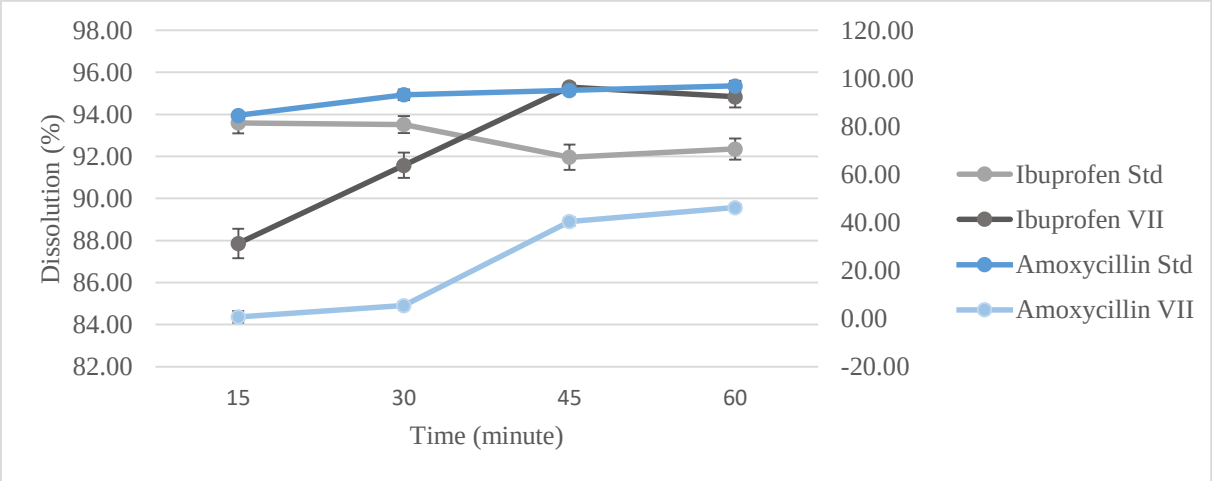

Figure 7. Dissolution test of the Alg/PVP/Ca/Sr hydrogels with ibuprofen and amoxycilin

4. Conclusions

In this research, alginate/PVP hydrogel synthesis has been carried out by crosslinking Ca^{2+} and Sr^{2+} ions. The combination produces a good swelling ratio (swelling, Q, %) and gel percentage (%Gel). Since the hydrogel has antibacterial properties against *Bacillus subtilis* and *Escherichia coli*, the tests for antibacterial properties must be developed by testing on various other types of bacteria and determining the minimum inhibition of the hydrogel so that it can apply in different fields, such as wound dressings. In a drug delivery system, hydrogel works under alkaline conditions and lies in the digestive tract.

5. Acknowledgement

This research was a grant from the Polytechnic of AKA Bogor, Indonesia.

6. Conflicts of interest

The authors claim that they have no conflict to declare.

7. References

[1] Guo, Xi, et al. "Structures, properties and application of alginic acid: A review." *International Journal of Biological Macromolecules* 162 (2020): 618-628. Doi: 10.1016/j.ijbiomac.2020.06.180.

[2] Varaprasad, Kokkarachedu, et al. "Alginate-based composite materials for wound dressing application: A mini review." *Carbohydrate polymers* 236 (2020): 116025. Doi: 10.1016/j.carbpol.2020.116025.

[3] Nie, Jingyi, et al. "Construction of ordered structure in polysaccharide hydrogel: A review." *Carbohydrate polymers* 205 (2019): 225-235. Doi: 10.1016/j.carbpol.2018.10.033.

[4] Wang, Tingting, et al. "Preparation and properties of ZnO/sodium alginate bi-layered hydrogel films as novel wound dressings." *New Journal of Chemistry* 43.22 (2019): 8684-8693. Doi: 10.1039/c9nj00402e.

[5] Ehterami, Arian, et al. "Chitosan/alginate hydrogels containing Alpha-tocopherol for wound healing in rat model." *Journal of Drug Delivery Science and Technology* 51 (2019): 204-213. Doi: 10.1016/j.jddst.2019.02.032.

[6] Satish, Aishwarya, et al. "Triiodothyronine impregnated alginate/gelatin/polyvinyl alcohol composite scaffold designed for exudate-intensive wound therapy." *European Polymer Journal* 110 (2019): 252-264. Doi: 10.1016/j.eurpolymj.2018.11.032.

[7] Jin, Sung Giu, et al. "Development of a novel sodium fusidate-loaded triple polymer hydrogel wound dressing: Mechanical properties and effects on wound repair." *International journal of pharmaceutics* 497.1-2 (2016): 114-122. Doi: 10.1016/j.ijpharm.2015.12.007.

[8] Treenate, Pitchaya, and Pathavuth Monvisade. "In vitro drug release profiles of pH-sensitive hydroxyethylacryl chitosan/sodium alginate hydrogels using paracetamol as a soluble model drug." *International journal of biological macromolecules* 99 (2017): 71-78. Doi: 10.1016/j.ijbiomac.2017.02.061.

[9] Wu, Tiantian, et al. "Formation of hydrogels based on chitosan/alginate for the delivery of lysozyme and their antibacterial activity." *Food chemistry* 240 (2018): 361-369. Doi: 10.1016/j.foodchem.2017.07.052.

[10] Zia, Tahmina, et al. "Development of inter-polymeric complex of anionic polysaccharides, alginate/k-carrageenan bio-platform for burn dressing." *International journal of biological macromolecules* 157 (2020): 83-95. Doi: 10.1016/j.ijbiomac.2020.04.157.

[11] Rajalekshmy, G. P., and M. R. Rekha. "Strontium ion cross-linked alginate-g-poly (PEGMA) xerogels for wound healing applications: in vitro studies." *Carbohydrate Polymers* 251 (2021): 117119. Doi: 10.1016/j.carbpol.2020.117119.

[12] Makarova, Anastasiya O., et al. "Ion-induced polysaccharide gelation: Peculiarities of alginate egg-box association with different divalent cations." *Polymers* 15.5 (2023): 1243. Doi: 10.3390/polym15051243

[13] Zayed, Gamal M., et al. "In vitro and in vivo characterization of domperidone-loaded fast dissolving buccal films." *Saudi pharmaceutical journal* 28.3 (2020): 266-273. Doi: 10.1016/j.jsps.2020.01.005.

[14] Abasalizadeh, Farhad, et al. "Alginate-based hydrogels as drug delivery vehicles in cancer treatment and their applications in wound dressing and 3D bioprinting." *Journal of biological engineering* 14 (2020): 1-22. Doi: 10.1186/s13036-020-0227-7.

[15] Karmakar, Sandip, et al. "Recent progress in alginate-based carriers for ocular targeting of therapeutics." *Food Hydrocolloids for Health* (2022): 100071. doi:10.1016/j.fhfh.2022.100071.

[16] Chen, Yu, et al. "Synthesis and characterization of a novel superabsorbent polymer of N, O-carboxymethyl chitosan graft copolymerized with vinyl monomers." Carbohydrate Polymers 75.2 (2009): 287-292. Doi: 10.1016/j.carbpol.2008.07.022.

[17] Saha, Nabanita, et al. "PVP-CMC hydrogel: An excellent bioinspired and biocompatible scaffold for osseointegration." *Materials Science and Engineering: C* 95 (2019): 440-449. Doi: 10.1016/j.msec.2018.04.050.

[18] Ajji, Z., et al. "Synthesis of pH-responsive hydrogel based on PVP grafted with crotonic acid for controlled drug delivery." *Radiation Physics and Chemistry* 170 (2020): 108612. Doi: 10.1016/j.radphyschem.2019.108612

[19] Afriani, Kartini, and Tri Sutanti Budikania. "Synthesis and Characterization of Hydrogel of Chitosan-Poly (N-Vinyl-2-Pirrolidone) (PVP)-Alginate for Ibuprofen Release." *The Journal of Pure and Applied Chemistry Research* 9.3 (2020): 201-211. Doi: 10.21776/ub.jpacr.2020.009.03.558

[20] Wang, Wenbo, and Aiqin Wang. "Synthesis and swelling properties of pH-sensitive semi-IPN superabsorbent hydrogels based on sodium alginate-g-poly (sodium acrylate) and polyvinylpyrrolidone." *Carbohydrate Polymers* 80.4 (2010): 1028-1036. Doi: 10.1016/j.carbpol.2010.01.020.

[21] Sadeghi, Mohammad, and Mojgan Yarahmadi. "Synthesis and characterization of superabsorbent hydrogel based on chitosan-g-poly (acrylic acid-coacrylonitrile)." *African Journal of Biotechnology* 10.57 (2011): 12265-12275. Doi: 10.5897/AJB11.925.

[22] Risbud, Makarand V., et al. "pH-sensitive freeze-dried chitosan–polyvinyl pyrrolidone hydrogels as controlled release system for antibiotic delivery." *Journal of controlled release* 68.1 (2000): 23-30. Doi: 10.1016/s0168-3659(00)00208-x

[23] Abral, Hairul, et al. "Highly transparent and antimicrobial PVA based bionanocomposites reinforced by ginger nanofiber." *Polymer Testing* 81 (2020): 106186. Doi: 10.1016/j.polymertesting.2019.106186

[24] Duceac, Ioana A., et al. "Design and preparation of new multifunctional hydrogels based on chitosan/acrylic polymers for drug delivery and wound dressing applications." *Polymers* 12.7 (2020): 1473. Doi: 10.3390/polym12071473.

[25] Agüero, Lissette, et al. "Alginate microparticles as oral colon drug delivery device: A review." *Carbohydrate polymers* 168 (2017): 32-43. Doi: 10.1016/j.carbpol.2017.03.033.