Jusami
Homepage: http://jusami.batan.go.id
Jurnal Sains Materi Indonesia
Akreditation No : 36/E/KPT/2019
Date 13 Dec 2019
ISSN 1411-1098
E-ISSN 2614-087X

SYNTHESIS AND CHARACTERIZATION OF HPMC/HAP/Fe_3O_4 COMPOSITE FOR HYPERTHERMIA APPLICATION

Muflikhah[1], Wildan Zakiah Lubis[1], Irma Septi Ardiani[2], Khoirotun Nadiyyah[2] and Sulistioso Giat Sukaryo[1]

[1]Center for Science and Technology of Advanced Materials - National Nuclear Energy Agency
Kawasan Puspiptek, Serpong 15314, Tangerang Selatan
[2]Department of Physics, Faculty of Science - Institut Teknologi Sepuluh Nopember
Kampus ITS Sukolilo, Surabaya 60111
E-mail:muflikhah@batan.go.id

Received: 4 May 2020 *Revised: 10 July 2020* *Accepted: 17 July 2020*

ABSTRACT

SYNTHESIS AND CHARACTERIZATION OF HPMC/HAp/Fe_3O_4 COMPOSITE FOR HYPERTHERMIA APPLICATION. Magnetic material become subject of intense research for hyperthermia application, and injectable magnetic hyperthermia for bone cancer is one of this research interest. In this study, composite of hydroxyapatite (HAp) and Fe_3O_4 in Hydroxypropyl-methyl cellulose (HPMC) matrix (HPMC/HAp/Fe_3O_4) has been synthesized in gel form that are expected can be applied for injectable bone substitute (IBS) in hyperthermia therapy. Composites were made using conventional methods by mixing HAp powder with ferrofluid Fe_3O_4 in HPMC solution. The composition of the composites were varied with the mass comparison of HPMC: HAp: Fe_3O_4 was 1: 0: 0; 1: 3: 0; 1: 2: 0.5; 1: 1: 0.25; and 1: 0: 3. The physical, chemical, and magnetic properties of the composites were characterized using X-Ray Diffractometer (XRD), Fourier Transform Infrared Spectrometry (FT-IR), Particle Size Analyzer (PSA), and Vibrating Sample Magnetometer (VSM). The XRD characterization results of the HPMC/HAp/Fe_3O_4 composite showed the crystalline phase of the constituent components. Saturation magnetization of the HPMC/HAp/Fe_3O_4 composite was 2.72 emu/g and 1.79 emu/g for the composition of 1: 2: 0.5 and 1:1:0.25 respectively. HPMC/HAp/Fe_3O_4 composite has superparamagnetic and biocompatible properties, so that can be applied as IBS in hyperthermia therapy for bone cancer.

Keywords: Hyperthermia, (Hydroxypropyl)methyl cellulose, Hydroxyapatite, Magnetite, Injectable Bone Substitute (IBS)

ABSTRAK

SINTESIS DAN KARAKTERISASI KOMPOSIT HPMC/HAp/Fe3O4 UNTUK APLIKASI HYPERTHERMIA. Penelitian material magnetik untuk terapi hipertermia terus berkembang, salah satunya dalam bentuk injectable magnetik hipertermia untuk kanker tulang. Pada penelitian, disintesis komposit hidroksiapatit (HAp) dan Fe_3O_4 dengan matriks Hydroxypropyl-methyl cellulose (HPMC), sehingga dihasilkan gel komposit HPMC/HAp/Fe_3O_4 yang diharapkan dapat diaplikasikan untuk injectable bone substitute (IBS) dalam terapi hipertermia. Komposit dibuat dengan metode konvensional dengan mencampurkan serbuk HAp dengan ferrofluid Fe3O4 dalam larutan HPMC. Komposisi dari komposit divariasi dengan perbandingan HPMC/HAp/Fe_3O_4 adalah 1:0:0; 1:3:0 ; 1:2:0,5; 1:1:0,25; dan 1:0:3. Sampel komposit yang terbentuk dikaraterisasi sifat fisika, kimia, dan magnetiknya menggunakan X-Ray Diffractometer (XRD), Fourier Transform Infrared Spectrometry (FT-IR), Particle Size Analyzer (PSA) dan Vibrating Sample Magnetometer (VSM). Hasil karakterisasi XRD komposit HPMC/HAp/Fe_3O_4 menunjukkan fasa kristalin dari komponen penyusunnya. Magnetisasi saturasi dari gel komposit HPMC/HAp/Fe_3O_4 sebesar 2,72 emu/g untuk komposisi 1:2:0,5 dan 1,79 emu/g untuk komposisi 1:1:0,25. Komposit HPMC/HAp/Fe_3O_4 bersifat superparamagnetik yang bersifat biokompatibel, sehingga dapat diaplikasikan sebagai IBS dalam terapi hipertermia untuk kanker tulang.

Keywords: Hyperthermia, (Hydroxypropyl)methyl cellulose, Hydroxyapatite, Magnetite, Injectable Bone Substitute (IBS)

INTRODUCTION

Cancer is a disease that become one of the biggest source of death in the world [1]. Osteosarcoma is a type of bone cancer that may occurs in adults and children [2]. Besides bone cancer itself (osteosarcoma), bone is the body part that most often becomes cancerous metastasis [3]. Frequent treatment of osteosarcoma and bone metastasis includes tissue removal surgery, chemotherapy, and radiotherapy [2,3]. However, this action has several side effect both physically and psychologically. Chemotherapy has side effects because the chemicals used are not only kill cancer cells, but also can attack healthy cells, while radiotherapy can also cause damage to muscle tissue [2–4]. Hyperthermia is the solution to this problem because it is effective in treating osteosarcoma [2].

Magnetic materials, especially nano-sized ones, received great attention in the field of research recently. This is because magnetic material (iron oxide) can be applied in various fields, such as contrast agents on magnetic resonance imaging (MRI), targeted drug delivery systems, sensor devices, magnetic hyperthermia and bio-separation [5,6]. In the application of magnetic hyperthermia, magnetic material acts to produce heat which is converted from magnetic energy when subjected to external magnetic fields [7]. In this case, superparamagnetic nanoparticles become a promising material because they can penetrate deeper parts of the tumor, do not damage skin or tissue muscle, and can be controlled with external magnetic fields [1,8].

Recently magnetic materials for hyperthermia therapy are in the form of thermoseed ferromagnetic implants, intravenously, and magnetic fluid. However they have some difficulties when applied, for example thermoseed must be appropriate in its installation and requires surgery after use. Whereas through intravenous or magnetic fluid has difficulty in determining the amount of material to be used in the target tissue, besides that magnetic fluid may flow into healthy tissue around the tumor (biofouling) [4,7]. The solution to this problem is by modifying magnetic materials with ceramics, polymers, inorganic or organics materials [7,9]. Nowadays, research of magnetic hyperthermia is developing using injectable magnetic hyperthermia by combining magnetic Fe_3O_4 with polymers such as Poly Ethylene Glycol (PEG), Poly Vinyl Alcohol (PVA), Hydroxypropyl Methylcellulose (HPMC) [4,8,10]. HPMC is polymer that most used by researchers as a matrix in the manufacture of injectable bone substitute (IBS) [11–13]. Beside as a matrix, HPMC also important for drug delivery systems [14–16]. The use of polymer as a matrix is very important in grafting injected biomaterials for orthopaedics as well as drug delivery systems. It is due to that material can follow the shape of the bone part that will be filled and equal to the body's extracellular matrix [11,16].

In the application of hyperthermia therapy for bone cancer, it needs materials that can stimulate growth / regenerate bone which damaged by cancer. One of those materials is hydroxyapatite (HAp) [13]. Hydroxyapatite ($(Ca_{10}(PO_4)_6(OH)_2$) is a biomaterial that similar to the composition of bone. It has good biocompatibility and bioactivity that can stimulate new bone growth [13]. The research on magnetic materials for hyperthermia conducted by Mondal et al., 2017 used HAp coating Fe_3O_4 (IO-HAp) which synthesized in-situ. However, this material has disadvantages of not being able to use as IBS [7]. Sneha et al., 2015 synthesized Fe_3O_4/HAp composites for bone cancer therapy conventionally by mixing HAp powder with Fe_3O_4 [1]. However, the product also cannot directly be applied by injection. The synthesis of injectable magnetic hyperthermia using HPMC/Fe_3O_4 by Wang et al., 2017 shows that the tumor can be ablated after being heated for 180 seconds. Our group's previous research has successfully synthesized IBS (HPMC/HAp) with the absence of magnetic material for bone substitute but it cannot be applied for hyperthermia [13]. Therefore, in this research, we modified HPMC/HAp composite with Fe_3O_4 as IBS and hyperthermia agent.

In this study, HPMC/HAp/Fe_3O_4 has been synthesized by mixing HAp (synthesized from fish bones) with Fe_3O_4 in the form of ferrofluid in the HPMC matrix. This direct-mixing synthesis method is easier, cheaper and more green compared to the synthesis of HAp- Fe_3O_4 in hydrothermal and spray-drying methods. The HPMC/HAp/Fe_3O_4 composite material is expected to act as IBS (from the role of HAp) as well as hyperthermia substance (from the role of magnetic materials) by utilizing HAp from natural ingredients, fish bones [17].

EXPERIMENTAL METHOD

Materials

Fe_3O_4 in the ferrofluid form which synthesized with co-precipitation method (refer to Sulungbudi *et al*., 2017) were used without surface modification [18]. Magnetite were synthesized using $FeCl_2.4H_2O$ and $FeCl_3.6H_2O$ from Sigma-Aldrich without further purification as precursors. Hydroxypropyl-methyl cellulose (HPMC) powder from Sigma-aldrich H7509 were used as a matrix without purification. Hydroxyiapatite (HAp) which produced from Barramundi fish bone by Center for Application of Technology of Isotope and Radiation (PAIR)- BATAN, and Deionized Water.

Method and Procedure

The synthesis of IBS HPMC/HAp/Fe_3O_4 composites were prepared in 5 variation of mass

composition of each starting materials, HPMC : HAp : Fe_3O_4 were 1:0:0 ; 1:3:0 ; 1:2:0.5 ; 1:1:0.25 ; dan 1:0:3. Synthesis has been done with conventional (direct-mixing) method that referred to Sneha *et al*., 2015 with some modifications [1]. HPMC solution was prepared with concentration of 2 % w/v in 50 mL, by dissolving the HPMC powder into 1/3 volume of DI-water 90 °C. After the HPMC dissolves, cooled DI-water were added to reach total volume 50 mL and stirred using a magnetic stirrer for 30 minutes. HPMC/HAp composites has been done by mixing HAp powder into HPMC solution then stirring for 45 minutes at 40 °C. HPMC/HAp/Fe_3O_4 composites have been prepared by introduced Fe_3O_4 nanoparticles into HPMC/HAp mixture and stirred for another 30 minutes.

A mount of composite samples were drop in a petri disc, then dried at room temperature to form membrane in order to observe their phase and functional group. The phase of the composite were characterized using PANalytical X-Ray Diffractometer (XRD). Functional group analysis of the sample have been conducted using Bruker Tensor 27 Fourier Transform Infrared Spectrometry (FT-IR) using Attenuated Total Reflectance (ATR). The magnetic strength were measured using Oxford Vibrating Sample Magnetometer (VSM) 1.2 T, size of composite particles were analysed by the Zetasizer Nano ZS type Particle Size Analyzer (PSA), Malvern.

RESULT AND DISCUSSION

Phase characterization of HPMC/HAp/Fe_3O_4 composite in dry membrane form have been done using XRD. This characterization aimed to see the crystalline phase in the composite and compared with the diffraction pattern of its constituent elements. Identification of the peaks were confirmed by matching the peaks with the database.

Diffractogram of the samples with composition variation of HPMC: HAp: Fe_3O_4 are 1:0:0 ; 1:3:0 ; 1:2:0.5 ; 1:1:0.25 ; 1:0:3 shows in Figure 1. Peaks in the diffractogram of HPMC/HAp/Fe_3O_4 composite shows the characteristic peak both HAp and Fe_3O_4. Characteristic peak of HAp with the highest intensity shown at 2θ= 31.7° (211). Highest characteristic peak intensity of Fe_3O_4 shown at 2θ= 35.5° (311). Another characteristic peaks of HAp shown at 2θ 30°; 32,9°; 39.8; 40.2°; 49°; 53° (*Crystallography Open Database* (COD) 96- 900-2215), and peaks of Fe_3O_4 are at 2θ 30°; 43°; 53°; 57°; 63° (*Crystallography Open Database* (COD 96-900-5813). In this research, characteristic peaks of HAp and Fe_3O_4 in HPMC/HAp/Fe_3O_4 composites are consistent with the XRD characterization results in a study conducted by Mondal et al., 2017, where hyperthermia material was synthesized by coating Fe_3O_4 with HAp in-situ became iron oxide-HAp (IO-HAp) [7]. The peak of HPMC in HPMC/HAp/Fe_3O_4 composites appears in

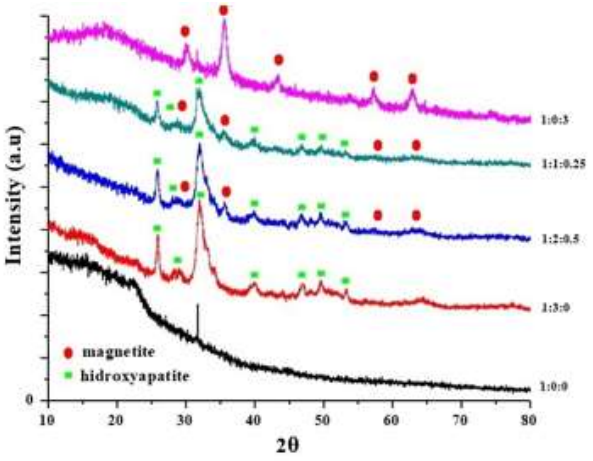

Figure 1. Diffractogram of HPMC/HAp/Fe_3O_4 compo site with mass composition variation.

widening peak around 2θ 20° with low intensity, which indicates an amorphous phase. This result corresponds to HPMC membrane X-ray diffraction in the Barros et al., 2015 research [19]. The results of XRD characterization of HPMC/HAp/Fe_3O_4 composites in this research show there is no structural changes in each composite constituent, nor the formation of new phases.

Identification of functional groups using FTIR on HPMC/HAp/Fe_3O_4 composites is shown in Figure 2. It can be observed from FTIR spectra of all samples that there are peaks of absorption areas of 3442 cm^{-1} which are O-H functional groups (intermolecular bonds). The Fe-O function group which is characteristic of the Fe_3O_4 compound appears in the absorption area of 671 cm^{-1} and 567 cm^{-1} (spectra c, d, and e). The characteristic peak of P-O functional group of hydroxyapatite show in absorption area 1039 cm^{-1} (PO_4^{3-} *stretching*), 605 cm^{-1} (PO_4^{3-} *bending*). Peak in the absorption area of 1458 cm^{-1}; 1411 cm^{-1} belong to CO_3^{2-} from HAp (spectra b, c, and d) [20][21]. The peaks in the absorption area of 2850 cm^{-1} (CH aliphatic), 2922 cm^{-1} (C-CH_3 stretching vibration), 1637 cm^{-1} (CC stretching vibration) and 948 cm^{-1} (C-OH

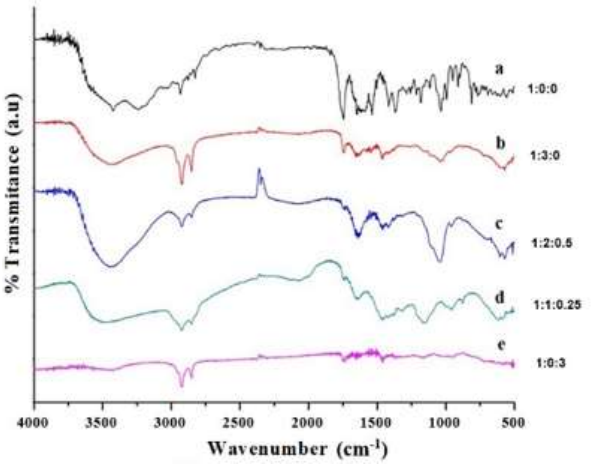

Figure 2. FTIR spectra of HPMC/HAp/Fe_3O_4 composite with mass composition variation.

stretching vibration) are the characteristic peaks of HPMC. Composites HPMC/HAp/Fe_3O_4 (figures c and d) show samples with a composition of HPMC: HAp: Fe_3O_4 is 1: 2: 0.5 have a peak area of absorption of phosphate groups (PO_4^{3-}) and hydroxyl (OH) groups that are sharper than samples with compositions HPMC: HAp: Fe_3O_4 1: 1: 0.25. The higher the intensity of absorption, indicate that more PO_4^{3-} and O-H content in the sample. The absorption area of functional group of each composite is shown in Table 1.

Table 1. The absorption area of functional groups of HPMC/ HAp/Fe_3O_4 composite.

Functional Group	Wavenumber (cm^{-1})				
	1:0:0	1:3:0	1:2:0.5	1:1:0.25	1:0:3
O-H (*stretching vibration*)	3425; 3240	3414	3442	3485	3446
Fe-O (*stretching vibration*)	-	-	671; 567	609	516
CO_3^{2-}	-	1458	1458	1469	-
PO_4^{3-} *stretching*	-	1031	1039	1161	-
PO_4^{3-} *bending*	-	565	605	-	-
C-CH_3 (*stretching vibration*)	2933	2922	2922	2922	2922
C-H alifatik	2827	2848	2850	2850	2850
C-O (*stretching vibration*)	1035	-	-	-	-
C-C (*stretching vibration*)	1747	1741; 1652	1637	1635	1737
CH_2 (*bending* vibration)	1537	-	-	-	-
C-CH_3 (*bending* vibration)	1371	-	-	1311	1458
C-OH (*stretching vibration*)	810	-	960	958	950

When FTIR spectra of HPMC before and after being composite are compared, there is shifting in the hydroxyl group absorption area. This shift occurs due to the hydrogen bonding between each component. In addition, there are functional groups that have the same absorption area also contributing to the increase in the intensity of displacement. The FTIR analysis results indicate that after the composites have been formed, the composites still have their origin characteristics.

Magnetic properties analysis of HPMC/HAp/ Fe_3O_4 composites have been carried out using VSM (Vibrating Sample Magnetometer). The hysteresis curve of each samples with various mass composition of HPMC:HAp:Fe_3O_4 are shown in Figure 3.

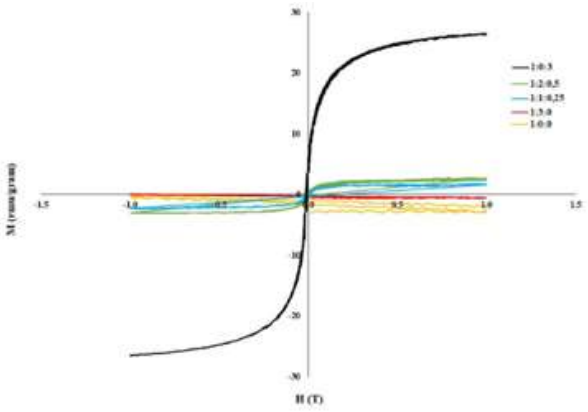

Figure 3. Hysteresis curve of HPMC/HAp/Fe3O4 composites.

Hysteresis curve in figure 3 shows that Fe_3O_4 classified as soft magnet that has a tight area. The area of the hysteresis curve indicates the energy that needed for magnetization. In soft magnets, the energy for magnetization is little. The magnetization curve of Fe_3O_4 produces hysteresis with a zero coercivity value (Hc), that indicates Fe_3O_4 nanoparticles behave superparamagnetic.

Table 2. Magnetization saturation of HPMC/HAp/Fe_3O_4 composites.

Variation of composition HPMC:HAp:Fe_3O_4	Ms (emu/g)
1:0:0	0
1:3:0	0
1:1:0,25	1.79
1:2:0,5	2.72
1:0:3	26.39

The magnetic saturation of the samples are presented in Table 2. HPMC:HAp:Fe_3O_4 composite with mass ratio of 1: 0: 3 has the largest saturated magnetization, 26.39 emu/g. The magnetization saturation (Ms) value of Fe_3O_4 nanoparticles in ferrofluid form which used in this study was 60 emu/g, so the Ms value of Fe_3O_4 theoretically in the composite 1:0:3 was 45 emu/g. Composite with a composition ratio 1:2:0.5 has magnetization saturation values 2.72 emu/g, while has magnetization saturation values for composite 1:1:0.25 is 1.79 emu/g. The greater the percentage weight of Fe_3O_4 that used, the higher the magnetic moment of Fe_3O_4, so the value of magnetization saturation also higher and its distribution will be easier to be controlled in the treatment area [22]. The composite with composition ratio of 1:2:0.5 has Ms value 2.72 emu/g, while composite 1:1:0.25 has Ms value 1.79 emu/g. The decreasing in the saturation magnetization value of the sample with a composition ratio of 1: 2: 0.5 and 1: 1: 0.25 due to the external magnetic field was blocked by HPMC and HAp. Another factor that contributes to the results of sample magnetization saturation is the magnetite sample in the form of liquid (gel) that contain of H_2O which become barrier when the sample approached by a magnetic field. The VSM test results from samples 1:0:0 and 1:3:0 do not show the magnetic characteristics of the material, therefore there is no hysteresis curve. However, in the application of hyperthermia which acts to absorb magnetic waves only magnetic material, so that which plays a large role is the initial value of the magnetic material itself. The saturated magnetization values of several similar studies can be seen in Table 3.

Based on magnetization saturation data of several hyperthermia materials (presented in Table 3), the Ms values seem diverse. The references mention that Ms value is depend on initial magnetic material that used for hyperthermia application. A good hyperthermia material

Table 3. Magnetization saturation value of some magnetic composites for hyperthermia application.

Material	Ms (emu/g)	Referense
Iron Oxide-HAp	40.6	[7]
Magnetic-HAp powder	3.42-20.92	[23]
Fe_3O_4-HAp	7.34	[1]
Magnetite-HAp	34.6	[24]
Fe_3O_4-PANI	26.34	[25]
HAP coated Fe_3O_4	0.32	[22]
HPMC- Fe_3O_4	(Ms Fe_3O_4= 50 emu/g) not mentioned (Ms Fe_3O_4= 90 emu/g)	[8]
HPMC/ Fe_3O_4	26.39	this experiment
HPMC/HAp/Fe_3O_4 (1:1:0.25)	1.79	this experiment
HPMC/HAp/Fe_3O_4 (1:1:0.5)	2.72	this experiment

is which has fast heating rate when approached by a magnetic field [23].

Particle size distribution of HPMC/HAp/Fe_3O_4 composites was measured by Particle Size Analyzer (PSA) using the Dynamic Light Scattering (DLS) method. In this study, the average particle size of the magnetic nanoparticles of Fe_3O_4 was 268.08 nm (crystallite size of 11.54 nm), and particle size of HAp was 100 nm-1 ìm. Table 4 is the average value of composite particle size from the results of PSA analysis on HPMC/HAp/Fe_3O_4 composites with variations in composition. The composite particle size distribution of HPMC/HAp/Fe_3O_4 is shown in Figure 4.

The particle size distributions curve in Figure 4 show good particle distribution that indicate HPMC/

Table 4. Particle size distribution of HPMC/HAp/Fe_3O_4.

No	HPMC/HAp/Fe_3O_4	Average particle size (nm)
1	1:3:0	3044
2	1:2:0.5	4704
3	1:1:0.25	2064
4	1:0:3	2154

HAp/Fe_3O_4 composites are stable (no agglomeration). It can be seen that the greater the composition of Fe_3O_4 and HAp in the composite, the larger the particle size. Where before the composite formation, pure HPMC had an average particle size of 67.09 nm, while after mixed with Fe_3O_4 and HAp, the average value of particle sizes ranged from 2-4 ìm.

CONCLUSION

Biocompatible composite materials for hyperthermia in bone cancer application has been successfully synthesized. Hydroxyapatite powder derived from fish bones was composited with Fe_3O_4 in the HPMC matrix and thus produced in the stable gel/paste form according to particle size distribution. The characterization of magnetic properties indicate composites are superparamagnetic. Based on the characterization result of HPMC/HAp/Fe_3O_4 composite

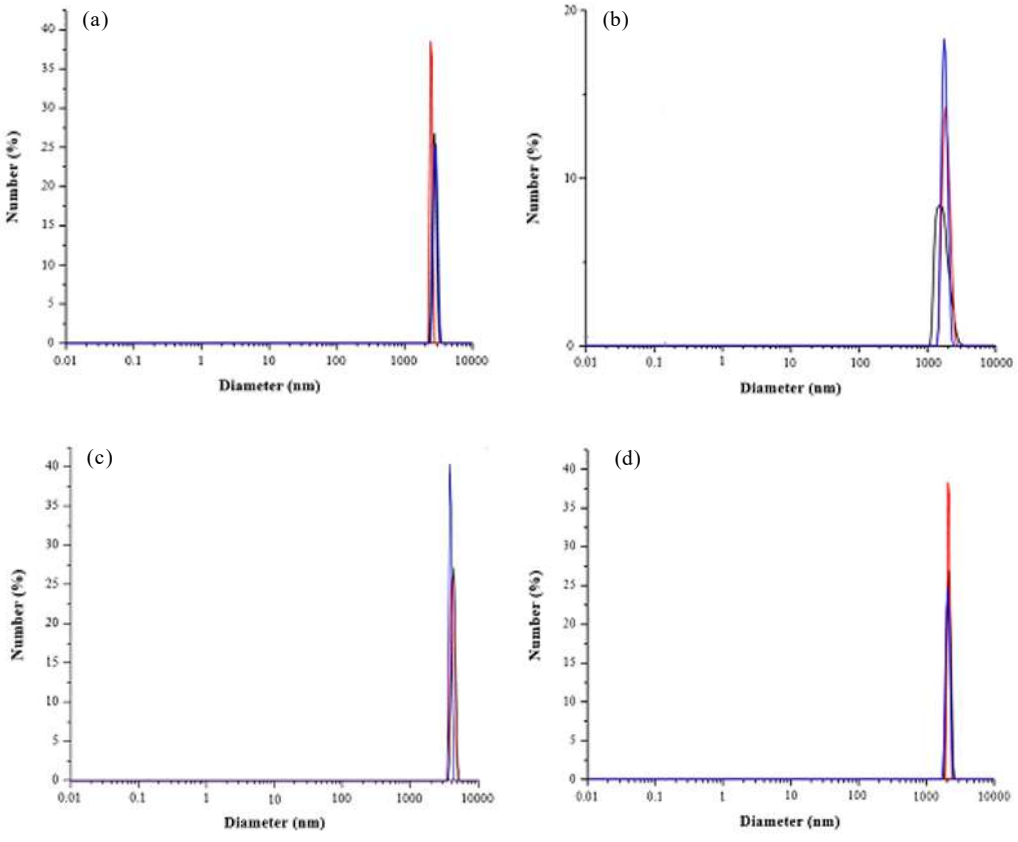

Figure 4. Particle size distribution of HPMC/HAp/Fe_3O_4 with various composition (a). 1:3:0; (b). 1:2:0.5; (c). 1:1:0,25; (d). 1:0:3.

as dual-response both as IBS and hyperthermia substance, there is no counter to the research with similar field. Further testing may be conducted to know the performance of this composite material as IBS hyperthermia substance.

REFERENCES

[1] M. Sneha and M. Sundaram, "Preparation and Characterization of an Iron Oxide-Hydroxyapatite Nanocomposite for Potential Bone Cancer Therapy," *International Journal Of Nanomedicine*, Vol. 10, pp. 99–106, 2015.

[2] K. Nakajima, T. Yanagawa, H. Watanabe, and K. Takagishi, "Hyperthermia Reduces Migration of Osteosarcoma by Suppression of Autocrine Motility Factor," *Oncol. Rep.*, Vol. 28, No. 6, pp. 1953–1958, 2012.

[3] A. Matsumine, K. Takegami, K. Asanuma, T. Matsubara, T. Nakamura, A. Uchida, and A. Sudo, "A Novel Hyperthermia Treatment for Bone Metastases Using Magnetic Materials," *Int. J. Clin. Oncol.*, Vol. 16, No. 2, pp. 101–108, 2011.

[4] C.Xu, Y. Zheng, W. Gao, J. Xu, G. Zuo,Y. Chen, M. Zhao, J. Li, J. Song, N. Zhang, Z. Wang, H. Zhao, and Z. Mei, "Magnetic Hyperthermia Ablation of Tumors Using Injectable Fe_3O_4/Calcium Phosphate Cement," *Acs Appl. Mater. Interfaces*, Vol. 7, pp 13866"13875, 2015.

[5] G. Unsoy, S. Yalcin, R. Khodadust, G. Gunduz, and U. Gunduz, "Synthesis Optimization and Characterization of Chitosancoated Iron Oxide Nanoparticles Produced for Biomedical Applications," *J. Nanoparticle Res.*, Vol. 14, pp. 1-13, 2012.

[6] H. C. Wu, T. W. Wang, J. S. Sun, W. H. Wang, And F. H. Lin, "A Novel Biomagnetic Nanoparticle Based on Hydroxyapatite," *Nanotechnology*, Vol. 18, 2007.

[7] S. Mondal, P. Manivasagan, S. Bharathiraja, M. S. Moorthy, V. T. Nguyen, H. H. Kim, S. Y. Nam ,K. D. Lee, and J. Oh, "Hydroxyapatite Coated Iron Oxide Nanoparticles: A Promising Nanomaterial for Magnetic Hyperthermia Cancer Treatment," *Nanomaterials*, Vol. 7, No. 12, p. 426, 2017.

[8] F. Wang, Y. Yang , Y. Ling, J. Liu, X. Cai, X. Zhou, X. Tang, B. Liang, Y. Chen, H. Chen, D. Chen, C. Li, Z. Wang, B. Hu, and Y. Zheng, "Injectable and Thermally Contractible Hydroxypropyl Methyl Cellulose/Fe_3O_4 for Magnetic Hyperthermia Ablation of Tumors," *Biomaterials*, Vol. 128, pp. 84–93, 2017.

[9] Muflikhah, W. Zakiah Lbs, G. T. Sulungbudi, dan Mujamilah, "Efek Dialisa Terhadap Ferrofluid (Fe_3O_4-HNO_3)," *Proceeding* Seminar Nasional Ke 58 Temu-Ilmiah Jaringan Kerjasama Kimia Indonesia, Kimia Dalam Pembangunan, 2017.

[10] P. J. Kondiah, Y. E. Choonara, P. P. D. Kondiah, T. Marimuthu, P. Kumar, L. C. Du Toit, and V. Pillay, "A Review of Injectable Polymeric Hydrogel Systems for Application in Bone Tissue Engineering," *Molecules*, Vol. 21, 2016.

[11] H. N. Maulida, D. Hikmawati, and A. S. Budiatin, "Injectable Bone Substitute Paste Based on Hydroxyapatite, Gelatin and Streptomycin for Spinal Tuberculosis," *J Spine*, Vol. 4, No. 6, p. 266, 2015.

[12] M. Schmitt, P. Weiss, X. Bourges, G. Amador Del Valle, and G. Daculsi, "Crystallization at The Polymer/Calcium-Phosphate Interface in A Sterilized Injectable Bone Substitute IBS," *Biomaterials*, Vol. 23, No. 13, pp. 2789–2794, 2002.

[13] Y. W. Sari, R. P. Rudianto, N. A. Nuzulia, and S. G. Sukaryo, "Injectable Bone Substitute Synthesized from Mangrove Snail Shell," *Journal Of Medical Physics And Biophysics*, Vol. 4,Vol. 4, No. 1, Pp. 115–121, 2017.

[14] S. C. Joshi, "Sol-Gel Behavior of Hydroxypropyl Methylcellulose (HPMC) in Ionic Media Including Drug Release," *Materials*, Vol. 4, No. 10, pp. 1861–1905, 2011.

[15] N. A. Abdel-Zaher, M. T. H. Moselhey, and O. W. Guirguis, "Ultraviolet-Ozone Irradiation of HPMC Thin Films: Structural and Thermal Properties," *Adv. Mater. Res. (South Korea)*, Vol. 6, No. 1, pp. 1–12, 2017.

[16] X. Zhou, L. Wang, Y. Xu, W. Du, X. Cai, F.N Wang, Y. Ling, H. Chen, Z. Wang, B. Hu, and Y. Zheng, "A pH and Magnetic Dual-Response Hydrogel for Synergistic Chemo-Magnetic Hyperthermia Tumor Therapy," *Rsc Adv.*, Vol. 8, No. 18, pp. 9812–9821, 2018.

[17] A. Handayani, S. G. Sukaryo, dan Deswita, "Preparasi dan Karakterisasi Hidroksiapatit Berpori dari Tulang Ikan," *J. Sains Mater. Indones.*, Vol. 14, pp. 47–50, 2012.

[18] G. T. Sulungbudi, Yuliani, W. Z. Lubis, S. Sugiarti, and Mujamilah, "Controlled Growth of Iron Oxide Magnetic Nanoparticles Via Co-Precipitation Method and $NaNO_3$ Addition," *J. Sains Mater. Indones.*, Vol. 18, No. 3, pp. 136–143, 2017.

[19] S. C. Barros, A. A. Da Silva, D. B. Costa, C. M. Costa, S. Lanceros-Mendez, M. N. T. Machiavello, J. L. G. Ribelles, F. Sentanin, A. Pawlicka, and M. M. Silva, "Thermal-Mechanical Behavior of Chitosan Cellulose Derivate Thermoreversible Hydrogel Films," *Cellulose*, Vol. 22, pp. 1911–1929, 2015.

[20] F. Ren, Y. Ding, And Y. Leng, "Infrared Spectroscopic Characterization of Carbonated Apatite: A Combined Experimental and Computational Study," *J. Biomed. Mater. Res. - Part A*, Vol. 102, No. 2, pp. 496–505, 2014.

[21] M. F. Goes, M. A. Sinhoreti, S. Consani, And M. A. Silva, "Morphological Effect of The Type, Concentration and Etching Time of Acid Solutions on Enamel and Dentin Surfaces," *Braz. Dent. J.*, Vol. 9, No. 1, pp. 3–10, 1998.

[22] N. Tran and T. J. Webster, "Increased Osteoblast Functions in The Presence of Hydroxyapatite-Coated Iron Oxide Nanoparticles," *Acta Biomater.*, Vol. 7, No. 3, pp. 1298–1306, 2011.

[23] C. Han Hou, C. Wei Chen, S. Mou Hou, Y. Ting Li, and F. Huei Lin, "The Fabrication and Characterization of Dicalcium Phosphate Dihydrate-Modified Magnetic Nanoparticles and Their Performance in Hyperthermia Processes In Vitro," *Biomaterials*, Vol. 30, No. 27, pp. 4700–4707, 2009.

[24] Mujamilah, A. F. Syidik, G. T. Sulungbudi, and A. Karo-Karo, "Synthesis and Characterization of Magnetic-Hydroxyapatite Composite Using One-Spot Coprecipitation Method," *Jurnal Sains Materi Indonesia,* Vol. 18, pp. 81–86, 2017.

[25] D. L. Zhao, H. L. Zhang, X. W. Zeng, Q. S. Xia, and J. T. Tang, "Inductive Heat Property of Fe_3O_4/ Polymer Composite Nanoparticles In An Ac Magnetic Field for Localized Hyperthermia," *Biomed. Mater.*, vol. 1, no. 4, pp. 198–201, 2006.