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# An Overview of Synthesis and Characterization of Hydroxyapatite-Zeolite Composites for Bone Implant Application

*This review is focused on potential or already implemented applications of hydroxyapatite (HA) - zeolit composites as a human bones implant. The methodology is to synthesize and broaden the collection of literature published in the last ten years. The reviews are divided into two main sections, namely the synthesis and the characterization of HA-zeolite composites as candidates for human bone implants. Each article that has the same topic, whether it is about synthesis or characterization, is grouped, reviewed, and synthesized. The review generally covers important aspects of material testing and the results of the study. All reviewed literature shows that HA-zeolite composites can be produced by various methods. The chemical and morphological properties are suitable with the nature of human bones. The composites are also suitable as coatings on metal bone implants from Ti6Al4V and SS316L. In conclusion, HA-zeolite composites are potentially used as human bone implant material.*

***Keywords:*** *Hydroxyapatite, zeolite, bone implant, morphology, mechanical properties.*

## 1. INTRODUCTION

Some biomaterial properties must be considered in the engineering of bone implants such as biocompatibility and bioactivity, resistance to corrosion and wear, toxicity, and the applied-load. Metals and their alloys are biomaterials that dominate in bone-implant engineering applications due to its suitable mechanical properties, especially in load-bearing. However, the wear and tear lead some of them to release potentially harmful Co, Cr, Al, Ni, or V ions [1]. Therefore, it should be avoided so that implant failure does not occur [1, 2].

Non-metallic materials that are widely used in biomedical applications are polymers and ceramics [3]. However, they exhibit weaknesses such as low biocompatibility, lack of mechanical properties, and poor integration with adjacent tissues [4]. To overcome this problem, calcium phosphate-based ceramics, which are the main elements of human bones, have begun to be explored as biomaterials [5, 6]. Bone as a composite material with anisotropic and hierarchical structure shows strong and lightweight properties. The basic components of bone consist of collagen, hydroxyapatite, and water molecules [7, 8]. Bone can adapt itself to the mechanical and biological environment through a bone remodeling process [9, 10]. External and internal remodeling occur simultaneously in order to modify the external geometry and internal structure. That process occurs in response to morphological changes due to the application of mechanical loads. It is carried out as self-adaptation to a number of changes in its geometric shape and tissue [10].

Bone is a composite material consisting of inorganic and organic components [11, 12]. The organic component consists of type I collagen which is a protein with repeated amino acids in the triple helix structure (up to 8%). The inorganic phase consists of calcium phosphate in the form of HA crystals (65% -70%) and bone water about 8% [11, 13, 14]. HA is brittle and collagen is a brittle compensator so that bone elasticity can be maintained [15, 16]. The HA is a calcium phosphate ceramic with a chemical formula ($Ca_{10}(PO_4)_6(OH)_2$), which is a crystalline compound with a hexagonal lattice. HA has been widely used for biomedical applications especially as a bone implant material because of its chemical composition which is similar to bone [17, 18, 19]. However, some disadvantages in HA were found, such as low dissolution rate compared to bone [20, 21]. In addition, the inherent nature of HA is difficult to change through structural and synthetic arrangements [22, 23]. Hence, the development of bioactive composites through improved structure and compatible properties is very important. HA cannot be used for load-bearing applications due to lower mechanical properties [24, 25]. To overcome this problem, it is recommended to use biomaterials that can compensate for low mechanical strength but have good biocompatibility and bioactivity properties. It has been reported that silica-based materials show better ability than HA alone in increasing bone tissue reconstruction [26, 27]. Also, silicate-based materials are able to lead the nucleation and growth of a bone-like apatite layer in simulated body fluids (SBF) [28, 29].

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In this review, zeolites, a class of silica-based porous materials, was chosen as a source of silica by considering its non-toxicity, large surface area, modifiable porosity, and high mechanical strength [30-35]. In earlier work, it was reported that zeolites have been widely applied in artificial bone engineering that can reliably improve the quality of bone tissue repair [36]. In its application for bone tissue engineering, zeolites are able to act as a reservoir of oxygen and send it to cells and are able to inhibit bone resorption [37, 38].

The HA-zeolite composites are potentially used as bone substitutes. The availability of sufficient literature is needed so that the production and characterization of HA-zeolite composites can be understood in-depth in order to create bone implants. The aim of this review is to provide an integrated overview of the current state of HA-zeolite composites in their implementation as candidates for human bone implant material.

## 2. METHODS FOR SYNTHESIS OF HYDROXYAPATITE-ZEOLITE COMPOSITE

Synthesis of HA-zeolite in various methods has been carried out in diverse applications. It was reported that the synthesis of HA-zeolite takes high-priced chemicals and a long time to ready [39]. Therefore, the microwave method was introduced as an alternative solution to overcome the disadvantages of the synthesis method in order to provide nanocomposites with short processing time. The use of microwave-assisted wet precipitation method in the synthesis of HA-zeolite was introduced by Iqbal et al [40]. It was reported that the HA-zeolite composite was successfully fabricated by this method. The composite was evaluated in vitro in a simulated body fluid (SBF) and then confirmed that the HA-zeolite composite formed supports the normal human osteoblast cell adhesion on its surface.

Zeolites, HA, and HA-zeolite composites were also synthesized by the hydrothermal method [41, 41, 43]. They reported that HA-zeolite composites synthesized by the hydrothermal process have been effectively synthesized from steel slag by adding NaOH and $H_3PO_4$ through the aging process at 90°C for 48 hours. Early in the aging process, Mg and Ca are reacted with phosphate and precipitated as HA [44]. After 48 hours of aging, the crystallized HA and faujasite type of zeolites are separated and formed through the crystallization process. The adsorption properties of HA-zeolite synthesized were similar to the uncontaminated zeolite and HA properties. The chemical composition and molar ratio are summarized in Fig. 1.

Ryu et al [45] reported that they had succeeded in the hydrothermal synthesis of HA-zeolite composites from high blast furnace slags. The analysis was carried out at the varied temperature, i.e. room temperature, 50, 90, 120, and 150°C. The effect of temperature reaction on the properties (crystallinity, content, and dimension) of HA-zeolite composites synthesized was analyzed. They reported that HA can be synthesized earlier (50°C) than zeolites (faujasite type) which can be synthesized at 90°C and 120°C. Also it was reported that the HA content and crystallinity of the specimen increases until the temperature rises to 90°C. A subsequent rise in temperature, no changes in the specimen can be observed. The highest specific surface area is reached at 90°C while the smallest is at 150°C.

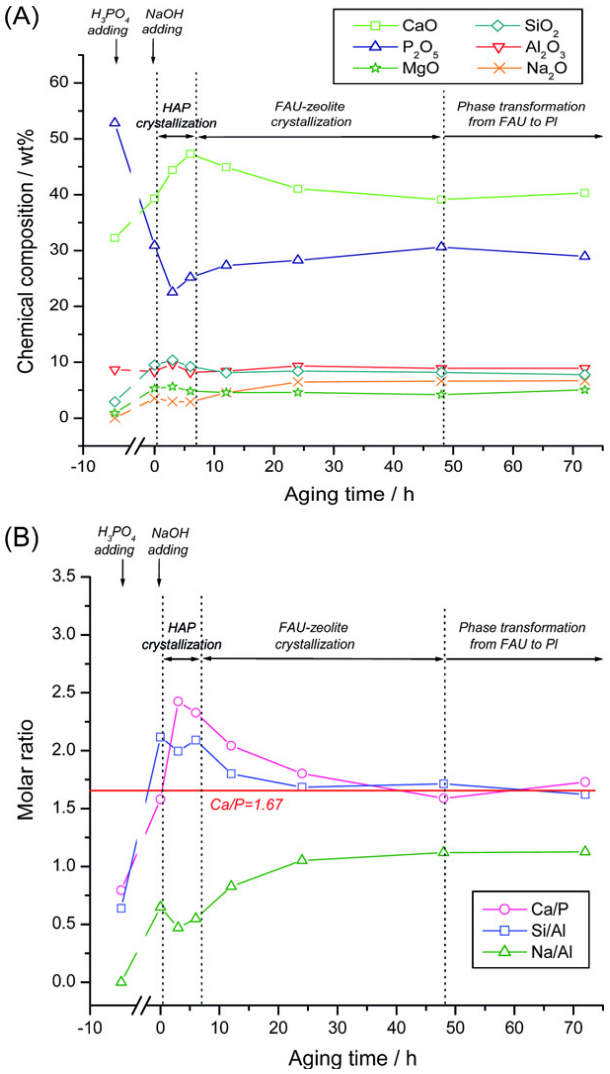


**Figure 1. The relationship of alteration of chemical composition (A) and molar ratio of Ca/P, Si/Al and Na/Al against a change of aging time [44].**

Khanday & Hameed [46] has successfully synthesized the HA-zeolite composites activated by palm ash through the hydrothermal method by varying palm ash and electric arc furnace under alkaline conditions. It was reported that carbon and zeolite components increased during the synthesis process due to an increase in the ratio of oil ash. As a result, the surface area and porosity of HA-zeolite composites increased by 53% and 73%, respectively. Based on the final character of the material that is deposited, it was reported that the HA-zeolite composite was the best candidate for the application of pollutant adsorption.

The HA-zeolite composite synthesis technique in the form of suspension has been introduced by Khorasani et al [47]. HA is synthesized from tetrahydrate of calcium nitrate (Ca $(NO_3)$ $2.4H_2O$) and di-ammonium phosphate $((NH_4).2HPO_4)$ combined with zeolite solution obtained from dissolution of zeolite powder. Tetrahydrate calcium nitrate and di-ammonium phosphate are added to the stirred HA-zeolite solution. The suspension formed was HA-zeolite nano-composite.

The BHA has been successfully added to clinoptilolite-alumina composites to produce materials that are applied to artificial bone [48]. The final composite is manufactured by sintering method at 1000°C and 3000°C. Further studies [49] have been carried out in order to evaluate its biocompatibility through an examination of cytotoxicity and cytocompatibility. They have reported that the material possesses no toxic effects. Kalkandelen and co-workers [48, 49] recommend that BHA/clinoptilolite-alumina composites are materials that are potentially used for bone engineering applications.

## 3. CHARACTERIZATION OF HYDROXYAPATITE-ZEOLITE COMPOSITE

### 3.1 Crystalline Characteristics of Hydroxyapatite-Zeolite Composite

Only a few data can be found related to the crystallinity of HA-zeolite composites. However, it has been reported by Ryu and co-workers [45] related to the crystallinity of HA-zeolite composites manufactured through a hydrothermal synthesis of Blast Furnace Slag (BSF) as shown in Table 1 [45]. It is shown in Table 1 that the crystallinity of the specimen is similar when the reaction temperature rises to 50°C from the initial temperature of 0°C. However, the crystallinity doubled when the temperature was increased to 90°C. In other words, it can be stated that crystallinity has a tendency to increase with increasing reaction temperatures.

**Table 1. Crystallinity of the materials synthesized using blast furnace slag [45]**

| React.Temp. (°C) | Amorp. Phase (%) | Cryst. (%) | Phases (%) | Quant. Cont. (%) |
|---|---|---|---|---|
| RT | 64 | 36 | HA | 36 |
| 50 | 66 | 34 | HA | 34 |
| 90 | 37 | 63 | HA | 50 |
| | | | Zeolite | 13 |
| 120 | 43 | 57 | HA | 50 |
| | | | Zeolite | 7 |
| 150 | 30 | 71 | HA | 46 |
| | | | Hydroxyso-dalite | 25 |

React. Temp: Reaction Temperature; RT: Room Temperature; Amorp. Phase: Amorphous Phase; Cryst.: Crystallinity; Hydroxy.: Hydroxysodalite; Quant. Cont.: Quantitative Content.

A sample of HA-zeolite composites synthesized by microwave techniques by varying the zeolite content of 5, 10, 25, and 50 wt% have successfully heated at 1000 °C for 2 hours by Iqbal et al [40]. The results of observations using XRD [Fig. 2] have reported that zeolite has been incorporated into HA and the peak for the composite of 5 wt% HA-zeolite corresponds to the crystal structure of HA. The peak intensity of HA was reported to decrease by increasing zeolite concentrations to 25 wt% (Fig. 2b-c). However, the peak of apatite was reduced even tends to disappear by the presence of zeolite concentrations in the range of 50wt% (Fig 2d). The crystal size is the same as the one produced by previous studies [50], i.e 49, 50, 44, and 53 nm for composites containing 5, 10, 25, and 50wt.% zeolites, respectively.

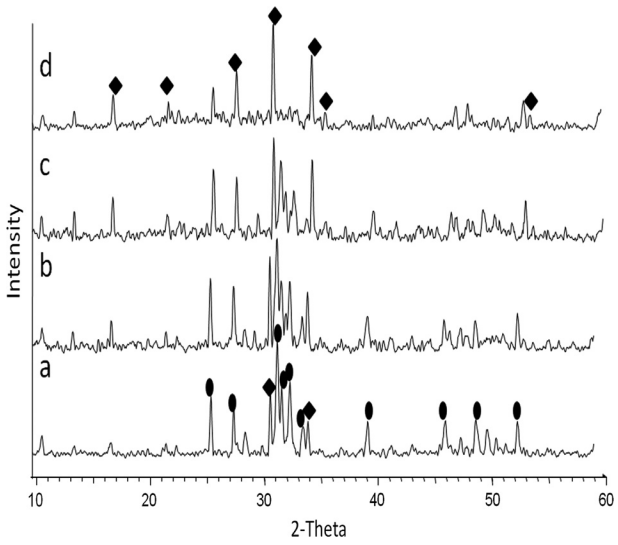


**Figure 2. XRD images of heat treated samples: (a) 5wt% zeolite – HA, (b) 10 wt.% zeolite – HA, (c) 25 wt.% zeolite – HA, and (d) 50wt.% zeolite – HA. The zeolite and HA are denoted by ♦ and ●, respectively [40].**

### 3.2 Morphology of Hydroxyapatite-Zeolite Composite

Some biocompatible ceramics have been combined with HA in order to obtain bioactive and biocompatible composites. Leong et al. [51] have evaluated the effect of temperature on the hardness and microstructure properties of HA-Zr composite which was produced by sintering techniques. The results show that hardness increased 3 times compared to commonly used methods. Another study conducted by Taherian et al. [52] who have synthesized mesoporous silica-HA nanocomposite bioactive by the sol-gel method. The TEM analysis showed the presence of HA crystalline confinement by a layer of silica material. Biocompatibility is evaluated and shows the presence of silica biocompatible behavior which is increased by the presence of HA in nanocomposites. The adsorption ability of HA-zeolite composites produced by the precipitation method has been evaluated by Nishida et al [53]. The HA-zeolite composite is used as an adsorbent composite to remove cobalt ions from aqueous solutions. They report that HA-zeolite composites have better surface adsorption compared to pure HA which is around 65% of cobalt (II) in pH close to 6 and temperatures around 30°C. The level of surficial adsorption lower by metal ion content [53, 54].

It has been earlier reported that the porous apatite layer can strengthen the application of bone tissue engineering [55]. Furthermore, the surface morphology of HA-zeolite composites synthesized by microwave techniques after being immersed in SBF for 336 hours as shown in Fig. 3 has been reported by Iqbal et al [40]. They reported that the spherical particle layers are observed to be denser by increasing the zeolite content up to 10wt%, shown in Fig. 3a and 3b. The needle-like shape morphology is observed on the surface of the sample (Fig. 3c) which then forms a cluster structure (Fig. 3d).

A nano-hydroxyapatite-zeolite composite with varying the zeolite content of 2.5 wt%, 5 wt%, and 7.5 wt% have been successfully synthesized by Khorosani et al

[47]. The morphology and grain size were analyzed using SEM and TEM, shown in Fig. 4. The team has reported that the size of pure HA particles and their composites is in the range of 40-200 nm. Its surface morphology is characterized by increased particle accumulation with more homogeneous size by solicitation zeolite content. They recommend that nano-composites HA-7.5 wt% zeolites are suitable for human bone implant material [47]. The crystals morphological of the HA-zeolite nano-composite that have been produced by Khorasani et al. [47] are mostly cylindrical and elliptical with crystallite sizes between 17-77 nm.

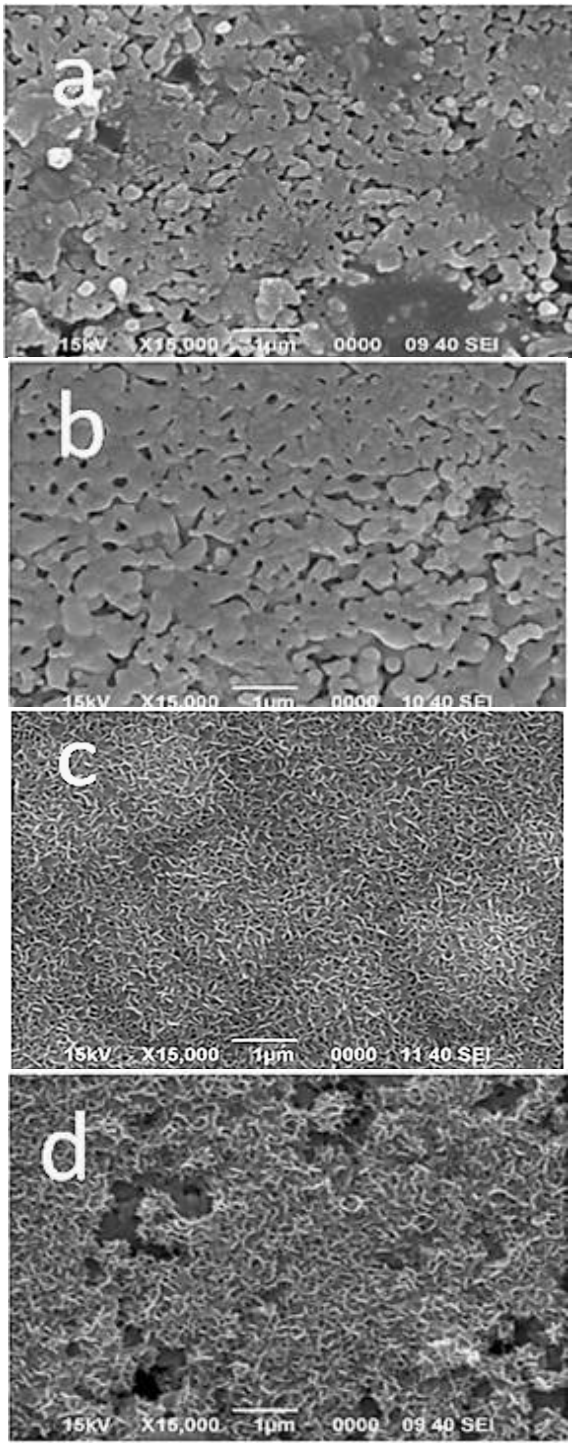


**Figure 3. Surface morphology of sample after 336 hours immersed in SBF solution (a) 5wt% zeolite – HA, (b) 10 wt% zeolite – HA, (c) 25 wt% zeolite – HA, and (d) 50wt% zeolite – HA [40].**

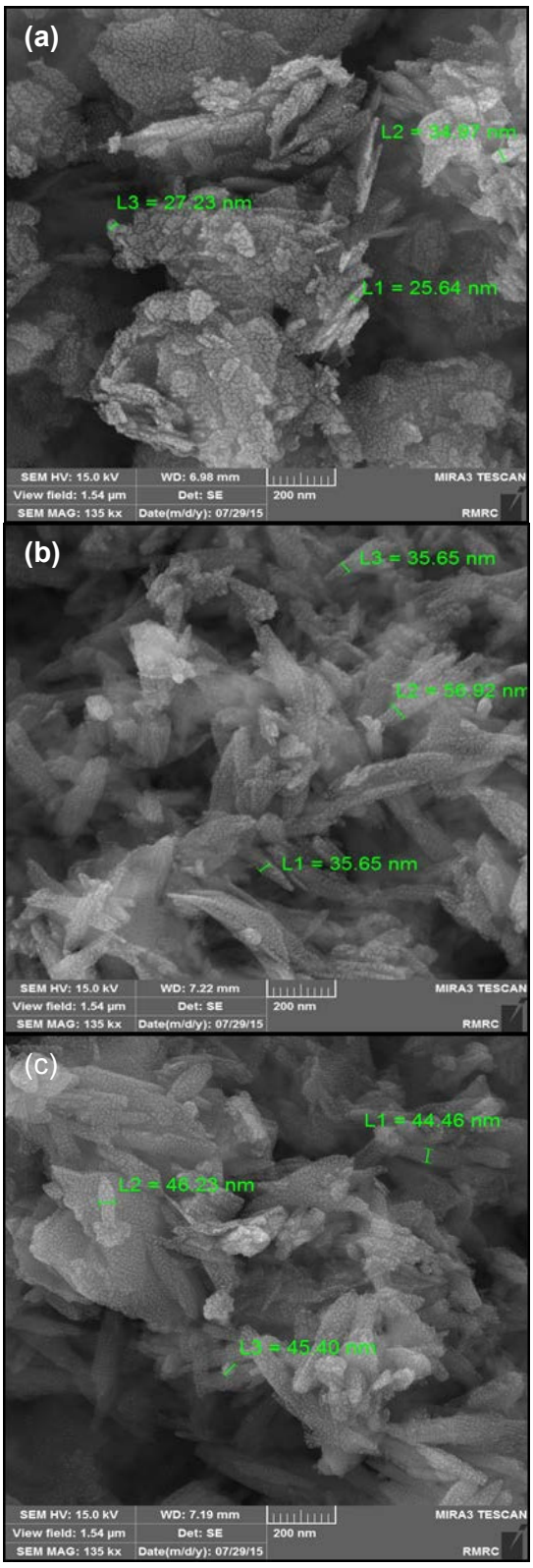


**Figure 4. SEM morphology zeolit-HA nanocoposite with zeolite content of 2.5wt% (a), 5wt% (b), and 7.5wt% (c) [47].**

It was reported by Ryu et al [45] that HA-zeolite composites synthesized with BFS have a pore size distribution in mesoporous (Fig. 5). This is very beneficial because it can increase the ability to arrest contaminants [56-58]. A relatively high surface area was found in specimens synthesized at room temperature and 90$^{o}$C. An interesting note stated by Ryu et al is that the absorption capacity of contaminants from HA-zeolite potential is higher than pure HA. This situation occurs

because zeolite has a greater surface area and adsorption capacity than HA. Furthermore, Ryu et al [45] confirm previous studies conducted by Kuwahara and co-workers [59, 60] who have reported that HA can complement the ability of zeolites that can only absorb cations.

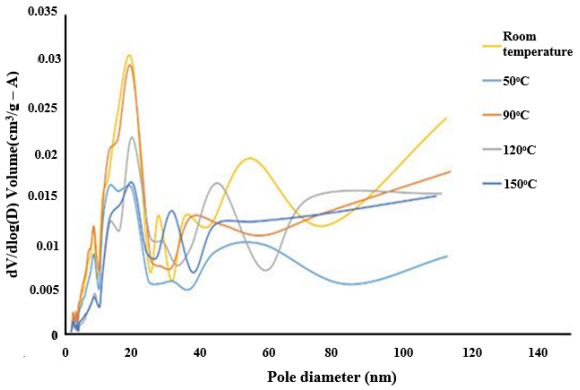


**Figure 5. The HA-zeolite pore distribution synthesized using blast furnace slag at various reaction temperatures [45].**

### 3.3 Hydroxyapatite-Zeolite Composite for Bone Mimetic Coatings

In recent years, surface modification of implant material like surface coating has been intensively evaluated in order to gain a better resistance of material surface for wear, corrosion, and chemical environment, while maintaining the biocompatibility, non-toxicity and mechanical properties of the implant material. For this goal, alkaline treatment and plasma spraying have been successfully applied for the surface coating of the implant with calcium phosphate-based or HA materials [61-64]. Another approach is the chemical vapor deposition technique, especially in the application of surface coatings from diamond-like carbon [65-67]. Doubkova et al. [68] have utilized synthetic zeolite crystalline coatings as a coating material. Their work confirms previous studies that zeolites are suitable as substrates for combining metal ions [69, 70], and implant coatings material [71, 69]. The use of zeolite for biomedical applications has been outlined in a topical review [72].

The HA-zeolite composite was also developed as a coating material in stainless steel and titanium alloys [73]. It was reported that the HA-zeolite layer is super hydrophilic and better in the case of corrosion resistance than Ti6Al4V alloys. It was also reported that the composite coating can maintain the suitability of the elastic modulus between the coating and bone, and has an osteoconductive effect on human fetal osteoblastic. These phenomena are concluded by Bedi et al [73] that the HA-zeolite composite coating can enhance implant osteointegration and accelerate post-surgical restoration. This phenomenon can be considered as a response to the results of previous studies [74-76] which reported that mismatches of elastic modulus caused bone fractures and implants to relax with increasing time indicating poor osteointegration.

The surface morphology, EDS analysis, contact angel of MFI coating, MFI coated, and uncoated Ti6Al4V and SS316L were shown in Fig. 6, while XRD images of MFI-HA coating shown in Fig.7. The crystalline structure of the Mordenite Framework Inverted (MFI)-HA composite layer on Ti6Al4V and SS316L is shown in Fig. 6A-D, while elemental analysis on the surface and hydrophilicity of the layers are shown in Fig. 6E and Fig. 6F, respectively [73].

The Figs. 6 shows clearly that the crystal structure of the nano-micro mixture dominates the morphology of the layer where the nano-HA crystal is used together with the MFI crystal. The overall coating morphology is matching the coating structure for the bone mimetic even though HA recrystallization produces needle-like crystals.

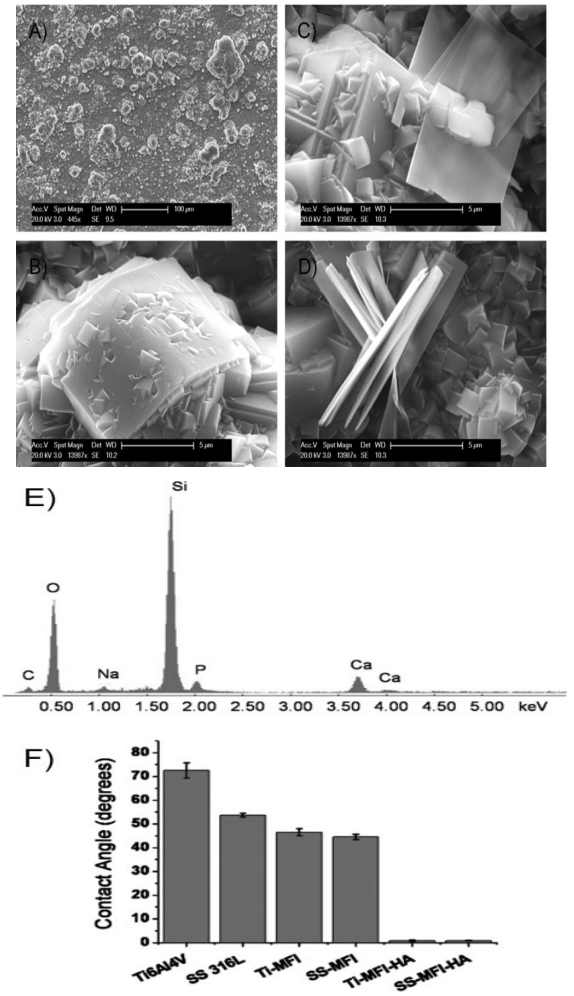


**Figure 6. Surface morphology of (A) the coating of MFI-HA on Ti6Al4V substrate, (B, C) intergrowth on MFI-HA surface for 4 hours MFI synthesized, (D) MFI-HA surface intergrowth after 4 hours MFI synthesized, (D) HA crystalline structure observed after 4 hours MFI synthesized. (E) EDS analysis after 4 hours MFI synthesized. (F) The contact angle of MFI-HA coating, MFI coated, and uncoated Ti6Al4V substrates [73].**

### 3.4 Mechanical Properties of Hydroxyapatite-Zeolite Composite

The mechanical properties of the HA-zeolite composites are little reported by researchers so it is not easy to present an in-depth and comprehensive review of these properties. Kalkandelen et al [48] have reported that they successfully performed mechanical characterization of BHA added to clinoptilolite-alumina ($Al_2O_3$) composite. Green samples were prepared from BHP added to clinoptilolite (Cp) and $Al_2O_3$ which varied in contents at 5, 10, and 15wt%. Green samples are com-

pacted and then sintered at atmospheric pressure at 1000°C and 1300°C for 4 hours. It was reported that there was a significant increase in mechanical properties in Cp-$Al_2O_3$/BHA composites sintered at 1300°C in modulus of elasticity (1275 Mpa), microhardness (305 HV), and compression strength (105.6 MPa). In comparison, the mechanical strength values of composites sintered at 1000°C are 540 MPa, 305 HV, and 31 MPa for modulus of elasticity, microhardness, and compression strength, respectively. Also, it was reported that sintering temperature exerts a sufficient effect on material shrinkage (Fig. 8).

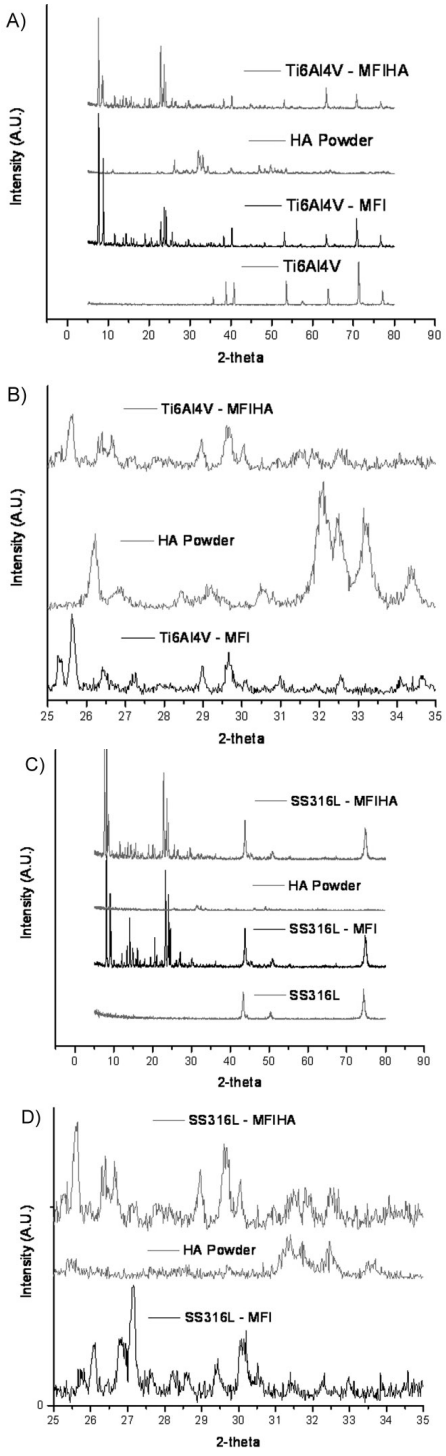


**Figure 7. XRD images of the MFI-HA coating on (A) Ti6Al4V substrate, (B) magnification of the HA peak on Ti6Al4V, (C) SS316L substrate, and (D) magnification of the HA peak of SS316L [73].**

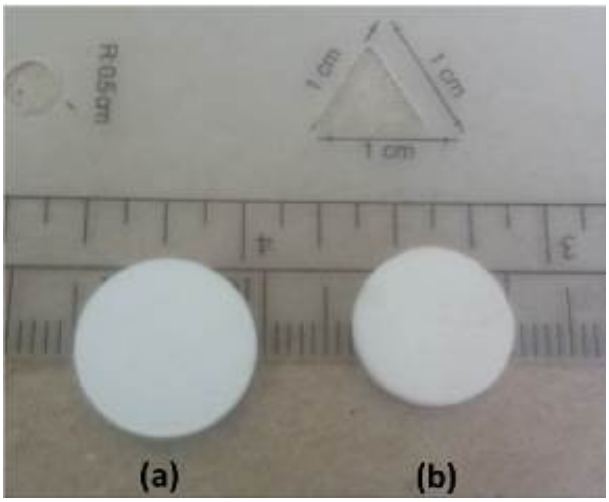


**Figure 8. Shringkage phenomenon on Cp-$Al_2O_3$/BHA composites: (a) green sample, and (b) sintered sample at 1300°C [48].**

## 4. CONCLUSION

The HA-zeolite composite has been successfully produced by various methods such as microwave-assisted wet precipitation, hydrothermal synthesis, and sintering method. Various material tests have been carried out to explore its potential for use as a human bone implant material. The HA-zeolite composites provide all biomaterial properties for bone implants such as chemical properties, crystal structure, surface morphology, biomaterial coatings, and mechanical properties. The HA-zeolite composite was suitable as a coating material in Ti6Al4V and SS316L substrate. That coating increases implant osseointegration and shortens the healing phase after implantation. Researchers whose paper has been reviewed suggested that HA-zeolite composites are suitable for use as human bone implant materials. However, biodegradation, body responses, and other aspects that have an impact on the ability of bioceramic composites to affect the body environment should also be considered. Unfortunately, only a few types of literature have reported the mechanical properties of HA-zeolite composites. Though mechanical properties are very important because many types of human bones function under load-bearing conditions. Therefore, further research is needed to obtain the mechanical properties of HA-zeolite composites as a human bone implant material.

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## ПРЕГЛЕД СИНТЕЗЕ И КАРАКТЕРИЗАЦИЈЕ КОМПОЗИТА НА БАЗИ ХИДРОКСИАПАТИТА И ЗЕОЛИТА КОД ПРИМЕНЕ КОШТАНИХ ИМПЛАНТА

**Пурномо, П.Х. Сетјарини, Т.В.Б. Ријади, Д. Сулистјанингсих**

Рад приказује могућност коришћења или већ у пракси коришћен композит од хидроксиапатита и зеолита за израду људског коштаног импланта. Методологија рада представља синтезу и проширење литературе објављене последњих десет година. Прикази су подељени у два главна одељка, тј. синтезу и карактеризацију композита као кандидата за производњу коштаних импланта. Сви прикази са истом темом, без обзира да ли се баве синтезом или карактеризацијом, су груписани, рецензирани и спојени. Рад указује на главне аспекте испитивања материјала и добијене резултате. Приказана литература показује да композити на бази хидроксиапатита и зеолита могу да се производе различитим методама. Хемијска и морфолошка својства одговарају грађи људских костију. Такође су погодни за израду превлаке на металним коштаним имплантима од Ti6Al4V и SS3316L. Може се закључити да постоји могућност коришћења композита на бази хидроксиапатита и зеолита као материјала за добијање људског коштаног импланта.