A polycaprolactone bio-nanocomposite bone substitute fabricated for femoral fracture approaches: Molecular dynamic and micro-mechanical Investigation

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Abstract

The application of porous bio-nanocomposites polymer has been greatly increased in the treatment of bone abnormalities and bone fracture. Therefore, predicting the mechanical properties of these bio-nanocomposites is very important prior to their fabrication. Investigation of mechanical properties like (elastic modulus and hardness) is very costly and time-consuming in experimental tests. Therefore, researchers have focused on mathematical methods and new theories to predict the artificial synthetic bone for orthopedic application. In this paper, porous bio-nanocomposites synthetic bone including nanocrystalline Hydroxyapatite (HA) nanoparticles and Titanium oxide (TiO_2) containing (0 wt%, 5 wt%, 10 wt%, and 15 wt% of TiO_2) as reinforcements and the biocompatible polycaprolactone (PCL) polymer as the matrix has been used for the fabrication of PCL-HA-TiO_2. Then, the mechanical test was conducted on the samples and the extracted value from the experimental test was compared with the analytical model using molecular dynamics (MD) method. Finally, these properties were compared with the Dewey micromechanics theory, and the error rate between the experimental method and the Dewey theory was reported. It was found that as the porosity percentage increased in the sample three-phase in composites, the model has a higher error in this theory. Then, due to the importance of hydroxyapatite in the fabrication of bone scaffolds, the obtained results of mechanical properties (Elastic modulus and Poisson's ratio) have been analyzed statistically. The application of these equations in the rapid prediction of Elastic Modulus and Poisson's ratio of the synthetic bone scaffolds made of hydroxyapatite is highly recommended.

Keywords: Porous bio-nanocomposites, Orthopedic bone implant, Micromechanical model, Titanium oxide, Polycaprolactone

1. Introduction

In the recent decade, regeneration and replacing hard tissue is a major problem in orthopedic and medical treatments around the world [1]. Recently, there has been great interest in replacing organs in the body for tissue engineering applications [2]. One of the most vulnerable parts of the human body is bones, according to statistics, a bone fracture occurs everywhere in the world with 9-10 million population affected by the bone trauma and bone fractures [3-4]. Bone tissue engineering science has proven to be a promising field for new ways to regenerate damaged tissues [5-6]. In fact, the purpose of tissue engineering is designing and fabrication of artificial tissues from natural or synthetic sources [7]. Several researchers have focused their studies on the use of biocompatible and biodegradable biomaterials, cells culture and relevant growth factors to repair damaged bones [8]. These biocompatible materials are called porous bony scaffolds [9]. Bone marrow is a porous microstructure with proper biological properties similar to those of the natural bone that grows in the live tissue [10-12]. These scaffolds are usually degraded and destroyed with time so that the new bone can grow and fill the defected space. Mechanical and biological characteristics should be taken into consideration after the production of bone scaffolds like compressive strength, degradability rate, scaffold porosity, and biocompatibility of the synthetic architecture [13-16]. In other words, bone scaffolds produced from natural composite and synthetic polymers can provide better bone scaffolds. Nowadays, the nanofillers or nanoparticles are being widely used in polymeric materials in order to improve mechanical properties under different loading and service conditions such as tensile strength properties. Monfared et al. [11] used nanosilica which was loaded into woven carbon fabric composites and observed proper mechanical and tribological properties for the same mixture. In another work conducted by Ayatollahi et al. [12, 29] the effects of multi-walled carbon nanotubes (MWCNTs) and nanosilica on tensile strength of woven carbon fabric-reinforced epoxy composites have been examined. Banerjee et al. [13] have studied the mechanical properties of bone scaffolds with proper biochemical reaction. In addition, to reduce the cost for fabrication of biocomposite with high material prices, the numerical methods have been applied to investigate the mechanical performance of porous bio-nanocomposite using molecular dynamics (MD) method as the laboratory studies are time-consuming and costly. Cordel et al. [14] applied the Finite Element Analysis (FEA) to analyze and fabricate porous scaffolds composite. In this paper, the prepared porous bio-nanocomposite made of (0 wt%, 5 wt%, 10 wt%, and 15 wt%) TiO_2, HA and PCL was simulated using the extracted data from the mechanical test using molecular dynamics (MD) based on molecular weight and weight percentages of TiO_2. Also, in this paper, merely modeling and comparing experimental results with Dewey's theory is expressed and the stages of fabrication of porous biocomposite are presented.

2. Materials and Methods for fabrication of porous spongy bone

In this study, porous bio-nanocomposite scaffolds consist of HA nanoparticles (50-100 nm, 98% purity, density of 3.31 g/cm^3, Elastic modulus 200-250 MPa, and Poisson's ratio of 0.27-0.29) were purchased from Merck Company (Germany). The TiO_2 with (0 wt%, 5 wt%, 10 wt%, and 15 wt%) percentages with (20-50 nm, 98% purity, density of 4.23 g/cm^3, Elastic modulus 220-250 MPa, and Poisson's ratio 0.28-0.29), was purchased from Merck Company combined with constant amount of HA powder using mechanical milling method. The PCL was used as matrix of bio-nanocomposite (98% purity, density of 1.31 g/cm^3, Elastic modulus 1000-1200 MPa, Poisson's ratio 0.38-0.4) was purchased from Sigma-Aldrich Company, United States. The solvent of PCL was selected as Dimethylformamide (DMF) manufactured by Sigma-Aldrich Company. The PCL was solved in specific amount of DMF solution (PCL-DMF) placed on a magnetic stirrer for 60-80 minutes to prepare homogenization solution. Then, the TiO_2 composed with HA powder with (0 wt%, 5 wt%, 10 wt%, and 15 wt%) percentages were placed in the ultrasonic bath at 30°C for 40 minutes, so that the HA and TiO_2 nanoparticles were homogeneous. Then, homogeneous solution was placed in the freezer for 40 hours at -65°C. In the end, frozen bio-nanocomposites solution was placed inside a freeze-drying machine made by Dorsa-Tech Company at -45°C by determining the initial conditions for the extraction of solvent and solutions from the bio-nanocomposite for 20 hours at 0.1 bar. Figure 1 shows the schematic of porous synthetic bio-nanocomposite scaffolds preparation and its further experimental procedure with the mechanical and biological analyzes. Figure 2 shows the application of PCL-HA reinforced with TiO_2 nanoparticle in femoral bone with cylindrical shape.

2.1. Simulation methodology

Three-phase bio-nanocomposite (PCL, HA and TiO_2) is composed of two crystalline reinforcements (HA and TiO_2) and a polymeric matrix (PCL). In this part, Materials studio software for simulation of the atomic structure has been used to investigate the mechanical properties. The synthetic HA with the chemical formula ($Ca_5(PO_4)_3OH$) is very similar to hydroxyapatite of the bone and also has good binding and mechanical properties. Figure 3 shows the atomistic model of HA crystalline with hexagonal shape and dimensions of 34.34×32.66×32×34 Å^3. The titanium oxide nanoparticles have been used as a supporter for modeling of bio-nanocomposite due to its high elastic modulus. The titanium oxide has biocompatibilities properties as one of the most common mineral oxides in the bone used as the pharmaceutical part that can act as antibacterial agent in the bone. Titanium oxide properties including high strength, fracture toughness, low density and corrosion resistance at very low temperatures to high temperatures make this powder as significant nanoparticle. Figure 4 shows the crystal form of titanium oxide as nanocrystalline, spherical and porous architecture.

As shown in Figures 4, these nanoparticles have an empty space that causes porosity after synthesize and the fabrication of bio-nanocomposites. The PCL architecture which is shown in Figure 5 (a-b) as a biodegradable thermoplastic polymer is obtained by chemical synthesis of crude oil. The PCL biopolymer has good resistance against water, oil, solvent, and chlorine. Also, it has a low melting point (58-60°C), short degradation rate and low viscosity and it can be easily processed. It is also used in the strength of orthopedic appliances, fully detachable bags, sutures, and fibers. Due to the low melting point, biocompatibility and high biodegradability, it can be used in medical treatment.

For molecular modelling of three-phase nanocomposite, simulation boxes have been constructed taking into account the molar ratio of the reinforcements and matrix as described in Table 1 using COMPASS force field. The unit cells of nanocomposite simulation box have about 1200 atoms. Thereafter, molecular dynamics ensembles for relaxation and energy minimization were used as follows:

1. Energy minimization and geometry optimization of the simulation box have been used with convergence tolerance of 1×10^{-4} (kcal/mol).
2. NVT ensemble was employed for 50 ps with a time step of 1 fs at 300 K to give sufficient energy to the particles to move towards balance. At this stage, the initial density of the system (0.9 gr/cm^3) is assumed to allow molecules and atoms to be displaced to move towards optimal mode.
3. Finally, the system is pressurized at 1 atm with a temperature of 300K under NPT ensemble to bring the system density to the actual value during 50 ps. In NPT to control the pressure and temperature, Berendsen thermostat and barostat were used.

After equilibrium of system the elastic modulus and Poisson's ratio of porous bio-nanocomposite were calculated using constant strain method.

2.2. Micromechanical modelling of Bone scaffold Evaluation

Due to the porosity of bone scaffolds, methods used to model porous materials can be used to achieve their mechanical properties. In recent years, many relationships have been proposed, either experimentally or analytically to obtain the elastic properties of porous materials [17-25]. The analytical methods presented can be divided into two categories in general. The first category of these methods is based on the theory of biocomposite materials. In this group of models, the segment is considered to be a special case of a two-phase composite material. The second category of these models is cellular solids. These models are based on solid-state minimum methods, in which the material is considered as a single phase, where the cavities penetrate. In this section, some of the most important models for calculating the effective Elastic Modulus of porous materials are presented. It should be noted that in the relations below, $\boldsymbol{E}$, $\boldsymbol{\nu}$, $\boldsymbol{\kappa}$, $\boldsymbol{\varphi}$, $\boldsymbol{\mu}$, and $\boldsymbol{\rho}$ represent Young's modulus, the Poisson's ratio, the volume modulus, the shear modulus, the porosity percentage, and the density respectively. In addition, the sub-clauses $\boldsymbol{s}$ and $\boldsymbol{p}$ also indicate porous and non-porous material [21-25]. It should be noted that all the analytical models are used to find mechanical properties such as the Elastic modulus. Finally, due to the high volume of computing, only the Dewey model was selected and the analytical properties obtained from this model were compared with the properties obtained in the laboratory testing. The mechanical properties of the porous scaffolds were investigated using a tensile strength machine (Iran's SANTAM-STM50 Manufacturing Machine). For this purpose, each sample was prepared with a length of 30 (mm) and a width of 10 (mm). Then, it was placed under loading at a rate of 0.2 (mm/min), the tensile strength and fracture toughness were evaluated. The outputs of the device are force and displacement, the initial width and initial length of each sample are stress and strain. Finally, using the slope of the stress-strain diagram, the Elastic modulus of each sample was obtained [20, 43].

2.2.1. Dewey's model (DM)

In this paper, Dewey's theory was used to determine Elastic modulus of porous bio-nanocomposites containing various amounts of Titania in the PCL-HA, where E, $\emptyset$ and ν_s are, respectively. Dewey model was proposed a linear relationship (1) to calculate Elastic modulus of porous bio-nanocomposites [15, 25, 43].

$$\frac{E_p}{E_s} = 1 - \xi\phi \tag{1}$$

The coefficient ζ in relation (1) is obtained by using equation (2):

$$\xi = \frac{(1-\nu_s)(27+15\nu_s)}{(2(7-5\nu_s))} \tag{2}$$

In order to predict and verify the relationship between the three-phase bio-nanocomposite elastic modulus and its porosity, we hypothesized the materials as to two phases, ceramics (HA-TiO_2) and a polymer phase (PCL). In a study conducted by Mancini et al. [16], it was seen that porosity increased with increasing HA amount as an additive. In addition, it was observed that by increasing the additives the crystallinity of product increased.

2.2.2. Rice's model (RM)

The proposed Rice model [17] for prediction of elastic modulus of porous material is shown in equation (3):

$$\frac{E_p}{E_s} = 1 - \exp(-r(1-\phi)) \tag{3}$$

The fixed value of **r** in the laboratory is equivalent to 0.5.

2.2.3. Heracovitch and Baxter model (HBM)

The Heracovitch and Baxter [18] define a model for porous material with spherical shape with the general cell technique. In this model, small cubic cells are used to estimate the spherical shape of the cavity. Relationship (4) shows this model:

$$\frac{E_p}{E_s} = 1 - 1.15\phi^{2/3} \tag{4}$$

2.2.4. Gibson's model (GM)

Gibson proposed the relationship (5) to calculate elastic modulus of porous material [19, 25].

$$\frac{E_p}{E_s} = \frac{\rho_p}{\rho_s} = (1-\phi)^{\eta} \tag{5}$$

The η value for open and closed porosity is assumed as 2 and 3, respectively.

2.2.5. Roberts and Garboczi model (RGM)

Roberts and Garboczi suggested relationships (6-7) to calculate elastic modulus and Poisson's ratio of porous material [20, 25].

$$\frac{E_p}{E_s} = (1-\frac{\phi}{m})^{n} \tag{6}$$

$$\nu_p = a + (1-\frac{\phi}{b})(\nu_s - a) \tag{7}$$

The parameters m, n, a, and *b* are experimental and their values for different states are given in Table 2.

2.2.6. Ramakrishnan and Arunachalam model (RAM)

Ramakrishnan and Arunachalam [21, 43] proposed a model for measuring the elastic modulus of porous biocomposite, which has good accuracy for porosity less than 40%. This model contains no special formulation for the proposed two-phase composite materials and is provided merely for the simulation of porous materials. The mathematical relationship of this model can propose as equation (8):

$$\frac{E_p}{E_s} = \frac{(1-\phi)^2}{(1+\chi\phi)} \tag{8}$$

Where the relation (9) is as follows.

$$\chi = 2 - 3\nu_s \tag{9}$$

2.2.7. Wang and Tseng model (WTM)

Wang and Tseng provided a model for estimating the mechanical properties of two-phase composite materials containing spherical particles with random distribution [22, 25]. The researchers have used the results of the proposed model, extracted analytical and explicit expressions for the effective properties of porous materials based on the mechanical properties of the material and their porosity. According to this model, the effective volume modulus and shear modulus of porous material are expressed using equation (10-11).

$$\kappa_p = \kappa_s \left\{ 1 + \frac{30(1-\nu_s)\phi(3\Lambda + 2\Theta)}{3\alpha + 2\beta - 10(1+\nu_s)\phi(3\Lambda + 2\Theta)} \right\} \tag{10}$$

$$\mu_p = \mu_s \left\{ 1 + \frac{30(1-\nu_s)\phi\Theta}{\beta - 4(4-5\nu_s)\phi\Theta} \right\} \tag{11}$$

Which relationships (12-15) are as follows:

$$\alpha = 2(5\nu_s - 1) \tag{12}$$

$$\beta = -7 + 5\nu_s \tag{13}$$

$$\Lambda = \frac{(-12 + 18\nu_s - 15\nu_s^2)\phi}{4(-7+5\nu_s)^2} \tag{14}$$

$$\Theta = \frac{1}{2} + \frac{(107 - 98\nu_s + 65\nu_s^2)\phi}{16(-7+5\nu_s)^2} \tag{15}$$

Elastic modulus and Poisson's ratio of porous architecture are obtained by inserting relationships (10-11) into equations (16-17):

$$E_p = \frac{9\kappa_p \mu_p}{3\kappa_p + \mu_p} \tag{16}$$

$$\mu_p = \mu_s (1 - 5\phi \frac{3\kappa_s + 4\mu_s}{9\kappa_s + 8\mu_s}) \tag{17}$$

2.2.8. Dilute Estimate method (DEM)

The dilute Estimate method is originally proposed for composite materials with a very small volume fraction of microparticles. As previously mentioned, the porous material can be considered as a special form of composite material with a phase of which (porosity) has zero stiffness. Therefore, the dilution estimation method can also be used to obtain the mechanical properties of porous materials with a low porosity percentage ($Ø > 1$). Note that for this method the porosity percentage should be small enough to be discounted from the mechanical interaction between the holes and channels in the bio-nanocomposite. Assuming the spherical shape for the holes, the volume modulus and the shear of a porous material are obtained using the dilution estimation method in the form of relations (18-19) [23, 25]:

$$\kappa_p = \kappa_s (1 - \phi(1 + \frac{3\kappa_s}{4\mu_s})) \tag{18}$$

$$\mu_p = \mu_s (1 - 5\phi \frac{3\kappa_s + 4\mu_s}{9\kappa_s + 8\mu_s}) \tag{19}$$

By obtaining volumetric, shear modulus and placing them in equation (16-17) can determine the elastic modulus and Poisson's ratio of porous architecture.

2.2.9. Differential scheme (DS)

The objective of the differential scheme is to overcome the limit ($Ø > 1$), which reduces the application of the dilution estimation method. The main idea of this method is to add gradual and porosity to the material until the ultimate porosity is achieved. In each step, the dilution estimation method is used to obtain the effective mechanical properties of the material. To this end, a very small percentage of porosity is applied to the material and the effective properties of the material obtained are calculated using the relationships (18-19). In the following, a very small part of the resulting material (porosity) is removed and instead replaced by the same porosity, and again using the dilution estimation method is used to obtain the mechanical properties of the new material that contains more porosity than the previous one. The process of separating matter and adding porosity leads to the achievement of two differential equations (20-21) for the calculation of the effective volumetric and shear modulus of porous material [20-25, 43]:

$$\frac{(1+\frac{4\mu_s}{3\kappa_s})(\frac{\mu_p}{\mu_s})^3}{2-(1-\frac{4\mu_s}{3\kappa_s})(\frac{\mu_p}{\mu_s})^{\frac{3}{5}}}=(1-\phi)^6 \tag{20}$$

$$\frac{\mu_p}{\mu_s}=\frac{(1-\frac{4\mu_p}{3\kappa_p})^{\frac{5}{3}}}{(1-\frac{4\mu_s}{3\kappa_s})^{\frac{5}{3}}} \tag{21}$$

It is significant that the equations (20-21) are true when ν_s is more than 0.2. When it is less than 0.2 for calculating the volumetric and shear modulus of the coupled differential used equations (22-23):

$$\frac{(1+\frac{4\mu_s}{3\kappa_s})(\frac{\mu_p}{\mu_s})^3}{2+(\frac{4\mu_s}{3\kappa_s}-1)(\frac{\mu_p}{\mu_s})^{\frac{3}{5}}}=(1-\phi)^6 \tag{22}$$

$$\frac{\mu_p}{\mu_s}=\frac{(\frac{4\mu_p}{3\kappa_p}-1)^{\frac{5}{3}}}{(\frac{4\mu_s}{3\kappa_s}-1)^{\frac{5}{3}}} \tag{23}$$

3. Results and Discussion

The PCL polymer with reinforced nanoparticles as bone implants has long been used in orthopedic field. However, these additives can be subjected to shear stress due to the high elastic modulus. As the hard metal placed in the bone with the ceramic implant, the bone is exposed to a recovered mechanical environment, thus it can re-absorb the surrounding area. Regarding the complete replacement of the hip, replacement of the bone in the proximal thigh bone is subjected to stress and strain in the femoral membrane after implantation of the hip joint, which causes the aseptic prosthesis (which is a very common problem) to be loosened. Other major disadvantages of metal and ceramic materials for tissue engineering applications are the lack of degradability in the biological environment and their limited processability. To simulate the porous bio-nanocomposites made of biopolymer and bioceramic in the molecular dynamics (MD) software, the total weight of nanocrystalline HA and TiO_2 was set as 25% of total weight and the constant value (75%) for PCL polymer as shown in Figure 6 (a-d). Then, the number of molecules was obtained and the simulation was performed. Elastic modulus, Poisson's ratio and porosity in laboratory test for nanocrystalline (HA and TiO_2) and polycaprolactone polymer are illustrated in Table 3. Also, Table 3 shows the obtained results from optical images and J-image software which taken from experimental analysis to measure the porosity values. As it is shown, the mechanical properties such as elastic modulus and Poisson's ratio have increased slowly with the addition of titanium powder. Although both tensile strength and the porosity value increased slowly, the mechanical performance of the porous bio-nanocomposite is addressed with the addition of titanium powder. Addition of higher amount of titanium powder can influence on porous bio-nanocomposite microstructure. The following changes (increase in strength and porosity value) are due to the high elastic modulus of titanium powder added to the HA and PCL microarchitecture. Therefore, it can be concluded that the porous synthetic bone has a Poisson's ratio and elastic modulus smaller than pure material in the MD simulation. The obtained results in the laboratory were compared with Dewey's theory in Table 4. The results showed that the Dewey theory for sample containing 10 wt% interlayered inorganic composites has an error near 60% corresponding to the laboratory testing of porous bony scaffold. Therefore, with increasing porosities value the tensile strength decreased and the computational error of the Dewey theory increased. In addition, it can be concluded that the Dewey theory is more practical for bio-nanocomposites with lower porosity rate (less than 50%). In orthopedic field the required porosity is 60-70% that can mimic with authentic human bone (spongy part) to transfer nutrient and blood through the porous microarchitecture. In Table 4, it is assumed that the Poisson's ratio and elastic modulus in non-porous mode are about 0.1 folds less than porous composites. Based on the fact that for the sample with the higher porosity, Elastic modulus and the Poisson's ratio in the Dewey model are represented in Table 4. As shown in Figure 7, the elastic modulus has an upward and downward trend for experimental and simulation analysis in Dewey theory. As a result, this model is not proposed for porous materials which have 100% error. Figure 8 showed the Dewey's model error for the ceramic phase (HA-TiO_2) and the polymer (PCL), which illustrated with increasing the porosity the Dewey's theory error increased. The following error is greater for ceramic materials and occurred less for polymers. Figure 9 (a-b) demonstrated the Dewey model is suitable to apply for the sample's with less than 50% porosity. On the other hand, as the porosity value increased the precision of the Dewey model reduced (this model does not have the required efficiency for bony scaffold). Dewey model does not have the ability to calculate elastic modulus for porosities above 50%. As the literature shows, there are various techniques to determine the micromechanical properties of porous scaffold prior to its fabrication. Several researchers investigated the molecular mechanic model of various materials like carbon allotropes [26]. In addition, in some cases addition of nanoparticles like copper oxide powder was evaluated as reinforcement to the chitosan (antimicrobial agent) [27-29]. The application of catalytic powder like MgO, bioglass and magnetite nanoparticles (MNPs) were investigated in several works with similar reaction like titanium oxide [7, 28]. Using PCL granules in the biomaterials domain and orthopedic surgeries has shown excellent outcome with proper bone adhesion and compression strength. Polycaprolactone as a hydrophobic semi-crystalline polymer with a molecular formula of $(C_6H_{10}O_2)n$ showed potential application in orthopedic filed. Also, it has excellent mechanical flexibility, good biocompatibility, simple and easy processability, low melting point (Tm=60°C) and non-toxicity. Aghadavoudi et al. [30-33] considered the mechanical properties of composite materials using MD without using any experimental examination. Addition of defect carbon nanotube (CNT) to epoxy based nanocomposite was determined using MD simulation to prevent additional mechanical testing which can predict the mechanical feature of the composites. Also, in another study the static analysis of functionally graded nanocomposite sandwich plates reinforced by defected CNT was evaluated using similar method [34-37]. Combining the intrinsic properties of polycaprolactone with the unique properties of the nanofilament structure (HA and TiO_2), provided a promising substance for medical applications, in other words, it can be used to reconstruct both hard tissue and soft tissue of the body. It can improve adhesion, growth, proliferation and cellular differentiation of the defected bone. For example, polycaprolactone nanoparticle scaffold strongly supports fibroblast, keratinocyte and preosteal growth; in addition, it is shown that PCL nanofibers can support a wide range of cells type. The combination of PCL with hydroxyapatite (main part of the bone) by various methods like solvent molding process or freeze-drying increases mechanical properties and growth of osteoblasts cells dramatically (compared to pure polycaprolactone). The construction of hydroxyapatite/polycaprolactone scaffold analysis showed that scaffolds with 10 wt% and 15 wt% Titania with constant amount of hydroxyapatite had the closest properties to human bone in terms of its mechanical properties. The elastic modulus was measured near the cortical bone. After seeding of the early osteoblastic cells, it was observed that the scaffolds have high proliferation and high activity of alkaline phosphatase [37-44]. The PCL composites used in the tissue engineering approaches with antimicrobial particles like Titania (TiO_2) and hybrid silver (AgO) has shown proper mechanical, chemical and biological characteristic in various studies [35, 42]. According to the orthopedic surgeons' statements, PCL has flexible nanostructure that can improve the elasticity of the bone. In addition, the PCL has low biodegradability rates to apply in the bone femoral part [38, 42]. Biocompatible composite is increasingly used for orthopedic surgeries and tissue engineering because of its advantages such as higher surface rates than traditional scaffolds, which increase scaffold cell-based interactions. In addition, the nanostructure properties of based polymer and bioceramic with small porosity size have a variety of medical applications in treatment of fractured bone. Among biocompatible nanofibers, polycaprolactone and natural biopolymers nanoparticles can provide better mechanical and biological properties with interest to use in medical applications close to spongy part of the bone. Within the following statements, it is obvious that fabrication of biocomposite is expensive. In that case, the micromechanical modelling can predict and estimate the elastic modulus in the dilute state (for low porosity). Unlike the Dewey method, the Rice with differential methods improved with increasing the porosity percentages. Rice's method has the worst performance among other methods (especially for low porosity), and the values obtained by this method differ greatly from laboratory findings. The differential method is more acceptable in low porosity value. A differential method is used to overcome the limitations of the dilution estimation method in predicting the mechanical properties of high porous materials which uses the formulation of this method for computations. The performance of the Gibson model, Roberts, and Garboczi model, and Wang and Tseng, Ramakrishnan and Arunachalam model are almost identical in the prediction of the elastic modulus approximation [20, 23, and 43]. These models are commonly used in low porosity estimates with errors of 20%. These models can present for laboratory findings and determination of elastic modulus corresponding to various porosity. In Figure 9, the values obtained for the Poisson's ratio of bony scaffolds made of hydroxyapatite have been plotted using Roberts and Garboczi, Wang and Tseng methods, and differential method estimation for different porosities. The Wang and Tseng methods are not able to calculate the Poisson’s ratio for porosities more than 80% and the values of the Poisson’s ratio obtained in these porosities are greater than 0.5, which is not acceptable. Among the studied models, the best performance in calculating the Poisson’s ratio for porosities less than 50% belongs to the Roberts and Garboczi method (with a maximum of 2.6% error) [20, 43].

4. Conclusion

This study shows with increasing titanium oxide the elastic modulus and the crystallinity of the samples increases. By increasing the crystalline phase, the porosity of the bio-nanocomposite is increased. With increasing porosity, the obtained elastic modulus in the laboratory increases. With the increase in porosity, the calculation error in the Dewey model for elastic modulus increases. For the bio-nanocomposites scaffold containing (10 wt% TiO_2), the detected error for higher porosity more than 60% was observed. By increasing the porosity, the difference between elastic modulus measured in the laboratory and elastic modulus in Dewey is increased more than 100% using Dewey's equation. This difference is higher for ceramics (HA-TiO_2) than polymer (PCL). According to the obtained results, the application of most models (other than the Rice model) in low porosity leads to obtaining acceptable responses, but with increasing porosity, the accuracy of the findings is greatly reduced. Among the examined models, the differential methods are the most suitable methods for finding mechanical properties in high porosity architecture (higher than 50% in bone scaffolds). One of the main reasons for the discrepancy between the values obtained from theoretical methods with the experimental results is the fact that they are no longer added to the microstructure of the material and assume simple geometric shapes for the cavities in the micromechanical methods. On the other hand, part of this error can be due to the lack of access to accurate information and the discrepancy between the reported values for the mechanical properties of raw materials used in the fabrication of scaffolds in various papers. In the final section of this research, due to the importance of HA in the fabrication of bone scaffolds, the results obtained for mechanical properties (elastic modulus and Poisson's ratio) have been analyzed statistically. The application of these equations in the rapid prediction of elastic modulus and Poisson's ratio of bone scaffolds is highly recommended to avoid the expensive cost of fabrication and preparation of bony scaffold for orthopedic approaches.

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Conflict of interest

The authors declare no potential conflict of interests.

Ethical approval

This study started after receiving its Scientific ethical approval from Isfahan University of Medical Sciences that registered inquiry and funding under the no. 16645 (clinical research section)

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Tables

Table 1: The number of molecules of HA, TiO_2 and PCL for simulation.

The number of molecules based on molecular mass			Weight percentage (HA, TiO_2 and, PCL)
PCL	**TiO_2**	**HA**	
66	**0**	**4**	**HA (25%) + PCL (75%)**
66	**6**	**4**	**HA (20%) + TiO_2 (5%) + PCL (75%)**
66	**12**	**2**	**HA (15%) +TiO_2 (10%) +PCL (75%)**
66	**18**	**2**	**HA (10%) + TiO_2 (15%) +PCL (75%)**

Table 2: The physical values of materials depend on geometry used in Roberts and Garboczi model [20].

The shape of the porosity	Spherical	Oval
m	0.818	0.798
n	1.650	2.250
a	0.221	0.166
b	0.840	0.604

Table 3: Poisson's ratio, Elastic modulus and porosity value of the experimental evaluation (HA, TiO_2 and PCL).

Material Properties	Poisson's ratio	Elastic Modulus (GPa)	Porosity (%)
HA-TiO_2 (0)-PCL	0.30	0.036	63
HA-TiO_2 (5%)-PCL	0.33	0.042	70
HA-TiO_2 (10%)-PCL	0.34	0.056	76
HA-TiO_2 (15%)-PCL	0.35	0.069	84

Table 4: Dewey model for porous bio-nanocomposites in comparison with Elastic modulus of experimental evaluation.

Dewey's model for porous bio-nanocomposites 10 wt% and comparison of Elastic Modulus with laboratory test (0 wt% TiO_2)							
Samples	$\vartheta_{p.exp}$	$E_{p.exp}(GPa)$	ϑ_s	ζ	$E_{S.Dewey}(GPa)$	$E_{p.Dewey}(GPa)$	Error calculating Young's modulus (%)
HA- TiO_2	0.270	0.250	0.170	2.76	0.150	0.108	**56.80**
PCL	0.360	0.003	0.260	1.76	0.002	0.001	**66.66**
Dewey's model for porous nanocomposites 20% and comparison of Elastic Modulus by laboratory (5 wt% TiO_2)							
Samples	$\vartheta_{p.exp}$	$E_{p.exp}(GPa)$	ϑ_s	ζ	$E_{S.Dewey}(GPa)$	$E_{p.Dewey}(GPa)$	Error calculating Young's modulus (%)
HA- TiO_2	0.270	0.255	0.170	2.76	0.155	0.069	**72.94**
PCL	0.360	0.003	0.260	1.76	0.002	0.001	**66.66**
Dewey's model for porous bio-nanocomposites was 30% and Elastic Modulus comparison was achieved with laboratory test (10 wt% TiO_2)							
Samples	$\vartheta_{p.exp}$	$E_{p.exp}(GPa)$	ϑ_s	ζ	$E_{S.Dewey}(GPa)$	$E_{p.Dewey}(GPa)$	Error calculating Young's modulus (%)
HA- TiO_2	0.271	0.260	0.171	2.76	0.160	0.0275	**89.42**
PCL	0.360	0.003	0.260	1.76	0.002	0.00094	**68.66**
Dewey's model for porous bio-nanocomposites was 40% and Elastic Modulus comparison was achieved with laboratory test (15 wt% TiO_2)							
Samples	$\vartheta_{p.exp}$	$E_{p.exp}(GPa)$	ϑ_s	ζ	$E_{S.Dewey}(GPa)$	$E_{p.Dewey}(GPa)$	Error calculating Young's modulus (%)
HA- TiO_2	0.271	0.265	0.171	2.76	0.165	-0.017	**106.41**
PCL	0.360	0.003	0.260	1.76	0.002	0.00059	**80.83**

Figures

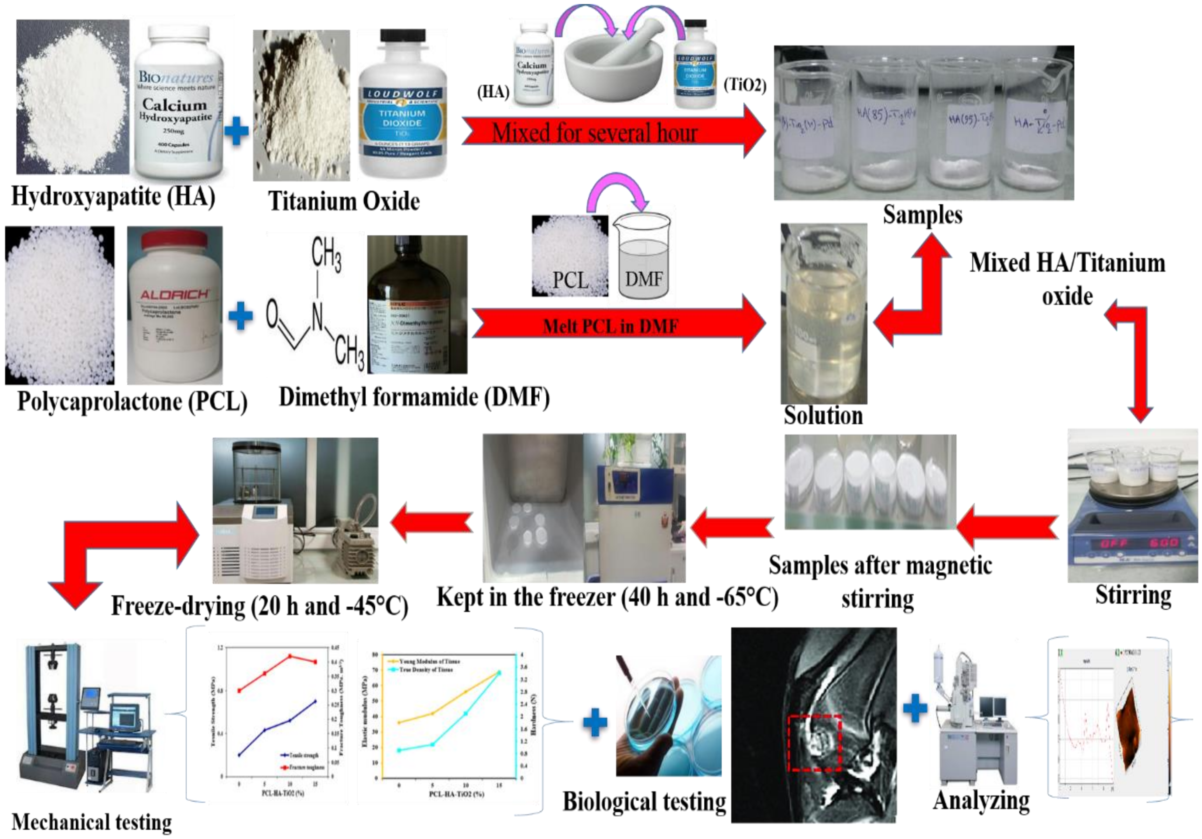

Figure 1: Schematic of PCL bio-nanocomposite scaffolds made by the freeze-drying method with HA and TiO_2 nanoparticles.

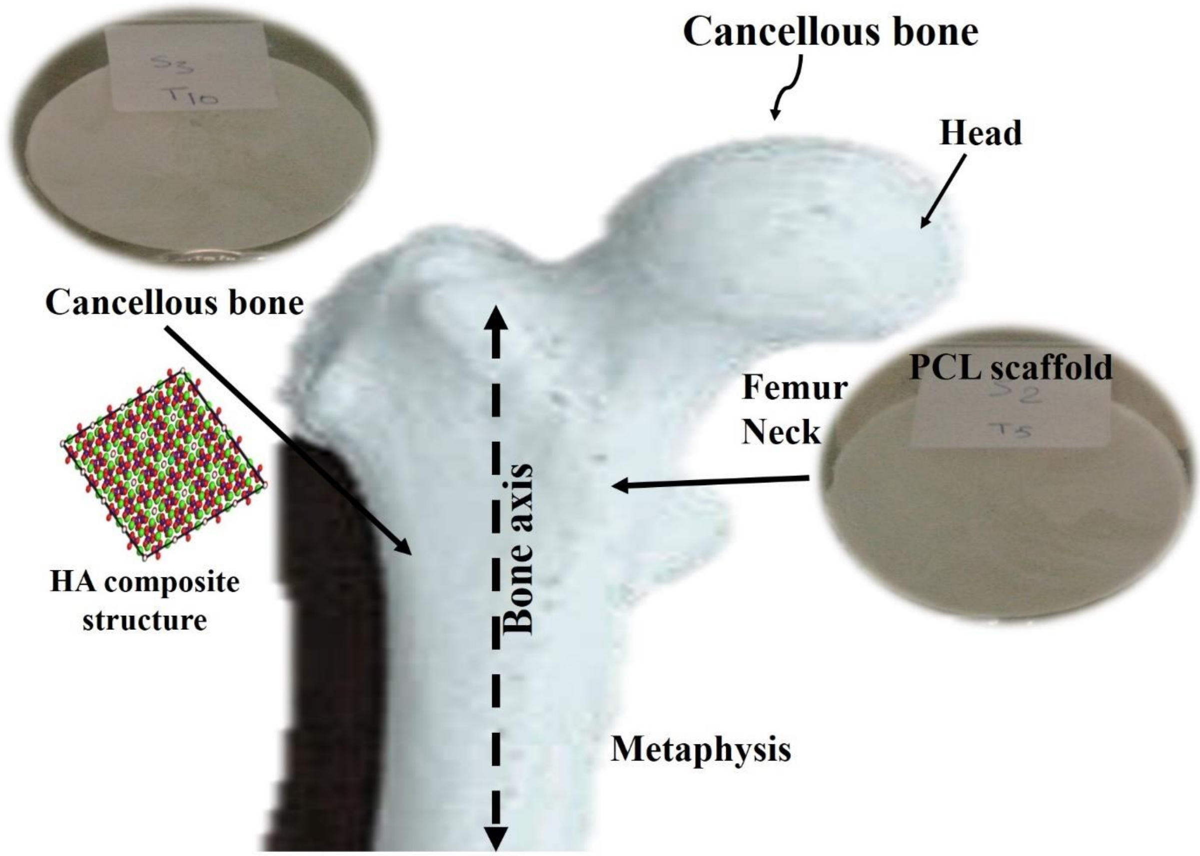

Figure 2: Schematic of femoral design using solid-work and the application of the porous PCL bio-nanocomposite reinforced with HA and antibacterial particles.

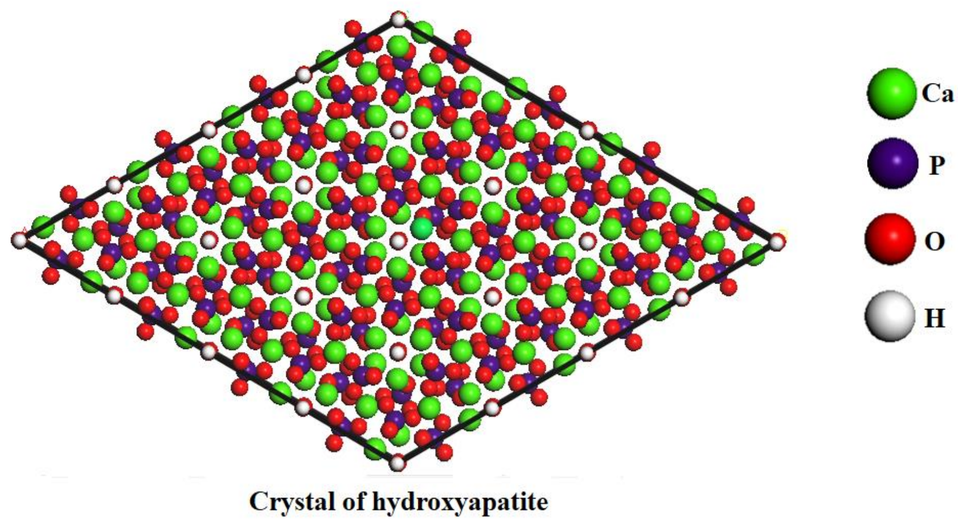

Figure 3: Simulation of porous nanocrystalline HA in the materials studio software.

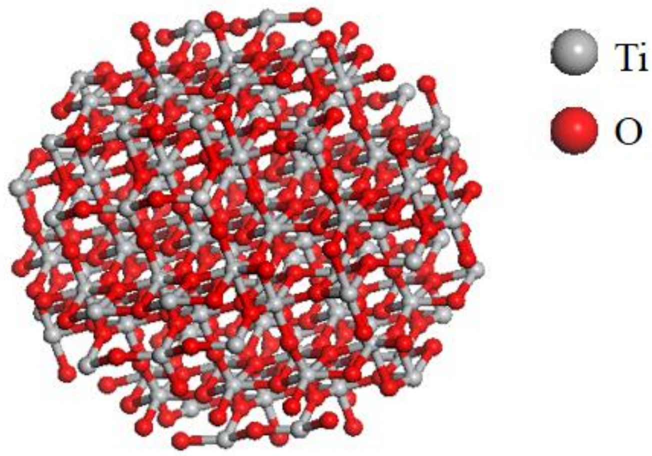

Figure 4: Simulation of spherical and porous nanocrystalline titanium oxide in the materials studio software.

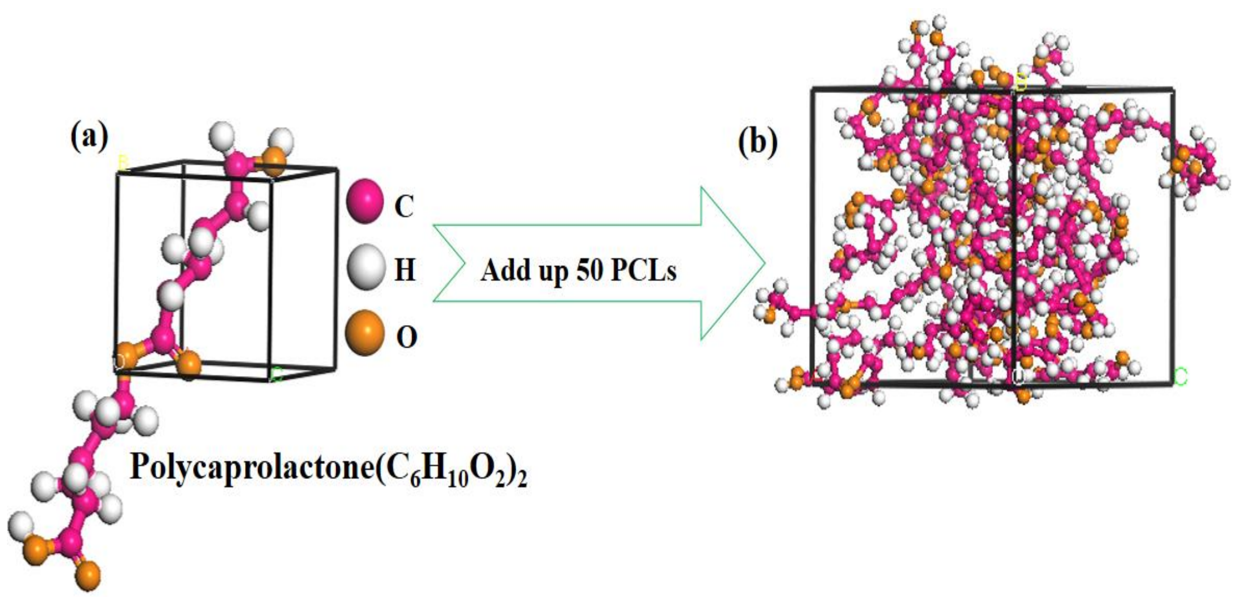

Figure 5: (a) Polycaprolactone polymer with double chain PCL structure and (b) Composite polymer simulated in the materials studio software.

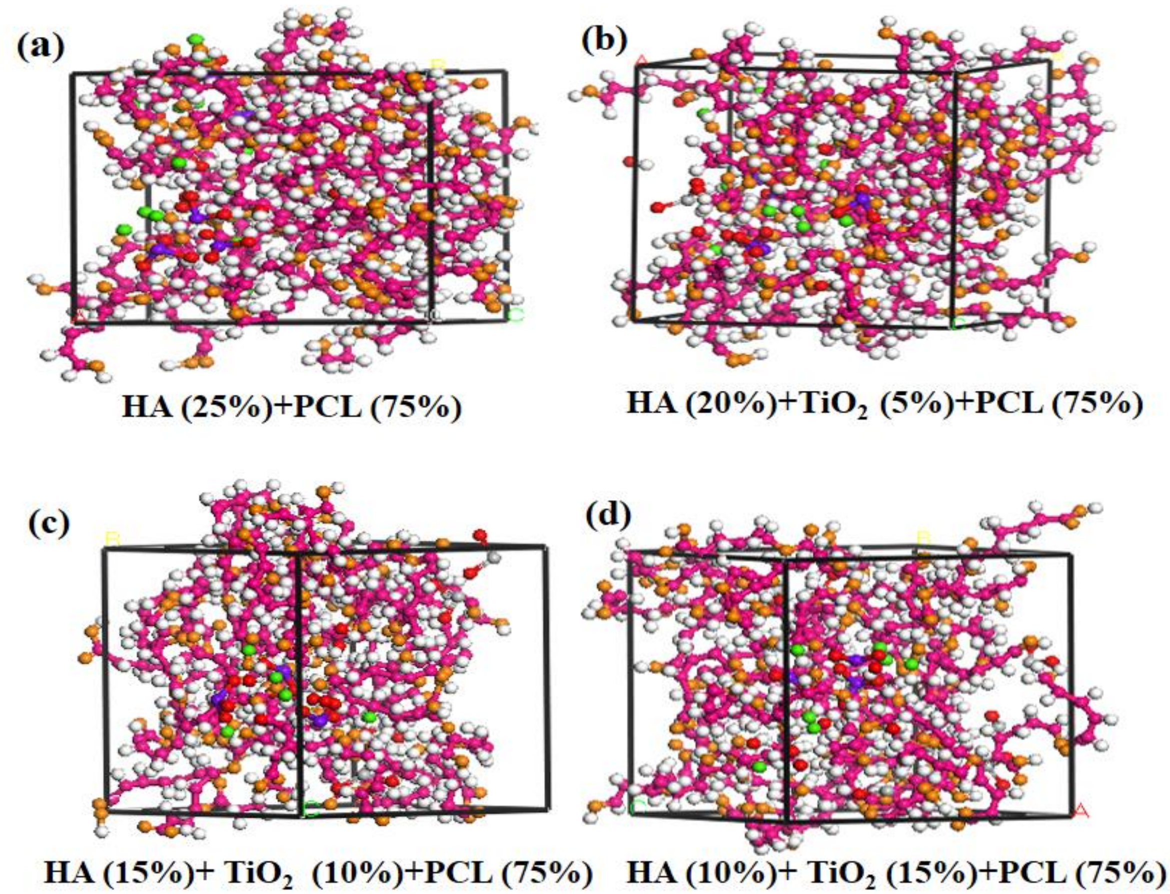

Figure 6: MD simulation of bio-nanocomposite containing of (a) 0 wt%, (b) 5 wt %, (c) 10 wt%, and (d) 15 wt % of TiO_2 in the HA and PCL microstructure simulated in the MD software for orthopedic approaches.

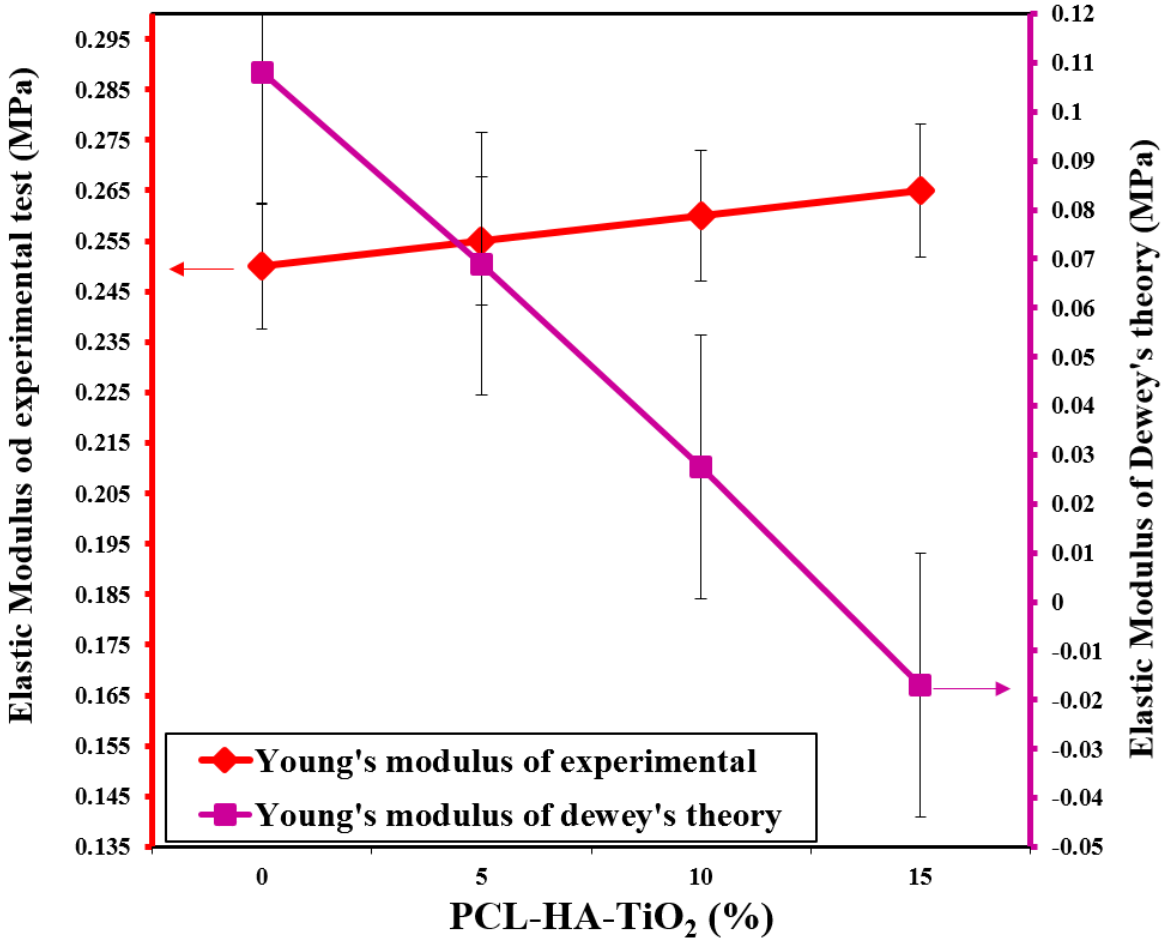

Figure 7: The comparison of the Elastic modulus obtained in the experimental with Dewey's theory.

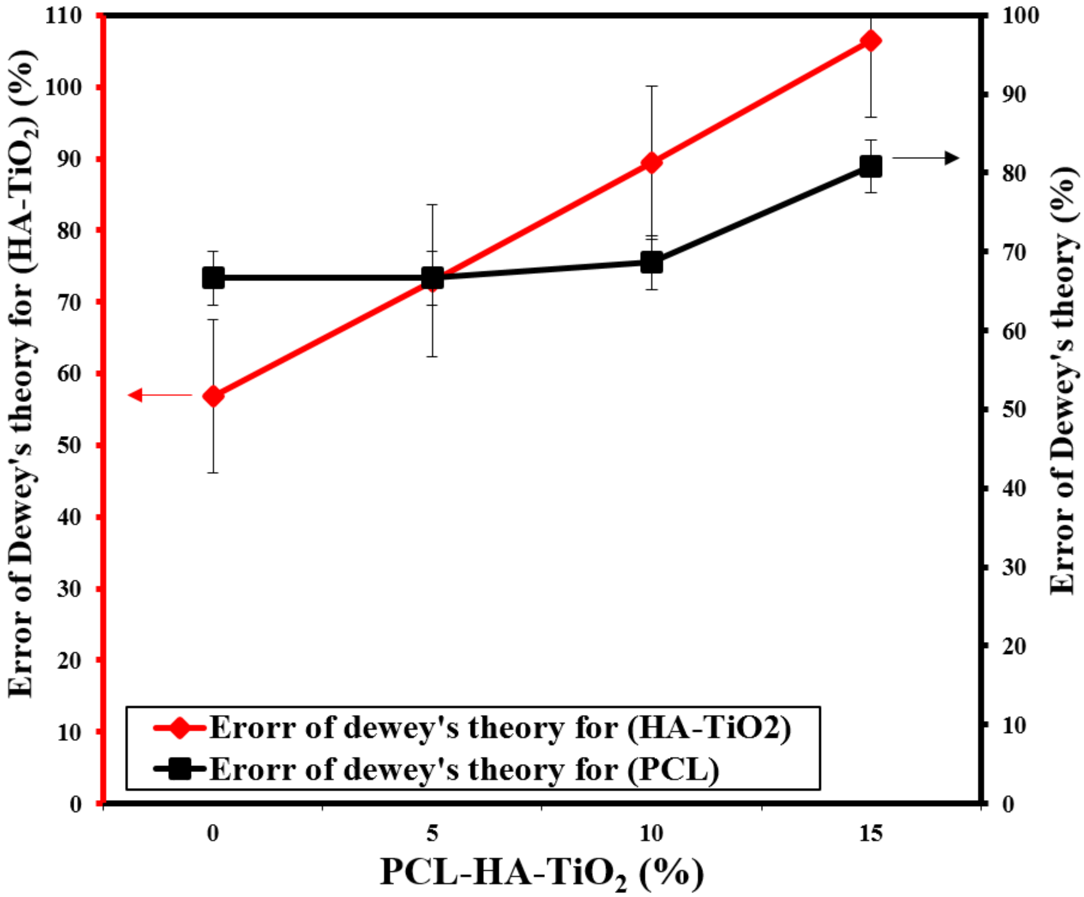

Figure 8: The percentage error in Dewey's theory for nanoparticles (HA, TiO_2) and polymer (PCL)

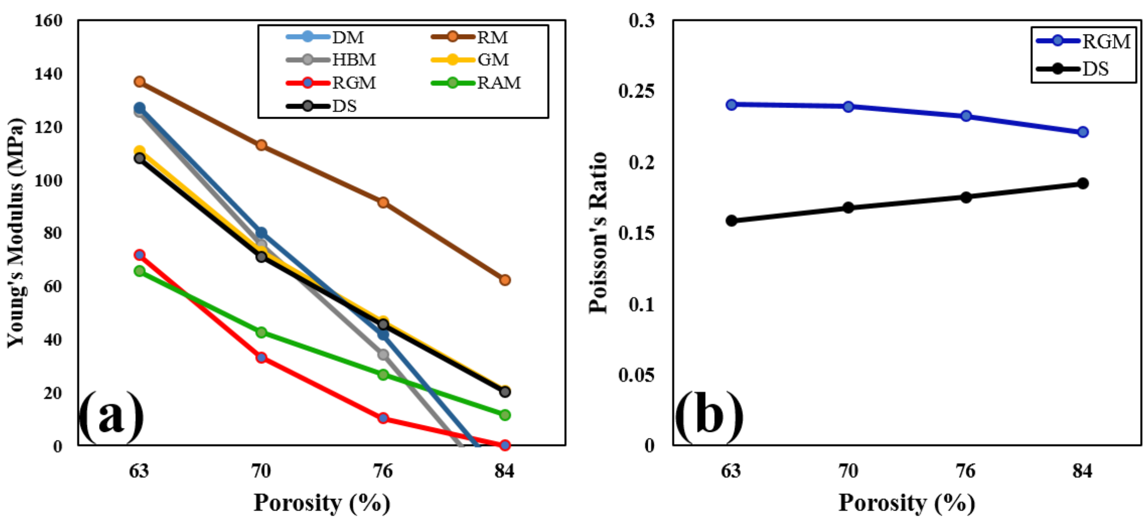

Figure 9: The comparison of the experimental results and micromechanical modelling of elastic modulus of porous synthetic bone scaffold in this study by means of (a) DM, RM, HBM, GM and RAM, RGM and DS (b) the obtained Poisson's ratio of RGM and DS model.