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RESEARCH PAPER

Artificial intelligence investigation of three silicates bioceramics-magnetite bio-nanocomposite: Hyperthermia and biomedical applications

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ABSTRACT

Objective(s): Bioactive silicate ceramics have favorable features for applying as off-the-shelf bone and artificial tissue. Calcium silicate can enhance the generation of an immediate bond with host bone without an intervening rough surface in the bone layer. However, the silicate bioceramics have some drawback regarding their mechanical properties and chemical stabilities.

Materials and Methods: In this study, magnetite nanoparticles (MNPs) as reinforcement were added to the three silicate bioceramics to investigate the physical and mechanical properties as well as their magnetic behavior as a case study and compare with other calcium silicate nanocomposite which are excellent candidates for hyperthermia applications. Then the artificial neural network (ANN) applied to the previous data to predict the mechanical and biological behavior of the bio-nanocomposite as output parameters. A predicted model was enhanced using ANN to measure the optimum size and reinforcement amount of the magnetite bio-nanocomposite. The results of the fabricated bio-nanocomposite were extracted experimentally corresponding to different MNPs weight fractions compared to the predicted model.

Results: The X-ray diffraction (XRD), scan electron microscopy (SEM) technique were used to compare the porosity and porous tissue microstructure. Thereafter, an analytical solution is presented to express explicitly the physical and mechanical responses of the bulk/scaffold bio-nanocomposite.

Conclusion: The obtained results showed the potential application of these calculations and analyses in a wide range of numerical studies. The comparison presented within the test and predicted values showed that the modeling outcomes were close to testing values.

Keywords: *Artificial neural network, Biomedicine, Magnetite nanoparticle, Nanocomposite, Tissue engineering*

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INTRODUCTION

Synthetic calcium phosphates (CaPs) as an inorganic element of bone and teeth are generally used as metallic and non-metallic implants to enhance the restoration of the bone defects due to their excellent bioactivity, biocompatibility, and osteoconductivity performance [1-3]. This class of ceramics has potential application to be used in the restoration bone problems such as bone trauma, bone disease, osteoporosis, bone necrosis, and sudden bone fractures [4-6]. Trace elements like magnetite nanoparticle (MNPs) may enhance and add some useful advantages to the CaPs bioceramics tuned the biological behavior, inflammatory and anti-osteoporotic characteristics [7-8]. Among the general bioceramics applied in tissue engineering like nanoparticle, powder, porous tissue, bulk, scaffold or bio-nanocomposite for developing the bone restoration, there is a fabulous application for using bio-nanocomposite composed of magnetite nanoparticles (MNPs) compared to other ceramics [9-10]. Continuously MNPs (like Magnetite (Fe_3O_4) & Hematite (Fe_2O_3)) with density of 5.1 g/cm^3 has not been examined regularly for biomaterials area considerably due to extraordinary toxicity and unmatched properties with human's organs. The magnetic properties of MNPs have been studied in advanced materials science by researchers for biomaterials applications like image resonance, hyperthermia treatment, drug delivery system

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and bone substitute approaches [11-13]. Applying the MNPs with hyperthermia application can kill the defected cells. The tumors temperature can increase between 42°C till 43°C in the tumor cite the MNPs applied and also can reduce tumor size using external AC magnetic field due to the hysteresis loops, e.g. Hydroxyapatite-strontium hexaferrite were produced as a novel bio-nanocomposite for hyperthermia approaches [14-18].

Frequently, the biochemical reaction of the bio-nanocomposite with various amount of MNPs reinforcement is a matter of debate among the biomaterials researchers, however, the safe range is not defined yet. When a clinical investigation is conducted the drawback of the product become quite obvious. On the opposite side, an increase of magnetite nanoparticle, zinc-doped nickel ferrite, and M-type strontium hexa-ferrite induces the mineral contour which changes bone mineralization. The ions like Mg, Fe, Si, and Zr have the ability to stimulate the bone formation, cellular activities, and proliferation of the osteoblast cells, for instance, mesenchymal stem cell (MSC) [19-28].

Among the improvement of artificial intelligence (AI) theory, the evaluation of the non-linear queries has grown an efficient technique. Artificial neural network (ANN) is known as one of the most important modeling methods in conjunction with the analytical method, which looks very more common for the evaluation of materials science outputs [22-24].

The ANN tools connected with getting knowledge from an initially collected data, which is called the training set or learning set, and later to control the system termination using analysis data with the advantage of reducing the time and cost in all the required experimental activities. The ANN tools typically involve the interconnection of simple computational elements known as neurons or nodes.

On the other hand, because of significant advances in applying the computational estimations like ANN and Adaptive Neuro-Fuzzy Inference System (ANFIS), several researchers have proposed to apply these tools to predict the critical parameters which are complex, time-consuming and expensive to measure in the laboratory area [25].

Table 1. The input and output parameters of the MNPs-ceramics nanocomposite specimens [12, 13, 18]

Sample	Matrix	Size	Porosity (%)	CS (MPa)	E (MPa)	FT (MPa. $M^{0.5}$)	Ref.
DI	0	30	80±1.8	2.2±0.13	170	3.5	[12]
30MNPs-DI	30	39	91±1.8	1.9±0.13	--	3.7	[12]
HT	0	30-40	91 ±1.2	1.8±0.13	96±15	1.24	[13]
20MNPs-HT	20	50-60	81±1.8	2.5±0.13	145±12	1.29	[13]
BR	0	31.3	55±1.8	1.6±0.13	120.2	1.12	[18]
30MNPs-BR	30	49.3	55±1.8	3.6±0.13	158.2	2.85	[18]

CS: Compressive strength, E: Elastic modulus, FT: Fracture toughness, DI: Diopside, HT: Hardystonite, BR: Bredigite

Table 2. Parameters of preparation of diopside, bredigite and akermanite using milling

Milling Parameter	Diopside	Hardystonite	Bredigite
HEBM speed (rpm)	400 rpm	650 rpm	650 rpm
BPR weight ratio	10:1	10:1	10:1
Ball number	3	4	3
Time of sintering (h)	4	3	4
Sintering temperature (°C)	1200°C	1150°C	1300-1350°C
Total weight of powder (gr)	10	10 gr	11 gr
MgO	1.38	1.54	1.42
SiO_2	4.4	4.62	3.94
$CaCO_3$	4.22	3.84	4.64
Reference	[12]	[13]	[18]

In other words, it is used to find cause-and-effect correlation easily. In the current study, the porosity, and apatite formation of the different type of MNPs bio-nanocomposite have been modeled using three case studies. Therefore, in this work, our aim is to consider the effect of the different amount of MNPs on the characteristic of diopside (DI), hardystonite (HT), and bredigite (BR) powder bio-nanocomposites.

A predicted model was enhanced using ANN to measure the optimum size and reinforcement amount of the MNPs in the bio-nanocomposite. The results of the bio-nanocomposite were extracted experimentally corresponding to different MNPs weight fractions.

Data collection

In this work, we collected information from three previous study and then briefly listed the out puts in Table 1 [12, 13, and 18]. Also, the inputs such as matrix percentages, size, and reinforcement amount in the nanocomposite has been reported in Table 1. The input and outputs has been investigated as the major cost function of our prediction by multilayer perceptron (MLP) model. The Bredigite-MNPs nanocomposite (BR-MNPs) results were used to determine the obtained model as a case study.

Neural network and prediction of the nanocomposite properties

The square regression of the study reported from the training datasets and testing datasets was near to 1. Finally the results were monitored and compared to those acquired parameters from three case studies. The accuracy of the model in modeling system is very important; therefore certain criteria were check to monitor the accuracy of the model. Finally, the obtained criteria can be selected and be guarantee that have superiority compare with other models. The ANN system in which each node is joint to another nodes (as shown in Fig 1), in case that the connections between the nodes can be either with + weight as excitatory, - weight as inhibitory, or even the connections can be near to zero as irrelevant. The 3-5-2 MLP, meaning that it is a network containing three input layers, five neurons hidden layer and two neurons for output layer as shown in Fig 2.

The analysis of the testing sets, the influence of the neurons in the hidden layer, the performance of the neurons in the network and the suitable configuration of the assumed model can be detected. Evolutionary tools are used in order to renew the candidate solutions. The advantages of using evolutionary tools are to obtain the valid and acceptable results from wide range of data base. As a matter of fact, these tools that have been offered are identical to what usually happens in normal life. While contemplating how the natures usually perform the mentioned task, every individual point or models can choose the best experience in life and follow, adapts and moves on to a better experience for the neighbours.

The information or data collected is divided into two classes, for example, firstly the testing datasets and the training datasets can improve the model's accuracy. The training datasets receptions within a model introduced to make it the ability for the model to discover the conditions that makeup better conditions. These are networks in which nodes are partitioned into subsets named layers, with no links from layer j to k if j > k. The activation function of the artificial neurons in ANNs implementing the backpropagation algorithm depend to a weighted sum (the sum of the inputs xi multiplied by their respective weights wji) as shown in formula 1.

$$A_j(X,W) = \sum_{i=0}^{n} x_i * w_{ji}$$

$$O_j(X,W) = \frac{1}{1+e^{A(X,W)}}$$

The simple output function is the sigmoidal function which is shown below.

As the test error is the difference between the original output and the required output, the error correlated to the weights, and there is a demand to modify the weights to reduce the failures. The purpose is to determine the error function for the output of each neuron as determined in formula 2.

$$E_j(X,W,d) = (O_j(X,W) - d_j)^2$$

The training data sets were out of 80% of the data and the remaining data (20%) applied for testing sets. To achieve minimum error in tested data a variety numbers of neurons in hidden layers and eventually minimum error occurred with 25 neurons were used.

Therefore, for prediction of modulus of elasticities 9 neurons used as input layers 25 neurons as hidden layers and 1 neuron as output layer.

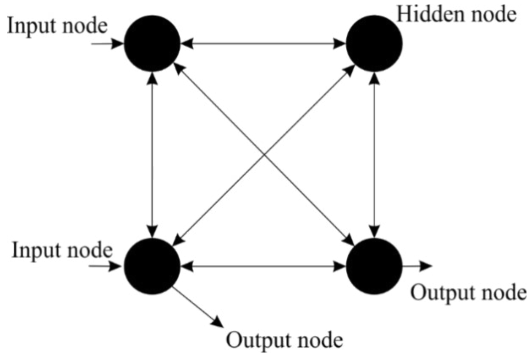

Fig 1. The connection of the network of input node and output node in this study

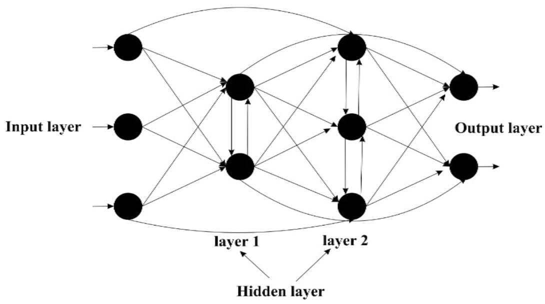

Fig 2. The input layer and the hidden layer

The Mean of Square Error (MSE), the Mean Absolute Error (MAE) and Relative Absolute Error (RAE) are among these criteria. The Compliance of predicted data with the experimental data also examined by the numerical value of the squared regression (R^2) which is the important parameter to estimate the precision of the model. Errors and regression value are taken from Equation (3-6) [26].

$$RAE = \frac{\sum_{i=1}^{n}|t_i - o_i|}{\sum_{i=1}^{n}\left|t_i - \frac{1}{n}\sum_i t_i\right|}$$

$$MAE = \frac{1}{n}\left[\frac{\sum_{i=1}^{n}|t_i - o_i|}{\sum_{i=1}^{n} t_i}\right]$$

$$RMSE = \frac{1}{n}\sum_{i=1}^{n}(t_i - o_i)^2$$

$$R^2 = \frac{(n\sum t_i o_i - \sum t_i \sum o_i)^2}{(n\sum t_i^2 - (\sum t_i)^2)(n\sum o_i^2 - (\sum o_i)^2)}$$

Concerning the simulating in the engineering and parameters of the processes, the compressive strength and the total porosity of the calcium silicates scaffolds were performed by Abdellahi et al. using gene expression programming (GEP) [26]. Another concerning issue is determination of bone apatite formation range which is an important issue in biomaterials engineering [27]. Also, Ferreira [28] explained the fundamental of GEP algorithm in 2001, which has obtained the support of the traditional genetic algorithm. The following algorithms have been implemented in many areas because of simple coding, fast convergence speed and strong ability to solve problems. One important application of GEP is symbolic regression or function finding, where the goal is to find equations that perform well for all fitness cases within a certain error of the correct value [26, 28]. The “function finding” application of GEP can be extremely important within the pharmaceutical field and biomaterials domain. The database used in this work was obtained from the previous work and the experimental tests were shown in Table 1 and 2.

MATERIALS AND METHODS

As a case study performed on three silicate bioceramics like diopside (DI), hardystonite (HT), and bredigite (BR) nanocomposite with magnetite nanoparticles from previous research with the physical parameters as shown in Table 2. The silicate-magnetite nano composite were used for hyperthermia application under AC magnetic field. Firstly, Abdellahi et al. in 2017 [12] purchased magnetite nanoparticles (MNPs) powder from Merck Company as reinforced particles to diopside (DI) powder. They synthesized diopside-magnetite nanocomposite at different percentages of magnetite using high energy ball milling (HEBM) for ten hours and then sintering at 600°C for three hours. In another study, Farzin et al. in 2017 [13] doped iron ion into hardystonite (HT) structure which synthesized using sol–gel technique. The results obtained from synthesizing the HT-MNPs nanocomposites showed that Fe^{3+} ions substitute to Ca^{2+} ions along the nucleation of $Ca_2ZnSi_2O_7$. The milling parameters and procedure to synthesize the HT is tabulated in Table 2. Khandan et al. in 2017 [18] synthesized the bredigite nanopowder as matrix using $Mg_3Si_4O_{10}(OH)_2$), SiO_2 and $CaCO_3$ and then blended according to the stoichiometry amount with MNPs using a planetary HEBM tools. The milling and physical parameter for synthesizing bredigite powder is also listed in Table 2. The MNPs were fabricated by the sol-gel technique according to the recent research [12, 13]. A bredigite-Magnetite nanocomposite containing various percentages of Fe_3O_4 (0 wt%, 10 wt%, 20 wt%, and 30 wt%) was fabricated with alcohol medium for obtaining a homogeneous combination. The grinding time was set on 60 min and the obtained powders were sintered at 1300-1350°C for 4 h to make homogenized nanocomposite. Up to now, there has been no study that directly compared these methods for the fabricated of a particular silicate bioceramic composite with MNPs.

Porosity study

The porosity of the all three magnetite bio-nanocomposites was evaluated by Archimedes rule using following formula.

$$Porosity = \frac{(Mwet - Mdry)}{(Mwet - Msubmerged)}$$

Where M_{dry} is the dry mass of scaffold, M_{wet} is the weight of pre_{wet} scaffold, and the $M_{submerged}$ is the mass of scaffold soaked in simulated body fluid (SBF, a saline for simulating the biological behavior same as blood plasma of human) according to the Kokubo test [27]. Briefly, the heated specimen soaked in the SBF liquid and then the sample removed from the liquid and weighted.

Bioactivity study

The biological behavior of the magnetite nanocomposites was evaluated in the SBF. The SBF saline was produced similar to the protocol explained by ISO 23317:2012, pH 7.4 and Kokubo procedure [27].

RESULTS AND DISCUSSIONS

The XRD patterns of the DI-MNPs nanocomposites containing 0 wt % and 30 wt % are depicted in Fig 3a. As it is seen in the XRD pattern sharp peaks of magnetite nanoparticles are overlapped with diopside peaks that cannot be distinguished precisely from one another. Table 1 proves that by raising the MNPs amount from 0 wt% and 30 wt%, the DI peaks shift approaching the higher angles. This event guarantees the replacement of Ca^{2+} ions with the ion radius of 0.099 nm via Fe^{3+} ions with the ion radius= 0.068 nm. Farzin et al. in 2017 [13] present the XRD patterns of the HT and its composite with 0.2 MNPs powders in Fig 3b. The outcome of their works showed that in the average particle size of the concerned HT and 0.2 MNPs -HT is in the range of 20 to 60 nm, respectively. In contrast to HT, the XRD pattern of 0.2MNPs-HT shift to higher angles. Increasing the MNPs amount from 0.0 MNPs to 0.2MNPs to HT leads to substituting of peaks to higher angles that can demonstrate the fusion of MNPs [13]. In another study, Khandan et al [18] shows that the XRD patterns of the pure BR and BR-30 wt% MNPs composite samples within the nanocomposite particle size in the range of 40-60 nm. It is seen in Fig 3c, only BR peaks ($Ca_7MgSi_4O_{16}$, JCDP: 036–0399) are present in XRD pattern. At 1300-1350°C, by increasing the temperature of the sample, some extra nanocrystalline phase were appeared at 2θ = 32° and 54° [18].

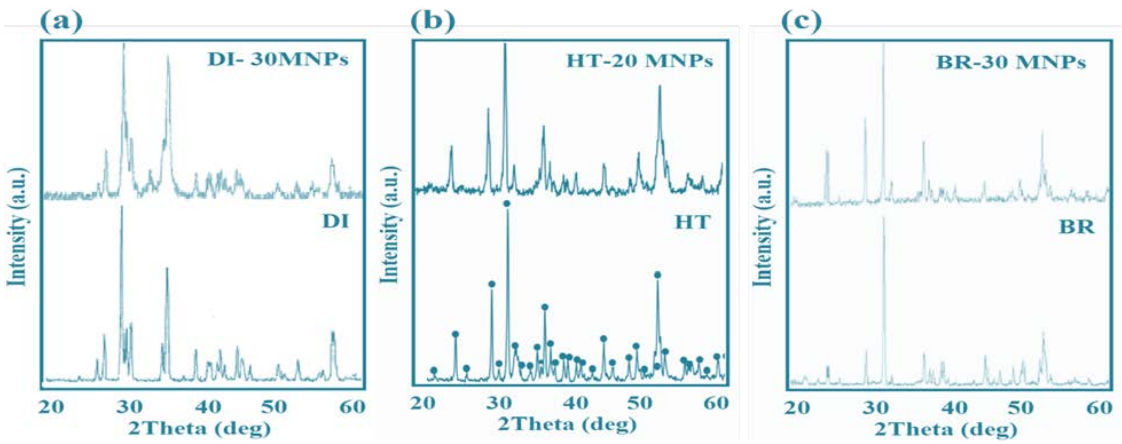

Fig 3. XRD pattern of prepared specimen containing (a) DI 0 wt % and 30 wt %, (b) HT 0 wt % and 20 wt %, and (c) BR 0 wt % and 30 wt % of MNPs in the nanocomposite [12, 13, 18], Figures reproduced from Reference [12, 13, 18]

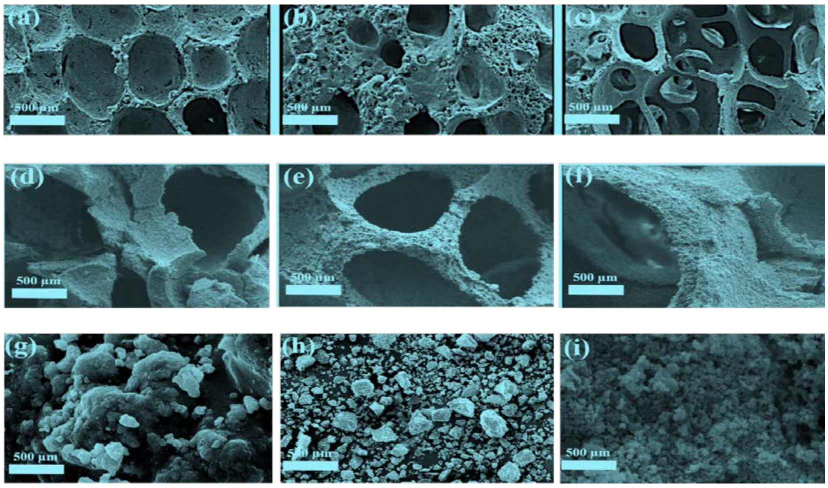

Fig 4. SEM micrographs of the milled nanocomposite containing 10 wt%, 20 wt%, and 30 wt% MNPs in (a-c) DI, (d-f) HT and (g-i) BR, Figures reproduced from Reference [12, 13, 18]

The surface and cross-section morphology of the fabricated DI scaffolds nanocomposites in the various amount of magnetite is displayed in Fig 4 (a-c). A smooth appearance of voids with an average diameter of 400-500 (µm) has been achieved at the moderate amount of MNPs (Fig 4a). While the sample with the higher amount of MNPs has higher degradation rate as the wall of the scaffold nanocomposite collapsed. Also, unlike other calcium phosphate bioceramics, bioactive glasses (BG) may not be easily processed into porous scaffolds without losing their bioactivity due to its high crystallization at high sintering temperatures. Almost all silicate bioceramics have the proper sense to form bone apatite-like after soaking in the SBF solution. Several kinds of literature have studied the ability of bioceramics to a bio-layer of tiny agglomerated white particles on the surface of specimens in SBF liquid as an indicator of 'in vitro bioactivity', due to proof that natural artificial bone tissue which can integrate with the host bone and hence form a fixed chemical bond with the bone implants. The obtained results by HT-MNPs indicated that increasing the MNPs reinforced the structure better than the sample with lowest amount of MNPs as shown in Fig 4 (d-f).

In addition, Fig 4(g-i) shows more compact and uniform distribution of particles in the matrix (white particles) after sintering with adding higher amount of MNPs. In conclusion to above reason, it is obvious that adding higher amount of MNPs can both enhance destroy the apatite formation of the nanocomposites. The model obtained in the current work also confirm that within the nanocomposite size in the range of 40-50 nm and 10-20 wt% MNPs additive the apatite formation have the highest values which confirms the experimental values. Also, Fig 4(a-c) illustrated the interconnectivity and the connection of holes and pores. Researchers like Hulbert and their co-workers showed the lowest pore size expected to enable ingrowth of encircling bone with blood supply is about 100–150 nm [29]. Their observations showed that the lowest pore size competent of filling with surrounding bones is very necessary. The following statements revealed that the pore size and an interconnected pore structure, as the one shown in Fig 4 (a-c) are suitable for osteoblasts ingrowth, rapid vascularization, and bone reconstructing. Farzin et al [13] show that the SEM micrographs of the scaffolds with different Fe_3O_4-doped content after 28 days of immersion in SBF solution. The result for soaked sample indicated that the shiny regions were produced on the surface of the scaffolds and an inner surface of the pores are formed as a result of contacting the scaffolds with SBF solution and saturated Ca^{2+} ions. Moreover, apatite formation starts to change the morphology and volume of the pores in the nanocomposite scaffolds. Khandan et al [18] present SEM image of BR before and after sintering process as shown in Figs 4 (g-i). It can be seen that much amount of BR particles have been sintered. The result obtained by Khandan et al. showed lower porosity compared to the previous works however the compressive strength value were significant with more MNPs [18, 32, 36]. According to SEM image, the crystallite size of BR powders was in the range of 40–70 nm. Additionally, the impact of calcination on the formation of BR particles is represented in Fig 4(g-i). Fig 5 present the prediction of the formation of apatite as an output and size of the nanocomposites versus matrix percentages as an input.

Table 3. The values of errors and also R2 of the model related to the training and testing datasets

Symbols	Compressive Strength/Biological Modelling		Porosity Modelling	
	Training	Testing	Training	Testing
R^2	0.954	0.940	0.975	0.970
MSE	0.031	0.062	0.96	0.750
MAE	0.052	0.521	0.762	0.745
RAE	0.089	0.021	0.382	0.425

Fig 5 indicates the effect of holes and pore size and introduces that higher porosity obtained when the size of particles and spacer amount increased. Carbon nanotube (CNT) have significant mechanical behavior and has been greatly applied to toughen the silicate bioceramics as well as magnetite nanoparticles [29-31].

Also, the clinical aspect of the CNT and magnetite nanoparticles must be investigated according to the biological standard with high precision due to the high toxicity of the MNPs and CNTs [32-41]. Major challenges associated with CNT-reinforced bioceramics include the inhomogeneous dispersion of CNTs and the insufficient interfacial strength between the two phases. Also, another type of ceramic named baghdadite has proper mechanical properties similar HT and BR [42-44]. Although higher porosity for the nanocomposites, obtained which leads to lower compressive strength of the scaffold but it should have proper balance between porosity and compressive strength of the nanocomposite. The accuracy of the model to predict the compressive strength, fracture toughness, roughness and total porosity of the scaffolds was measured by Equations from 7-8. According to the literature, bio-nanocomposites fabricated with magnetic nanoparticles encapsulated in an inorganic oxide matrix with new additives like silica is most applicable inorganic oxide that can acts as a suitable dispersing medium with better versatility in surface modification, also having hydrophilic property with biocompatibility in biomaterials applications [35].

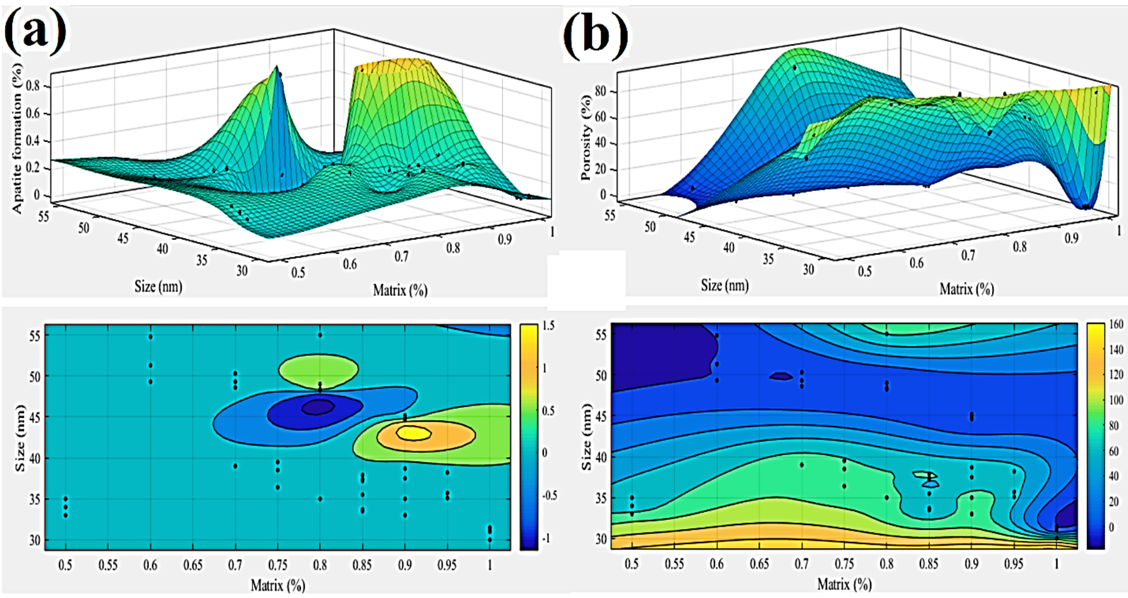

Fig 5. The prediction of (a) the apatite formation and (b) porosity value as an output and size of the bio-nano-composites and matrix percentages as an input

However, in the current study the silicate bioceramics were composed with magnetite nanoparticles have different biocompatibility, low degradation rate and high wettability property.

CONCLUSION

The bioceramics made of calcium silicate reinforced with magnetite nanoparticle used for hyperthermia applications. However, range of adding MNPs to the based bioceramics is a matter of debate in literatures due to high toxicity and weak chemical stability in high value. In this research, the proper amount of bioceramic-MNPs nanocomposite were predicated using MLP and ANN. Therefore, the results indicated that as the MNPs added to the base bioceramic can increase the size of the nanocomposite which is due to agglomeration and the cold welding phenomena between MNPs and bioceramic powder. The porosity result illustrated that addition of MNPs increase the porosity with the sample 20 wt% while it reduces the porosity in the sample containing 30 wt. % MNPs. Thus, compared to HT, DI, and BR bioceramics has high deposition rate and ability after 21 days of immersion in SBF. The following investigations can speed up the enhancement of silicate bioceramic applications as a next generation of bone substitutes. Thereafter, an analytical solution is presented to express explicitly the physical and mechanical responses of the bulk bio-nanocomposite. The obtained results show the potential application of these calculations and analyses in a wide range of numerical studies.

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CONFLICT OF INTEREST

The authors confirm that this article content has not any conflicts of interest.

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