ORIGINAL ARTICLE

Permeability Study of Functionally Graded Scaffold Based on Morphology of Cancellous Bone

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ABSTRACT

Introduction: Natural cancellous bone consists of inhomogeneous structures in which the porosity or pore size changes spatially. It becomes more challenging to exploit the potential of the designed scaffold to describe the complexity of bone architecture. In order to mimic cancellous bone architecture, a functionally graded scaffold (FGS) and uniform model based on pillar and hexagon unit cells have been successfully developed by using a Computer-Aided Design (CAD). This study aimed to determine the permeability of FGS and uniform scaffolds associated with the ability of cells to penetrate porous media. **Methods:** FGS and uniform scaffold were modelled based on the morphology of cancellous bone in bovine femoral condyle associated with porosity, Tb.Th, Tb.Sp, and BS/TV. The permeability and fluid movement through the scaffolds were analyzed using computational fluid dynamics. **Results:** The results show that the uniform scaffold has a strong correlation where the porosity increases, the permeability also increases. On the contrary, when the specific surface area increases, the permeability decreases significantly. When viewed on the scaffold PFGS and HFGS with 12NUC do not show a unique correlation, where the permeability value is proportional to the porosity level. Additionally, controlling NUC can be increasing BS/TV value. **Conclusion:** From the results explained in scaffold designing, it can mimic the morphology of cancellous bones such as Tb.T, Tb.Sp and BS/TV. It can be concluded that scaffold designed has fulfilled the requirements for the ideal scaffold because permeability value of the overall scaffold in the range of the cancellous bone.

Keywords: Permeability, Functionally graded scaffold, Cancellous bone, Computational fluid dynamics

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INTRODUCTION

Natural cancellous bone consists of inhomogeneous structures in which the porosity or pore size changes spatially. It becomes more challenging to exploit the potential of the designed scaffold to describe the complexity of bone architecture. In addition, parameters such as porosity distribution, trabecular thickness (Tb.Th), and trabecular separation (Tb.Sp) can be used as references in bone scaffold design because they are considered to have a strong correlation with modulus elasticity and permeability (1,2). Basically, compatibility between the modulus elasticity of the bone scaffold implant and host bone can be avoided from the stress shielding that causes the implant to loosen (3). Moreover, high permeability allows for the inflow of nutrients and the elution of metabolic waste and biodegradation products (4).

Regarding the segmental bone defects, which are mostly still surrounded by healthy bone tissue with various complex structures, a bone scaffold implant with the right combination of porosity is needed to provide a balanced modulus of elasticity and permeability between the scaffold and the host bone. Researchers think that besides graded porosity Tb.Th and Tb.Sp for the functionally graded scaffold (FGS) to mimic morphology of cancellous bone, morphology specific surface area (BS/TV) it can also be used as a reference in design, and researchers hypothesize that by controlling the number of unit cells, we can increase BS /TV without affecting the porosity value. However, permeability will significantly decrease.

On the development of bone tissue engineering, many studies have focused on nutrient transport of various designs with different porosity and pore sizes in the literature. However, these were selected only based on the experience of the researcher. In general, improper selection of porosity, pore size, sturt size, and surface area results in low cell attachment and cell proliferation, the rate of proliferation due to cell attachment and proliferation depends mainly on the size of the cell attachment site, and nutrition can be through scaffold to support cells to survive (5,6). Therefore, the right scaffold design is an essential step in providing good biological performance (7). Furthermore, to the researcher's knowledge, the current work has not focused on scaffold models that mimic the morphology of the reconstructed cancellous bone as references, such as porosity level, trabecular thickness, and trabecular separation. The present study focused on Functionally Graded scaffold (FGS) and Non-functional Graded Scaffold (NFGS) based on pillar octahedron and hexagon unit cell to investigate the effect morphology on permeability using Computational Fluid dynamic (CFD).

MATERIALS AND METHODS

Morphological Measurements

First, in this study, femoral condyle right leg back bovine female with dimensions of 9 mm × 9 mm × 12 mm was reconstructed using µCT into slices of 2D images with resolutions 764 pixels × 724 pixels × 17.20874 µm and then input into the mimics research software to obtain 3D structures and cut into four layers with each dimension 3mm × 3mm, as shown in (Figure 1a). Then the morphological measurements were carried out using the open-source FIJI image J software to get the value of Tb.Th and Tb.Sp as a reference scaffold design.

Scaffold Design

In this study, each scaffold model, such as the pillar octahedron scaffold non-functional graded scaffold, is labelled (PNFGS). The Functionally Graded Scaffold is labelled (PFGS). Hexagon Non-Functional Graded Scaffold is labelled (HNFGS). The number of units cell on the scaffold is labelled (NUC). Then scaffold structure is created using commercial Computer-Aided Design (CAD) based on cancellous bone morphology such as graded porosity, trabecular thickness (Tb.Th), and trabecular separation (Tb.Sp), where the entire scaffold structure is shown in (Figure 1b).

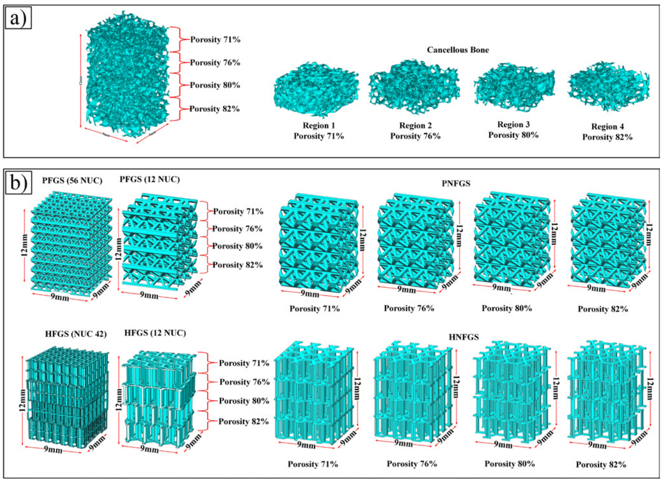

Figure 1 : Porosity distribution indicates (a). Cancellous bone **(B).** Open porous scaffold pillar octahedron and hexagon Non-functional Graded scaffold (NFGS) and Functionally Graded scaffold (FGS) with 12NUC and 42NUC.

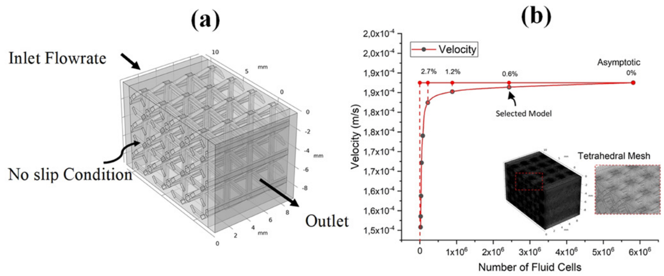

Figure 2 : Computational Fluid Dynamic. (a). Finite element boundary condition **(b).** Convergent mesh study.

Computational Fluid Dynamic (CFD)

A computational fluid dynamic is used to simulate the marrow movement through scaffold performed using COMSOL Multiphysics ® Software Burlington USA. The dynamic viscosity of the bone marrow is 0.4 Pa.s and density of 1060 kg/m^3 (8). Bone marrow was assumed to have a homogeneous fluid with an incompressible flow. During the CFD analysis, the boundary condition between fluid and solid was defined no-slip boundary. The inlet flow rate has been given with a value of 0.8 ml/min (9). The outlet was assumed to be zero pressure. The pressure drops (ΔP) are used in (equation 1) to calculate the permeability. Computational Fluid Dynamics (CFD) boundary condition is shown in (Figure 2a).

Convergent Mesh

Convergent mesh as shown in (Figure 2b) explain the effect of the number of fluid cells on the average velocity. With 2.43×10^6 fluid cells, the average velocity a satisfactory numerical convergent, with a margin of error of 0.6% when the average velocity is compared to the model with the smallest element size.

Permeability Calculation

The permeability of the various scaffolds was determined using Darcy's Law (10). Which can be formulated as follows:

$$K = \frac{Q * \mu * L}{A * \Delta P} \qquad (1)$$

Where K is the permeability in (m^2), Q is the flow rate in (ml/min), μ is the dynamic viscosity of the fluid in (Pa.s), L is the length of the sample in (mm), A is the cross-sectional area of the sample in (mm^2), and ΔP is the measured pressure drop in (Pa).

RESULTS

Morphology Analysis

Based on this study, the morphology of the uniform structure or HNFGS and PNFGS is specially designed with values close to the cancellous bone morphology, such as graded porosity, Tb.Th, and Tb.Sp from mean to maximum values are presented in (Table I) explains that the increasing porosity of Tb.Th and Tb.Sp values have the potential to decrease. So HFGS and PFGS scaffold, the value of Tb.Th and Tb.Sp is at the average value of the uniform scaffold. However, BS/TV value has a significant difference to cancellous bone. In addition, HFGS and PFGS with 42NUC and then rescaled with the same dimensions can potentially decrease the value of Tb.Th and Tb.Sp and if observed from the relationship between the porosity and BS/TV (Figure 3). Actually, BS/TV is a nonlinear function of porosity where for HNFGS dan PNFGS scaffold relationship is predicted using polynomial regression with a correlation coefficient R^2 = 0.99. It explains that with increasing porosity, we can see the optimum BS/TV value in scaffold design. Based on the exponential regression for PNFGS and HNFGS scaffold, the optimum BS/TV that can be achieved in this scaffold is 1.9 mm^{-1} with porosity 50%, while for the porosity of 71% - 82%, BS / TV is in the range of 1.1 mm^{-1} - 1.56 mm^{-1}. In addition, BS/TV for the PFGS and HFGS scaffold with 12NUC is at the average value of the uniform scaffold that is 1.396 mm^{-1} for PFGS scaffold and 1.408 mm^{-1} for HFGS scaffold than for PFGS, and HFGS scaffold with 42NUC in rescaling with same dimensions, BS/TV value increased from 2.79 mm^{-1} for PFGS and 2.81 mm^{-1} for HFGS.

Permeability Analysis

Based on the results of this study, (Figure 4a) explains the relationship between permeability and porosity

Table I : Morphological indicates of cancellous bone and bone scaffold

NUC	Model	Porosity	Tb.Th (mm)		Tb.Sp (mm)		BS/TV (mm^{-1})
			mean	max	mean	max	
-	Cb.Reg.1	71	0.215	0.438	0.668	1.509	3.910
	Cb.Reg.2	76	0.214	0.436	0.799	1.824	3.730
	Cb.Reg.3	80	0.207	0.398	0.825	1.825	3.050
	Cb.Reg.3	82	0.189	0.386	0.883	2.166	3.190
12	PNFGS	71	0.216	0.429	0.714	1.249	1.540
	PNFGS	76	0.184	0.383	0.785	1.347	1.400
	PNFGS	80	0.180	0.335	0.849	1.423	1.310
	PNFGS	82	0.161	0.316	0.882	1.499	1.250
	HNFGS	71	0.290	0.580	0.570	1.130	1.560
	HNFGS	76	0.252	0.563	0.642	1.188	1.430
	HNFGS	80	0.240	0.536	0.703	1.383	1.250
	HNFGS	82	0.224	0.474	0.761	1.339	1.190
	PFGS	77	0.185	0.366	0.808	1.380	1.396
	HFGS	77	0.252	0.538	0.669	1.308	1.408
42	PFGS	77	0.093	0.183	0.404	0.690	2.791
	HFGS	77	0.126	0.269	0.335	0.654	2.815

Cancellous bone Region : Cb. Reg
Trabecular Thickness : Tb.Th (mm)
Trabecular Separation : Tb.Sp (mm)
Bone Surface/Total Volume : BS/TV (mm^{-1})

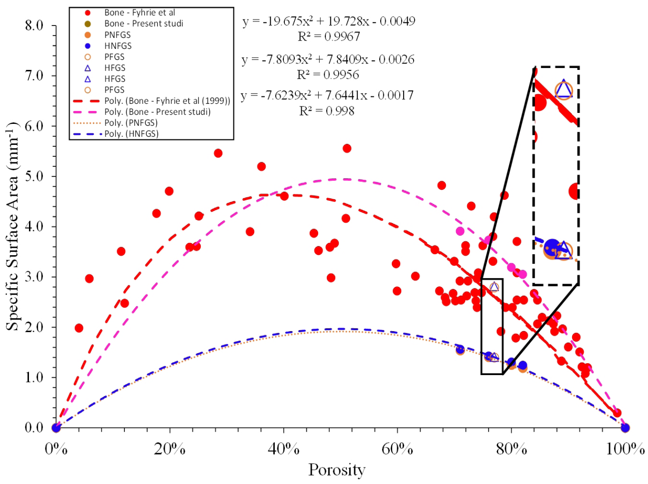

Figure 3 : Relationship between porosity and specific surface (BS/TV).

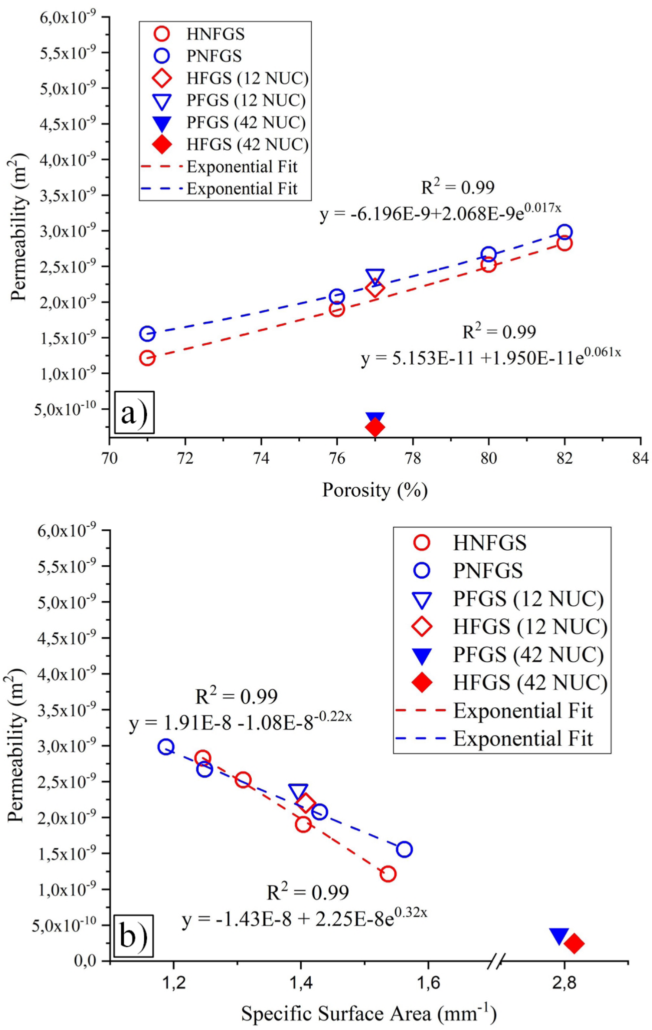

Figure 4 : Permeability analysis (a). Relationship between porosity and permeability bone scaffold **(b).** Relationship between specific surface area (BS/TV) and permeability bone scaffold.

predicted using exponential regression with a correlation coefficient $R^2 = 0.99$. This shows that porosity has a strong correlation with permeability. For HNFGS and PNFGS scaffold, increased porosity from 71% - 82% permeability value increases from 1.2×10^{-9} - 2.8×10^{-9}. For the PNFGS scaffold, permeability values are slightly greater at 1.5×10^{-9} - 2.9×10^{-9} and the permeability value of the PFGS and HFGS scaffold with 12NUC, the resulting value is the average uniform scaffold which is 2.2×10^{-9} for PFGS and 2.3×10^{-9} for HFGS. In addition, for PFGS and HFGS scaffold with 42NUC and in rescaling with the same dimensions, permeability value significantly decreased to 3.7×10^{-10} for the PFGS scaffold and 2.4×10^{-10} for the HFGS scaffold. Furthermore, (Figure 4b) shows the opposite relationship, which is predicted using exponential regression with a correlation coefficient $R^2 = 0.99$. For the HNFGS scaffold, permeability decreased from 2.8×10^{-9} - 1.2×10^{-9} with an increase in surface area from 1.2 - 1.53 mm^{-1}. For the PNFGS scaffold, permeability decreased from 2.9×10^{-9} - 1.5×10^{-9} with increasing BS/TV from 1.1 – 1.56 mm^{-1}. As for the HFGS and PFGS scaffold with 12NUC, BS/TV value is at the average value for uniform scaffold, so the resulting permeability value is the average permeability value of uniform scaffold with porosity of 71% - 82%. The influence of surface area on permeability is very significant where the scaffold PFGS and HFGS with 42NUC have the highest surface area but have the smallest permeability of the overall scaffold.

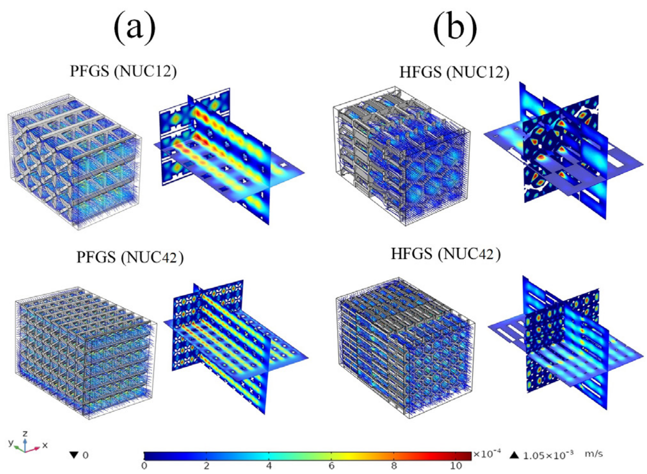

Figure 5 : Velocity streamlines porous scaffold. (a). Pillar octahedron functional graded scaffold (PFGS) with 12NUC and 42NUC **(b).** Hexagon functional graded scaffold (HFGS) with 12NUC and 42NUC.

Velocity Analysis

Based on the results of simulations, (Figure 5) describes the velocity distribution of fluid through the scaffold PFGS and HFGS with 12NUC and 42NUC. The red colour is shown as the maximum global with the value of 1.05×10^{-3} m/s and blue colour as the minimum global with a zero value. Although the flow rate and porosity used are the same, the resulting velocity distribution is different. It is seen that the HFGS and PFGS with 12NUC have a more concentrated red colour when compared to the HFGS and PFGS with 42NUC and rescaled with the same dimensions. It is observed that, the scaffold has a high maximum in the middle of the scaffold tends to have a high permeability value which means the HFGS and PFGS with 42NUC scaffold tend to have a longer time to circulate.

DISCUSSION

In bone tissue engineering, designing FGS scaffolds requires examining the hierarchical structure of the original tissue from the microbiological level to the tissue structure to recognize and utilize the relationship between structure and function to achieve the best regenerative performance. So that many studies only focused on cancellous bone morphology, such as Tb.Th, Tb.Sp, and graded porosity as references in design to achieving morphological characteristics that approach cancellous bones. Besides biomaterials, bone scaffold morphology has also been shown to have a very important role because many studies explain that mechanical integrity will significantly decrease with decreased Tb.Th or increased porosity and Tb.Sp value (11). Moreover, other morphologies such as BS/TV must also be considered so that scaffold can achieve the same morphological characteristics as cancellous bones because, based on previous studies, BS/TV is an important morphology where BS/TV is a place to facilitate protein adsorption, this protein can further stimulate osteogenic cell function, osteogenic cell adhesion, attachment, proliferation, differentiation, and biomineralization (12–14). It is known in this study that BS/TV is a nonlinear function of porosity where is comparable to the findings of Lu et al. (15). In addition, a nonlinear relationship also occurs in cancellous bones reviewed from various anatomical sites (16–18). So that BS / TV of cancellous bone can be used as a reference in designing bone scaffolds. This study uses HFGS and PFGS scaffold with the same dimensions and porosity, but the different NUC can increase BS /TV. However, Tb.Th and Tb.Sp will decrease. So, in this research from the overall morphology value has achieved the characteristics of the cancellous bone.

Furthermore, although scaffold morphology has achieved the characteristics of cancellous bones, there are requirements to achieve a suitable scaffold implant, especially permeability. Where permeability significantly contributes to supplying nutrients and oxygen to cells for survival. So, many studies focus on parameters that can actively control the permeability value. For example, the study by Reduan et al. (19) say that increasing porosity will increase the permeability value, which is comparable to this study. But in this study, increasing porosity above 50% will decrease the BS/TV value, this explains the greater porosity of the smaller fluid interaction with the scaffold surface, causing a small fluid pressure. According to Darcy's law, a low-pressure drop in the fluid is identical to a low permeability value (20). Regarding bone remodeling actually, bone structure requires a very high surface area to facilitate the attachment of cells to proliferate and differentiate so that it becomes a dense bone structure. It is also seen that the cancellous bone is a very high BS / TV value. Therefore, the morphology of healthy cancellous bones needs to be used as a reference in the implant scaffold design to see the range of Tb.Th and Tb.Sp value that nutrients and oxygen can pass through. So that we can control BS/TV in the range of cancellous bones with Tb.Th and Tb.Sp as a reference because it is known that controlling BS/TV can affect the value of Tb.Th and Tb.Sp. According to Van Bael et al. (21) the efficiency of seeding cells can be increased depending on many surfaces to facilitate cells attachment and the time available for cells to interact on the scaffold surface. Impens et al. (22) also explaining that small permeability value on the scaffold will increase the efficiency of seeding cells, this is logical because studies have shown that increasing BS/TV value on HFGS and PFGS scaffolds with 42NUC very significant decreases the permeability value and, when viewed from the velocity distribution of fluid in this research, the velocity value tends to be lower so these scaffolds can give longer time for the fluid through the scaffold. Therefore, the velocity distribution is another indicator for evaluating mass transport properties (23).

In this study, researchers assessed that HFGS and PFGS scaffold with 12NUC and uniform scaffold seen from permeability values do not show a unique correlation where HFGS and PFGS scaffold with 12NUC is very logical if permeability values are at the average value of uniform structure which is above 76% but below 80% because the average porosity is 77% and it is known that permeability is directly proportional to porosity. So in this study, scaffold structure was designed based on the morphology of cancellous bone such as graded porosity, Tb.Th, Tb.Sp, and BS/TV, the overall permeability value of the scaffold compared with previous studies on the cancellous bone (24–26). Presented in (Figure 6) explains the permeability of the scaffold in this study has been in the range of natural cancellous bone. In addition, if it is observed from the different permeability values of the FGS scaffold from each layer, which can be seen through the results permeability of the

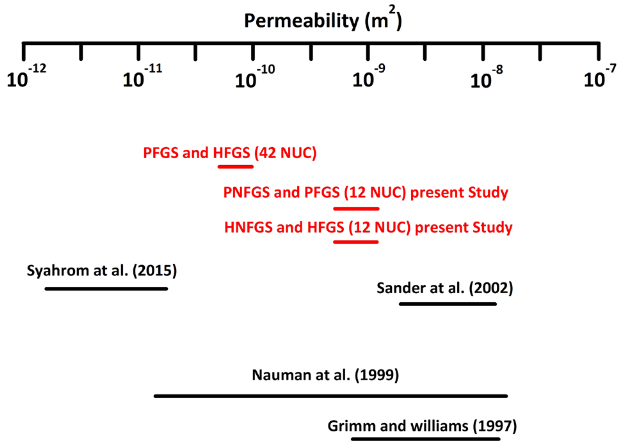

Figure 6 : Comparison permeability porous scaffold present study and cancellous bone.

uniform scaffold in this research that porosity increases, permeability increases. Based on the result from Ouyang et al. (27) explain the highest permeability value resulting in the lowest bone growth. The researcher argues that graded porosity in cancellous bone aims to adjust the remodeling to a smaller porosity at the optimum surface area. When bone tissue has sufficient density, porosity and specific surface area decreases, the cells attached to the structure also decrease (28). So that the remodeling activity will move towards the porosity which has a larger surface area. The researcher concludes that if you use a uniform scaffold as a scaffold, the remodeling process is not well distributed.

CONCLUSION

Based on this study, the researchers concluded that in HNFGS and FNFGS scaffold (uniform) with 12NUC porosity strongly correlates with permeability where increasing porosity will increase permeability value. When viewed on the scaffold PFGS and HFGS with 12NUC do not show a unique correlation where the permeability value is proportional to the porosity level. However, PFGS and HFGS scaffold with 42NUC, the porosity is the same, but the permeability tends to be small. This is because the difference between 12NUC and 42NUC greatly affects BS / TV value. And then the increase in the BS / TV value, the permeability value decrease. So that in developing bone scaffold design, controlling NUC, it can get BS / TV values to achieve the characteristics of cancellous bone morpohology. If globally viewed, the overall permeability value of the scaffold has been in the cancellous bone range. It can be concluded that scaffold designed has fulfilled the requirements for the ideal scaffold because permeability value the overall scaffold in the range of the cancellous bone.

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