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Original article

# Degradation rate and weight loss analysis for freeze-dried, decellularized, and deproteinized bovine bone scaffolds

**Ramadhan Pramudya Vidarta[1,2], David Buntoro Kamadjaja[3], Coen Pramono Danudiningrat[3], Muhammad Subhan Amir[3], Andra Rizqiawan[3], Anita Yuliati[4], Darmawan Darwin[5]**
[1]Magister Program of Clinical Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[2]Resident of Oral and Maxillofacial Surgery, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia
[3]Department of Oral and Maxillofacial Surgery, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia
[4]Department of Dentistry Materials Science, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia
[5]Research Center for Radiation Process Technology Research Organization for Nuclear Energy, National Research and Innovation Agency, Indonesia

***ABSTRACT***
***Background:*** *Mandibular defects, often caused by trauma, tumors, infections, and congenital issues, are commonly treated with bone grafts. Tissue engineering plays a crucial role in bone reconstruction, with scaffolds such as deproteinized bovine bone matrix (DBBM), freeze-dried bovine bone (FDBB), and decellularized FDBB (Dc-FDBB) being studied for their efficacy. Decellularization reduces the antigenic potential of FDBB. These scaffolds are designed to degrade within the body.* ***Purpose:*** *To analyze the weight loss and degradation rates of FDBB and Dc-FDBB materials, using DBBM as a control.* ***Methods:*** *This in vitro experimental study, conducted over 2 months, employed a cross-sectional approach to analyze the weight loss and degradation rates of FDBB, Dc-FDBB, and DBBM scaffolds in a simulated body fluid (SBF) solution.* ***Results:*** *Under dynamic immersion conditions, DBBM exhibited the highest daily weight loss at 0.741% and a degradation rate of 0.466 mg/cm$^2$/day, followed by Dc-FDBB at 0.568% and 0.418 mg/cm$^2$/day and FDBB at 0.525% and 0.385 mg/cm$^2$/day. Under static immersion conditions, DBBM also showed the highest weight loss at 0.255%, with a degradation rate of 0.165 mg/cm$^2$/day, followed by Dc-FDBB at 0.245% and 0.163 mg/cm$^2$/day, and FDBB at 0.168% with a degradation rate of 0.126 mg/cm$^2$/day. Significant differences were observed between scaffold groups (p = 0.000).* ***Conclusion:*** *DBBM, Dc-FDBB, and FDBB scaffolds meet the optimal requirements for tissue engineering materials based on their weight loss and degradation rates. DBBM demonstrated the highest values among the scaffolds analyzed.*

**Keywords:** *biomaterial; DBBM; Dc-FDBB; FDBB; maxillofacial defect; scaffold; tissue engineering*
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Correspondence: David Buntoro Kamadjaja, Department of Oral and Maxillofacial Surgery, Faculty of Dental Medicine, Universitas Airlangga, Jl. Prof. Dr. Moestopo 47 Surabaya, 60132 Indonesia. Email: david-b-k@fkg.unair.ac.id

## INTRODUCTION

Bone grafts are crucial in treating large bone defects caused by various factors such as trauma, tumors, infections, congenital defects, and compromised regeneration.[1,2] These defects, especially in the maxillofacial region, can impact appearance, masticatory, and speech functions, requiring the use of bone grafts for repair.[3,4] All these facts emphasize that large bone defects remain a challenge for maxillofacial surgeons.[1] Bone grafts are defined as materials implanted to heal bone defects, either alone or in combination with other materials, through the processes of osteogenesis, osteoinduction, and osteoconduction. Bone grafts are classified into autografts, allografts, and xenografts, each with advantages and disadvantages. The selection of the ideal graft depends on factors such as tissue viability, defect size, and biomechanical characteristics.[5,6]

Tissue engineering in bone reconstruction, involving scaffolds, cells, and growth factors, has gained attention in recent years for facilitating cell migration, binding, and tissue regeneration.[7,8] One example of a natural scaffold material is derived from animals.[9] Natural scaffold materials, such as bovine bone, are being explored as safe alternatives to address limitations in autogenous bone supply, donor morbidity, and immunological reactions in bone tissue engineering.[10] Some communities prefer bovine-derived

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materials for religious reasons. Additionally, the advantages of bovine biological properties are often prioritized over those of metal-based biomaterials.[11,12]

One type of bovine bone used as a biomaterial scaffold is the deproteinized bovine bone matrix (DBBM), which is prepared through a deproteinization process using high temperatures. This process removes all organic components of the bone while keeping its architecture intact. The primary differences between bovine bone matrix and bovine bone lie in their structural and biochemical properties, which influence their suitability and effectiveness for various types of bone defects. DBBM is slowly degradable, has high mechanical strength and clinical stability, and is, therefore, commonly used as a bone substitute for alveolar bone augmentation. DBBM is the most widely used material on the market.[13]

The similarity between bovine bone matrix and human bone lies in their structural and chemical resemblance, as both are composed of hydroxyapatite carbonate and type I collagen. This similarity makes DBBM effective for bone grafting and regeneration. Its use in medical and dental applications leverages this resemblance to provide support and scaffolding for new bone growth.

Another scaffold material is bovine bone processed by freeze-drying or lyophilization, referred to as freeze-dried bovine bone (FDBB) xenograft. The lyophilization process reduces antigenic potential, retains organic components, maintains the natural structure of bones, and produces calcium and phosphate crystals.[14] The FDBB scaffold is further decellularized to remove any remaining cells and DNA, eliminating the immunogenic risk after implantation. This process results in the decellularized FDBB (Dc-FDBB) scaffold.[15]

A scaffold is a 3D structure used as a temporary replacement for a damaged natural extracellular matrix (ECM), functioning as a site for attachment, anchoring, proliferation, migration, and differentiation of bone cells, as well as tissue regeneration.[16] An ideal bone scaffold must exhibit excellent biocompatibility, good biodegradability, appropriate mechanical and compressive strength, and sufficient porosity.[16] The scaffold in tissue engineering must also be degradable, allowing it to be broken down and eliminated from the body through natural processes. Degradation is influenced by various factors, including the structure and molecular weight of the component materials and the anatomical location where the scaffold is implanted.[17] The scaffold must degrade completely into non-toxic products. Additionally, the degradation rate must be appropriate to maintain its mechanical structure to support cell growth.[18]

The degradation test is a material solubility test, generally indicated by a change in weight and the detection of calcium and phosphorus ions after sample immersion. The sample immersion method can be performed statically or dynamically using scaffold materials.[19] The static immersion method, conducted in a synthetic solution that simulates the inorganic components of blood plasma, is an easy and straightforward approach for testing the stability of materials in the body. In contrast, the dynamic immersion method involves immersing the material in a constant flow rate, representing daily physiological activity, to simulate the bone marrow flow rate.[20]

In this study, in vitro experiments were conducted to analyze the weight loss and degradation rates of FDBB, Dc-FDBB, and DBBM scaffolds using static and dynamic immersion methods as part of the requirements for ideal scaffold properties.

## MATERIALS AND METHODS

In vitro experimental research was conducted for 2 months, between August and September 2022. This research was an experimental study comparing the degradation rates of FDBB and Dc-FDBB scaffolds and the control DBBM scaffold using static and dynamic immersion in a simulated body fluid (SBF) solution. SBF is an artificial solution used for its composition and ionic concentration, which are

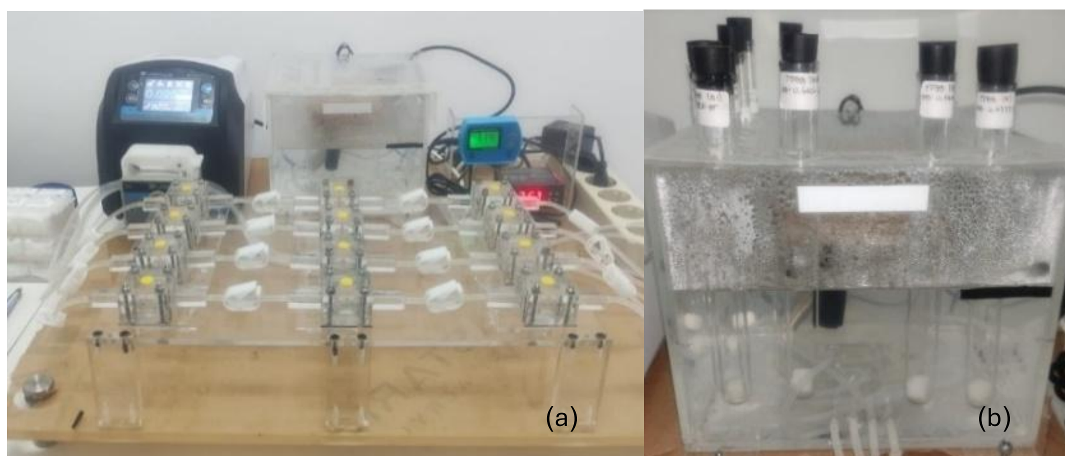


**Figure 1.** Immersion experimental rig: (a) Dynamic and static immersion experimental rig, (b) Water bath for static immersion and simulated body fluid.

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almost identical to human blood plasma. It has bioactive properties that can be maintained under mild pH conditions and physiological temperatures.[21] Based on the sample size calculation, the minimum number of samples for each group was at least three. The independent variable in this study was the type of scaffold material, while the dependent variables were scaffold weight loss and scaffold degradation rate. This research was conducted at the Research Center of the Faculty of Dental Medicine, Universitas Airlangga, after obtaining permission and an ethical certificate with letter number 180/HRRC.FODM/IV/2022.

All samples in this study were DBBM, FDBB, and Dc-FDBB scaffolds, which were ordered and processed at the Dr. Soetomo Hospital Tissue Bank, Surabaya. The samples were then cut into blocks measuring approximately 10 x 10 x 10 mm. Before testing, the scaffold blocks were weighed on a digital scale (Ohasuss® Pioneer Digital Analytical Balance) to determine their initial weight. Samples for the dynamic immersion method were placed in a chamber in a series of immersion experimental rigs during the testing phase, as shown in Figure 1.

In the dynamic immersion method, a Smart Peristaltic Pump (Lead Fluid® BT 101L, Smart Flow Peristaltic Pump, flow rate 0.00011–720 ml/min) is prepared and set at a constant flow rate of 0.025 ml/min to resemble the range of trabecular bone marrow flow rates. A volume of 500 ml of SBF fluid, maintained at a temperature of 37°C ± 1°C and a pH of 7.4, is flowed through the scaffold test chamber via a silicone hose to simulate the physiological conditions of body fluids.

In the static immersion test, the scaffold block samples were placed into the SBF liquid, which had a pH of 7.4 and was contained in a 10 ml test tube. The temperature of the SBF liquid was also maintained at 37°C ± 1°C in the water bath.

Degradation tests were conducted by immersing the material in both static and dynamic conditions. After immersion, the samples were dried using the vacuum freeze-dry method at –40°C for 24 hours. The weight of each sample was measured with a digital scale and recorded before being returned to the chamber or test tube on the first, third, and seventh days after immersion. The percentage of weight loss was calculated as the difference between the initial mass and the residual mass on a given day of observation, using Equation 1:

$$\Delta W\% = \frac{W_0 - W_i}{W_o} x100$$

$W_o$ is the initial weight of the scaffold, and $W_i$ is the weight after immersion. This was followed by calculating the rate of scaffold degradation using Equation 2:

$$\Delta Wm = \frac{W_0 - W_i}{AT}$$

The scaffold degradation rate ($\Delta W_m$) was calculated by dividing the difference in weight by the surface area (A) and the immersion period (T).[21] All data obtained were recorded for statistical analysis.

All statistical analyses were performed using SPSS version 26.0 (IBM, Armonk, NY, USA). The research data were tested for normality using the Shapiro–Wilk test and expressed as mean ± SD. Levene's test was used for the homogeneity test. The Kruskal–Wallis test was then carried out to determine differences in degradation rates between groups and was considered statistically significant at $p < 0.05$.

## RESULTS

Dynamic and static immersion methods were conducted on all types of scaffolds, with observations on the first, third, and seventh days of immersion. The weight loss of each scaffold was calculated as a percentage for each observation day using Equation 1, followed by calculating the average. The average percentage of weight loss per day is presented in Table 1. The data indicate a substantial average weight loss for the scaffolds. DBBM showed the highest average percent weight loss per day during observations, followed by FDBB and Dc-FDBB, both in dynamic and static immersion. The data also show an increase in weight loss for the scaffolds with each day of observation, as illustrated in the graph in Figure 2.

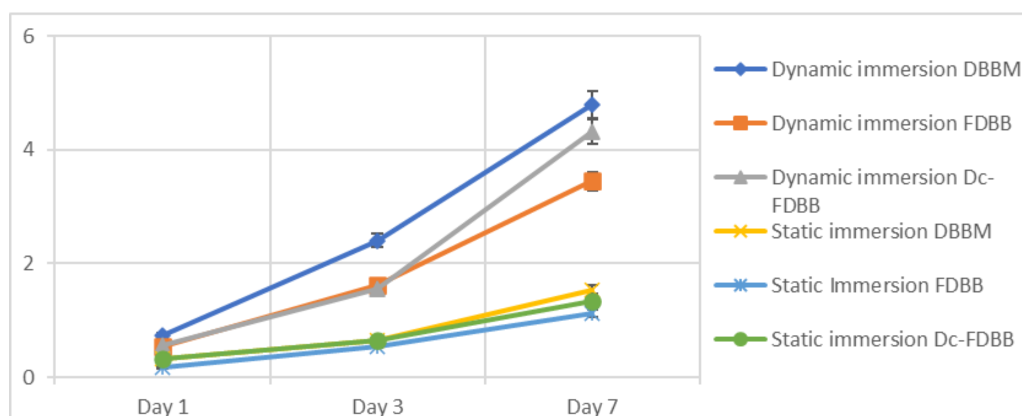


**Figure 2.** Graph of scaffold weight loss on each day of observation.

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The scaffold degradation rate was calculated using Equation 2. Similar to the average percentage of scaffold weight loss per day, the results of the dynamic and static scaffold immersion tests showed that the average DBBM degradation rate was the highest, followed by Dc-FDBB, with FDBB being the smallest. The results of the average scaffold degradation rate showed a large difference of up to four times between dynamic and static immersion. The average value of the degradation rate for each scaffold from each immersion test method is presented in Table 2.

The results of the immersion test for each group were normally distributed, as confirmed by the Shapiro–Wilk normality test ($p > 0.05$). The results of the Levene test on the scaffold degradation rate data showed that the significance value ($p < 0.05$) for FDBB indicated that the data were not homogeneous (heterogeneous).

The difference in degradation rates between groups in immersion (DBBM, FDBB, and Dc-FDBB) was analyzed using the Kruskal–Wallis test, which showed a significant difference in each group ($p = 0.000$), as presented in Table 3. It was concluded that there was a significant difference between the scaffold groups tested. To determine the differences in more detail between groups, the Mann-Whitney test was carried out, which showed a significant comparison between treatment groups ($p < 0.05$). The Mann–Whitney test results are shown in Table 4. Overall, there was a significant difference in the scaffold degradation rate values tested using static and dynamic immersion methods.

## DISCUSSION

The bone scaffold material must meet the scaffold requirements, including providing a temporary structure that will later degrade as new tissue forms within a certain period.[21] The rate of degradation must align with the rate of new bone formation so that when bone regeneration is

**Table 1.** Average percentage of scaffold weight loss per day

| Immersion method | Scaffold type | Average weight loss/day in % | ± SD |
|---|---|---|---|
| Dynamic | DBBM | 0.741 | 0.049 |
| | FDBB | 0.525 | 0.079 |
| | Dc-FDBB | 0.568 | 0.064 |
| Static | DBBM | 0.255 | 0.071 |
| | FDBB | 0.168 | 0.031 |
| | Dc-FDBB | 0.245 | 0.061 |

**Table 2.** Scaffold degradation rate values in static and dynamic immersion test

| Immersion method | Scaffold type | Average degradation rate in $mg/cm^2/day$ | ± SD |
|---|---|---|---|
| Dynamic | DBBM | 0.466 | 0.0423 |
| | FDBB | 0.385 | 0.1029 |
| | Dc-FDBB | 0.418 | 0.0834 |
| Static | DBBM | 0.165 | 0.0477 |
| | FDBB | 0.126 | 0.0187 |
| | Dc-FDBB | 0.163 | 0.0440 |

**Table 3.** Kruskal–Wallis test results data on scaffold degradation rate values

| Scaffold | DBBM | FDBB | Dc-FDBB |
|---|---|---|---|
| Kruskal–Wallis H test | 12.789 | 12.816 | 12.789 |
| Df | 1 | 1 | 1 |
| Asymp. Sig. | 0.000* | 0.000* | 0.000* |

* Significance $p < 0.05$

**Table 4.** Mann–Whitney difference test results for static and dynamic immersion

| Immersion | | DBBM | | FDBB | | Dc-FDBB | |
|---|---|---|---|---|---|---|---|
| | | Dynamic | Static | Dynamic | Static | Dynamic | Static |
| DBBM | Dynamic | | | | | | |
| | Static | 0.000* | | | | | |
| FDBB | Dynamic | 0.102 | 0.000* | | | | |
| | Static | 0.000* | 0.057 | 0.000* | | | |
| Dc-FDBB | Dynamic | 0.354 | 0.000* | 0.508 | 0.000* | | |
| | Static | 0.000* | 0.825 | 0.000* | 0.057* | 0.000* | |

* Significance $p < 0.05$

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complete, the scaffold material has fully degraded. The rate of degradation is influenced by hydrophilic properties, chemical composition, degree of crystallization, and scaffold geometry.[22]

Scaffold degradation occurs in a biological environment where water plays an important role, specifically by causing a reduction in scaffold mass.[23] Bone marrow moves in a fluid medium with a certain flow rate due to pressure differences from mechanical load cycles during biological activity. Bone marrow functions both as a medium for cell regeneration and as a source of nutrition for bones. The hydrolysis process, in which water contributes to scaffold degradation, is replaced by bone marrow movement in a fluid medium. In this study, SBF fluid was used as a substitute or simulation of bone marrow fluid in bones.[24]

In this research, the results showed that DBBM was the type of scaffold that experienced the most weight loss, followed by Dc-FDBB. FDBB was the type of scaffold that experienced the least weight loss during the immersion process. The standard time required for a scaffold to degrade can be considered good if it exceeds 10–14 days.[25] Other studies mention a minimum degradation time of 1–2 weeks, which is when bone repair begins with the elimination of damaged cells and replacement of the weak fibrin clot with a mechanically stronger structure, commonly called callus.[26] Degradation, in the form of weight loss or a decrease in scaffold mass, should neither be too slow nor too fast and should align with the bone remodeling process, typically lasting 3–6 months.[27,28]

Bio-Oss® Collagen graft composite xenograft scaffolds degraded by 99.3% and 99.1% within one year.[29] Other commercial xenograft scaffolds, such as InterOss® Collagen and OCS-B Collagen®, degrade within 3–6 months.[30]

The results of static and dynamic immersion tests of the scaffold showed that the degradation rate of DBBM had the highest average value, followed by Dc-FDBB. The FDBB scaffold had the lowest value of all the scaffolds tested. The rate of scaffold degradation is interrelated with the permeability, porosity, and mechanical durability of the structure. The degradation rate increases with higher permeability and porosity but decreases with greater mechanical durability of the scaffold structure.[31] According to research conducted by Yulianani et al.,[32] DBBM has the highest permeability value. In distilled water media, the average permeability levels of Dc-FDBB, FDBB, and DBBM scaffolds were $3.57 \times 10^{-10}$, $3.59 \times 10^{-10}$, and $3.7 \times 10^{-10}$, respectively.[32]

Permeability also depends on the thickness, strength, and ability of the scaffold to diffuse through the pores, which is influenced by the modulus of elasticity. Scaffolds with high stiffness, porosity, and large pore sizes can result in high permeability.[33] The permeability value is affected by the degree of porosity, which in turn influences the supply of nutrients, highlighting the relationship between permeability and mechanical strength. This is crucial for achieving optimal performance from an ideal scaffold structure.[34,35]

Pore size plays an important role in scaffold degradation, as greater porosity leads to higher permeability, ultimately resulting in faster degradation. Other parameters, such as pore homogeneity, morphology, and pore size, also affect the degradation of porous biomaterials.[36] Porosity is the percentage of pores within a volume of material. Relevant to this paper, research by Purba[37] found that the average porosity of DBBM showed the greatest results, at 69.194% ± 1.447, followed by Dc-FDBB at 66.712% ± 3.192 and FDBB at 62.310% ± 0.522. Meanwhile, pore size measurements revealed that the largest pores were in the DBBM group, at 511 ± 58 μm, followed by Dc-FDBB at 450 ± 31 μm and FDBB at 412 ± 12 μm. Commercial xenografts such as InterOss® Collagen and OCS-B Collagen® have porosities of 79.8% ± 0.4 and 82.8% ± 0.8, respectively.[30]

Micropores and porosity are important factors affecting the rate of scaffold degradation. Increasing the number of micropores and porosity causes a faster degradation rate because the scaffold is degraded by a dissolution process that occurs easily at the open micropore boundaries.[38] Scaffold pores must not be too large to prevent the formation of a layer of cells and epithelial cells slipping through; however, they must have a hydrophilic surface to increase cell adhesion while being large enough to allow vascular infiltration and angiogenesis.[39] Larger scaffold pore sizes ensure a good supply of nutrients but reduce the surface area for cell attachment and mechanical properties. Increased pore size enhances osteogenic and osteoblastic potential.[40]

Degradation, as well as mechanical and biological properties, is extensively controlled by manufacturing parameters, mixing methods, sources of raw materials, and the final form of scaffold products, such as powders, granules, pastes, and 3D scaffolds.[41] DBBM is made through a deproteination process conducted at a temperature of 1000°C, resulting in a high degree of porosity.[42,43] Removing organic and inorganic hydroxyapatite residue provides high pore connectivity, which influences the permeability value.[44] Large porosity can enhance osteogenesis but exponentially decreases mechanical strength and causes premature scaffold degradation.[45–47]

FDBB is processed at –80°C, which affects the rigidity and permeability of the scaffold, allowing for large deflections and low levels of stiffness that can influence the permeability of the scaffold.[48,49] The process for making Dc-FDBB consists of a decellularization process with 0.5% sodium dodecyl sulfate for 24 hours, which dissolves the cytoplasm, damages cell membrane proteins, removes glycosaminoglycans, causes water loss, and affects the matrix structure, increasing the porosity of Dc-FDBB. This is followed by freezing and drying processes.[50] The FDBB still contains protein. This is in accordance with Oftadeh et al.,[51] who state that the porosity of cancellous bone is in the range of 50%–90%, and with Fatihhi et al.,[52] who

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report the porosity of cancellous bone to be in the range of 45.5%–72.7%.

Degradation analysis is important to consider in the manufacture of biomaterials for bone regeneration applications to determine whether the material will degrade along with the formation of new bone in the bone remodeling cycle.[53] If a material is to be produced with a rapid rate of degradation, the initial porosity must not be too high, as rapid erosion of the scaffold can negatively impact the mechanical and structural integrity of the implant before it is replaced with newly formed bone. On the other hand, if a low biomaterial degradation rate and high mechanical strength are desired, the high percentage of cavities in the scaffold due to the presence of interconnected channels and pores may be one of the main reasons for accelerated degradation due to macrophages (via enzymatic lysis) and/or hydrolysis.[40]

The value of the degradation test, either from weight loss or scaffold degradation rate in the two immersion methods, both static and dynamic, showed a significant difference in statistical tests. The scaffold degradation test in the dynamic immersion method showed results that were four times greater or faster than those in the static immersion method. This is consistent with research conducted by Saad et al.,[19] where in the degradation test on the Mg alloy scaffold, the dynamic immersion method yielded results seven times greater than static immersion. Immersion remains the main standard for corrosion and degradation testing of scaffold materials.

In contrast to static immersion, where the SBF fluid is only brought close to the scaffold surface, dynamic immersion simulates the movement of bone marrow fluid through porous structures in cancellous bone. The interaction between moving bone marrow and cancellous structures induces mechanobiological mechanical stresses to the bone. Bone marrow movement in the cancellous bone can be considered the true limit for scaffold degradation testing.[20]

The limitation of this research is that it did not use more advanced measuring tools, such as MicroCT, to study the shape and structure of degraded scaffolds, which could provide data and values with higher accuracy. Nevertheless, degradation testing using static and dynamic methods remains the main standard in biomaterial degradation testing.

The degradation rate between DBBM, Dc-FDBB, and FDBB scaffolds showed significant differences, with DBBM having the highest value, followed by Dc-FDBB and FDBB. Scaffold degradation in this study is estimated to occur within 5–7 months based on weight loss and degradation rate. This does not show any significant differences compared with other scaffold materials that have been marketed and tested. Thus, it can be concluded that the DBBM, FDBB, and Dc-FDBB scaffolds have good potential and optimal degradation properties, meeting the requirements for bone tissue engineering materials.

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