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ORIGINAL ARTICLE

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Fabrication of Hydroxyapatite blended cyclic type Polylactic Acid and Poly (ε-Caprolactone) Tissue Engineering Scaffold

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Abstract

The ultimate goal of tissue engineering serves to repair, restore damaged tissue or organ due to accident or disease. In this research, we are aimed at investigating the feasibility of processing cyclic type polylactic acid (PDLLA)/poly(ε-caprolactone) (PCL)/hydroxyapatite (HA) biomaterial into tissue engineering scaffold (TES) with variable mechanical properties, well interconnected pore architecture, and controlled hydrophilicity. For this, an in-house built bone scaffold 3D printing (BS3P) system was applied to two biomaterials, namely PDLLA-PCL and HA-PCL. These two biomaterials were produced by optimizing the robotic control system. Morphological investigation by scanning electron microscope (SEM) revealed both TES formed by new materials able to show honeycomb-like architectures, excellent fusion at the filament junctions, high uniformity, complete interconnectivity, and controlled channel characteristics of the TES. Compression tests align with the typical behavior of a porous material undergoing deformation. In vitro cell culture study and confocal laser microscopy (CLM) showed enhanced cell adhesion, proliferation, and extracellular matrix (ECM) formation. The results demonstrated the eligibility of the BS3P system to produce TES, and the suitability of the new biomaterial scaffolds in enhancing cell biocompatibility.

KEYWORDS

3D printing, biopolymer, cell biocompatibility, hydroxyapatite, poly(ε-caprolactone), tissue engineering scaffold

1 | INTRODUCTION

Tissue engineering (TE) is a multidisciplinary field that involves the principles of engineering, material and medical sciences. The aims for the TE approach are to restore, repair or regenerate damaged tissues by seeding desired cells onto scaffolds for plantation.[1,2] The tissue engineering scaffolds (TES) provide a necessary support for the cells to attach, proliferate and form extracellular matrix (ECM).[2]

Bone is an important organ of the human body which gives structural support and shapes while providing protection, hematopoietic, calcium storage, metabolism and itself has the ability to regenerate and self-repair.[3] Defects in bone tissue such as fractures (may be caused by osteoporosis), trauma, disease, and congenital disorders represent an important essence for health care systems universally. Recently, bone regeneration has garnered extensive concern in the whole world and developed rapidly. Therefore, the usage of three-dimensional (3D) printed biomaterials for bone regeneration applications have gained increasing attention. The successful fabrication of 3D printed biomaterials is a vital factor in determining whether the materials are suitable as bone substitute.[4] Advanced technique in 3D printing has been used to develop TES including multi-

nozzle deposition manufacturing,[5] robocasting,[6] desktop robot based rapid prototyping (DRBRP) system[7] and pressure-assisted microsyringe technique.[8]

A promising TES should possess an interconnected porous structure to provide sufficient space for cells' uniform distribution and the delivery of oxygen and nutrients, as well as partly mimic the topology and biological functions of the ECM. Besides high porosity, the TES also should have good biocompatibility and osteoconductivity as it should be absorbable and can be replaced gradually by newly formed bone tissues.[4] Due to the critical success rate of TE for industrial scale manufacturing, the development of polymer and ceramic blended composite scaffolds are being developed to enhance mechanical performance, and to improve cell-material interaction on the TES.

Poly(ε-caprolactone) (PCL) is semi-crystalline aliphatic polyester with, good biocompatibility sustained biodegradability and excellent mechanical properties. However, PCL has drawbacks on its bioregulatory activity, hydrophobicity, neutral charge contribution and susceptibility to bacteria-mediated degradation.[9] Polylactide acid (PDLLA) is thermoplastic polymers which is known for its high elastic modulus, low T_g and its shape memory ability makes it eligible in 3D printing for medical application.[10] Thus, the properties and ability of PDLLA is possible to be improve by crosslinking, chemical modification and addition of copolymers.[10] Hydroxyapatite (HA) is a bioceramic material and the most important calcium orthophosphate in natural environment[11] which mimics intrinsic bone minerals with good biocompatibility, osteoconductivity and osteoinductivity. Its great features are due to its existence in the form of minute crystals as the main mineral component in bone tissue.[11] Combining natural and synthetic polymers/biopolymers enhance the advantages of each materials in achieving a promising scaffold feature with proper porosity, biodegradable rate and mechanical properties.[12] Therefore, incorporating HA in PCL and PDLLA is one of the best approach for bone TE.

The previous work done by Chern et al[13] fabricated the PCL scaffold using solvent casting/salt leaching method. The scaffold produced has a porosity of 88.1% and compressive modulus of 0.22 MPa. In comparison, the study done by Patrício et al[14] has fabricated the PCL scaffold using BioCell Printing method which is a new 3D printing technology for biomaterial. The PCL scaffold fabricated this way has possessed a compressive modulus of 18.7 MPa. The porosity of the scaffold is not stated in the report. By comparing both of these methods, 3D printing technology can fabricate a scaffold with higher mechanical properties and this can be taken as a reference for future work that dealing with fabrication of scaffold. Other than that, Williams et al[15] was able to produce PCL scaffold using selective laser sintering method that has porosity ranged from 0% to 79%. The highest elastic modulus of 122 MPa is possessed by the scaffold with 0% porosity. Another study that used selective laser sintering method has been carried out by Yeong et al[16] has produced a PCL scaffold with 88.5% porosity and 2.62 MPa tensile yield strength.

In this work, we investigated PCL blended biopolymer with cyclic type PDLLA (namely PDLLA-PCL) and HA blended biopolymer with PCL (namely HA-PCL) in processing into TES with reproducible and interconnected porous architecture by in house build bone scaffold 3D printing (BS3P) system. Morphological and mechanical properties of fabricated scaffolds were investigated. Besides we also presented results of cell culture studies with bone marrow stromal cells (BMSCs) which justify the potential use of these new biocomposite materials scaffolds for bone TE applications.

2 | MATERIALS AND METHODS

Poly(ε-caprolactone) (PCL) (Mn ~45 000), PDLLA (Mn ~30 000) and HA (particle size 10-40 μm) were obtained from Sigma Aldrich. Mixing ratio for biomaterials were listed in Table 1. For the fabrication of HA-PCL blended TES, 10 wt% HA was melt blended with 90 wt% PCL, while for the PDLLA-PCL, 10% PDLLA was melt blended with 90% PCL. Biocomposites were produced by mixing the chosen amount of biopolymer/HA into the selected ratio and leaves it for long stirring hour (up to 4 hours) through magnetic stirrer on hot plate of 160°C.

To fabricate the TES, each material was plotted into 0-90 single-angle architecture. 0-90 single-angle architecture was developed by plotting fibers at a specific angle −90° between two successive layers throughout the TES unit. In order to optimize the process using selected polymers, we have been varied parameters like nozzle size and filament distance (1.0 mm, and 1.5 mm). Fabrication parameters for both composites were listed in Table 2. All the scaffolds were built on a flat plastic platform ($50.0 \times 50.0 \times 5.0$ mm^3) and removed upon fabrication. Fabricated TES were cut (eg, $6 \times 6 \times 5$ mm^3) for further analyses. BS3P system which was previously used in the study done by Hoque et al[17] was employed to fabricate

TABLE 1 Composition of biomaterials for TES fabrication

	Matrix biomaterials (wt%)		
TES	**PCL**	**PLLA**	**HA**
PDLLA-PCL	90	10	0
HA-PCL	90	0	10

TABLE 2 Table showing the optimization of scaffold strut deposition for PDLLA-PCL and HA-PCL

TES	Liquefier temperature/°C	Extrusion pressure/kPa	Deposition speed/(mm/s)
PDLLA-PCL	75	300	6
HA-PCL	75	300	3

TES. These three translational movements have positioning accuracy of 0.05 mm and a minimum step resolution of 0.01 mm.[18] The geometric data can be generated by 3D computer model to generate sliced layers. Based on the data generated, suitable scaffolds can be built layer-by-layer. Each 2D sliced layer is composed of filaments with user-defined lay-down angle (θ), filament gap (G), filament diameter (D), and filament distance (L).

2.1 | Morphology study by scanning electron microscope

Scaffolds morphologies were observed under environmental scanning electron microscope (ESEM) (FEI Quanta 400F) at a current of 60-90 mA and voltage of 15 kV. Influences of design, biomaterials composition and cell behaviour on the TES were studied by observing exterior and interior (cross-sectional views) of the TES.

2.2 | Mechanical properties of tissue engineering scaffold

The mechanical characteristics of the TES were investigated via uniaxial compression test. Compression tests were performed to investigate the influences of TES materials effect on their mechanical properties. Samples (n = 6) were tested using a uniaxial testing machine (Instron 4502, Norwood, MA) with 10 kN load-cell (Canton, Norwood, MA) adopting the guidelines for compression testing of acrylic bone cement set in ASTM F451-99a.[7,14,19] TES were subjected to compression forces in X-, Y-, and Z-directions at a constant crosshead speed of 1 mm/min until 60% strain level.

2.3 | Bone marrow stromal cells isolation, culturing and seeding

Bone Marrow Stromal Cells (BMSCs) were separated from red blood cells by adding the sample onto Ficoll-paque layer in a tube and centrifuged at 1008 *g* for 30 minutes. Isolated cells were washed twice using phosphate buffered saline (PBS) (Gibco-Invitrogen, Carlbad, CA) before seeding. BMSCs were differentiated to osteoblast lineage in osteogenic medium. The osteogenic medium contains DMEM/Ham F12 medium (GIBCO, Invitrogen Co., NY), supplement with antibiotic (GIBCO), glutaMAX-1 (GIBCO), 10% fetal bovine serum (FBS) (GIBCO), 50 μg/mL L-ascorbic acid (Sigma-Aldrich CO., St. Louis, MO), 0.02 M HEPES buffer (GIBCO) 10 mM β-glycerolphosphate (Sigma-Aldrich CO), 10^{-8} molar dexamethasone (Sigma-Aldrich) and cultured in six-well plate. After the cells reach 80% of confluence, the cells were trypsinized using the 0.05% Trypsin-EDTA (Mediatech Cellgro) for cell expansion. At 80% confluence, cells were trypsinized and seeded onto the scaffold. Prior to cell seeding, the TESs ($5.0 \times 5.0 \times 5.0$ mm^3) were washed 3 times in sterile Dulbecco's Phosphate-Buffered Saline (DPBS) and sterilized using graded concentrations of ethanol. The TESs were freeze-dried for 24 hours and rehydrated in complete culture medium for 2 hours.[20,21] These scaffolds were introduced into 24 well plate and seeded with cell density of 1×10^5 cells/scaffold. The cell-seeded scaffolds were incubated under standard conditions for 4 hours to facilitate cell adhesion followed by addition of 1 mL of culture medium and incubated for 5 days. The culture medium was replaced every day during the cell culture period.

2.4 | Cell viability and proliferation by confocal laser microscopy

Bone marrow stromal cells were cultured on the TES materials to analyze cell adhesion, proliferation, and formation of ECM. TESs were cut into desired size ($6.0 \times 6.0 \times 5.0$ mm^3). After incubation, specimens were fixed in 3.7% formaldehyde followed by addition of 2 μM calcein AM and 4 μM EthD-1. LIVE/DEAD® Viability Assay Kit was used to determine live and dead cells. Confocal laser microscope (CLM) (Olympus IX70-HLSH100 Fluoview) was used to determine live and dead cells. Number of live cells per mm^3 was calculated from z-series images captured by CLM. Z-series is a sequence of optical sections collected at different levels perpendicular to the optical axis (the z-axis) within a specimen.

2.5 | Cell morphology by environmental scanning electron microscopy

The cell seeded constructs were removed from the culture media after 5 days. They were washed twice with DPBS and fixed with 4% glutaraldehyde for 2 hours. The constructs were then subjected to dehydration by series of graded dose of ethanol (20%, 50%, 70%, 90%, and 100%) and cell morphology on the scaffolds were observed on the ESEM (FEI Quanta 400F).

3 | RESULTS

3.1 | Scaffold morphology

The BS3P fabricated PDLLA-PCL and HA-PCL scaffolds were represented in Figure 1. The microarchitecture of BS3P fabricated scaffolds showed homogeneity and consistency in filaments which are deposited (average diameter ~1 mm) with interconnected and regular pore size. Morphological observations revealed that pure PDLLA-PCL TES were translucent. HA-PCL was found to be opaque with rough texture due to incorporation of HA. SEM observation showed no aggregates HA indicating homogenous distributed.

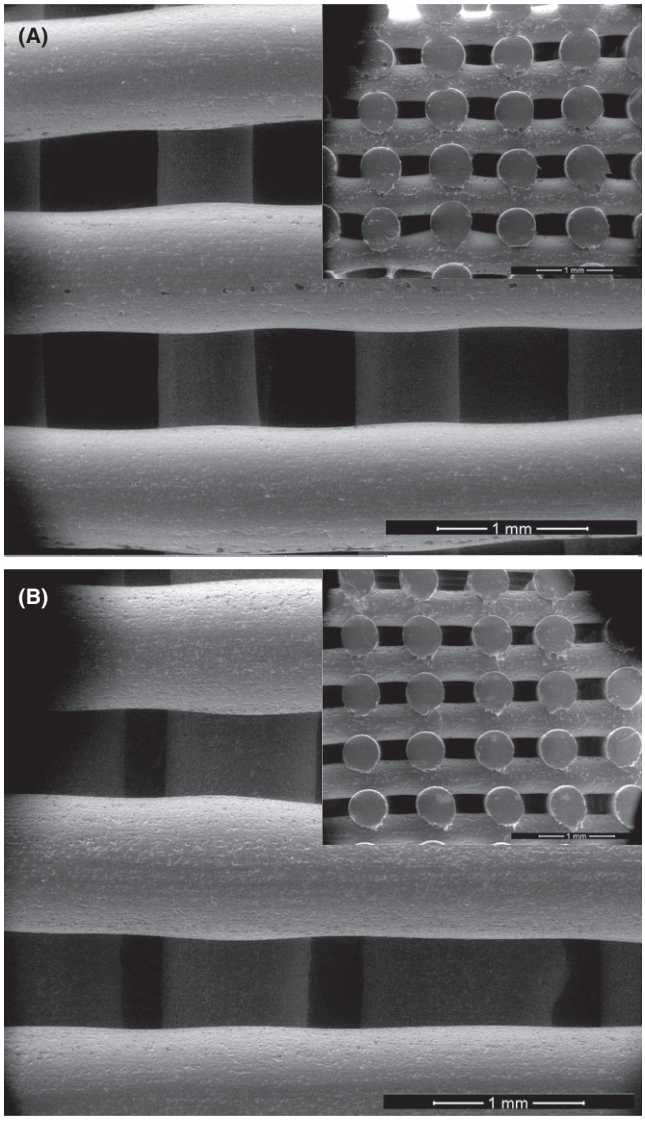

FIGURE 1 Scanning electron micrograph of (A) PDLLA-PCL and (B) HA-PCL TES. Plan view; inserts, cross-sectional view (magnification, ×60)

3.2 | Mechanical properties

Young's modulus, yield strength and yield strain values were reported in Table 3. In our study, scaffolds showed higher Young's modulus in X or Y axis as compare to Z axis. These properties mimics cancellous bone, where the Young's modulus can vary from 0.1 to 4.5 GPa depending on the bone mineral density and intrinsic trabecular orientation. Incorporating HA into PCL/PDLLA has significantly improved the mechanical properties of the scaffolds. The Young's modulus in axis-X, -Y, and -Z for HA-PCL were reported to be 639, 645, and 600 MPa, respectively. The yield strength and yield strain for HA-PCL were 27.7 MPa and 19.2%. Young's modulus for cortical, demineralized cortical and trabecular bone were reported to be 8 GPa, 2 GPa, and 0.8 MPa, respectively.[8] Therefore, these fabricated scaffolds exhibited enhanced stiffness compared to trabecular and lower stiffness relatively to cortical bone in terms of Young's modulus. Nevertheless, in order to mimic the load bearing properties of cortical bone, these scaffolds should be stiffer and stronger. However, we should understand that stiffness and strength in bone is a result of nanoscale organization between complimentary inorganic minerals and organic fractions. Factors like porosity, number of junction points and orientation of these fibers can also influence mechanical behavior of these fabricated TES. The above-mentioned properties of new biocomposite TES closely mimic cancellous bone making which could be a choice for bone applications.

3.3 | Cell-scaffold interaction study

Osteoblast-like cells showed their tentacle-like extensions of plasma membrane known as filipodia on the TES. Cells actively colonized the surface of the HA-PCL scaffolds after 1 day of culturing (Figures 2 and 3). There were more than 10 live cells/mm^3 in the HA-PCL TES. Fluorescent microscopy after live cell staining with LIVE/DEAD® Viability/Cytotoxicity assay kit at the end of 5 days revealed viable cells distributed on surfaces and within then matrix of HA-PCL TES.

TABLE 3 Mechanical properties of TES (L: 1.5 mm, D: 1.0 mm)

	Young's modulus (MPa)			Yield strength (MPa)	Yield strain (%)
TES	X-axis	Y-axis	Z-axis		
PDLLA-PCL	389	396	375	27.5	15.2
HA-PCL	639	645	600	27.7	19.2

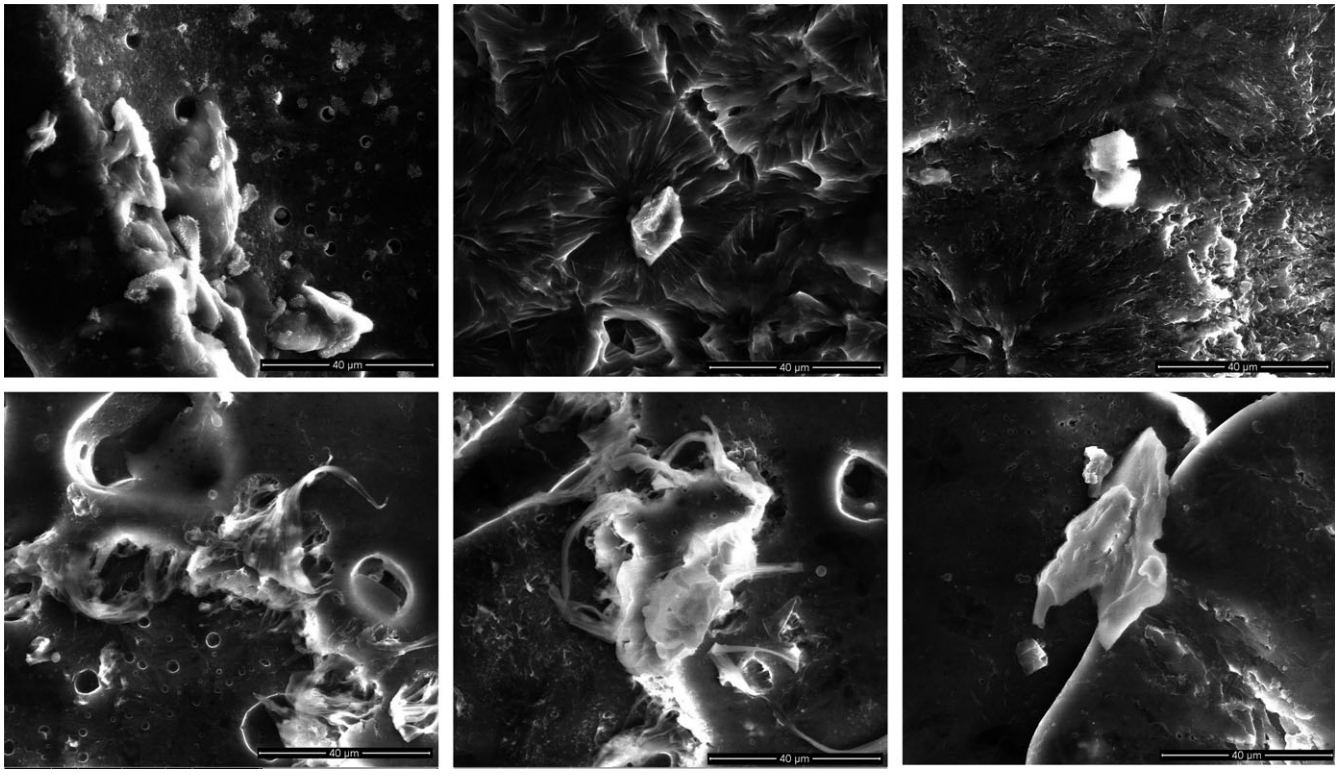

FIGURE 2 SEM of osteoprogenitor adhesion and spreading on the surface on PDLLA-PCL and HA-PCL scaffolds, after 1, 3, and 5 days. (D: 1.0 mm, L: 1.5 mm)

4 | DISCUSSIONS

The use of BS3P process for development of PCL and HA blended TESs were investigated. A new combination of biomaterials obtained by blending PCL with HA and PCL with PDLLA to enhance mechanical and surface properties of the TESs were studied. The XYZ position system precisely allows the system to deposit the polymer (layer by layer) with controlled architectures. The microarchitecture of BS3P fabricated scaffolds showed homogeneity and consistency of the deposited filaments (average diameter ~1 mm). This finding is also supported by Gomez-Lizarraga et al[22] as the ideal scaffold pores for bone regeneration with a diameter between 0.1 and 1.2 mm. The gross morphology of the TES showed excellent spatial arrangement with interconnecting pores and good fusion of the filaments at the surface. This shows good combination between the layers and filaments from the BS3P process. Hydrophobicity of PCL is one drawback for cell attachment.

The cell–scaffold interactions were carried out using osteoprogenitor cells. Osteoblast-like cells started attaching on all group of scaffolds 1 day after seeding. Higher magnification ESEM images showed, at the cellular scale, the different morphology of cell attachment and proliferation on the different scaffold material surfaces. Cells actively colonized the surface of the HA-PCL scaffolds after 1 day in the culture. Microscopically, it was inspected that the cells had attached and proliferated on the scaffold filaments, which showed cell agglomeration morphology. However, a few isolated cells were observed randomly attached on the PDLLA-PCL scaffold filaments. At the interconnected pores, cells appeared to grow along the filament across the pore architecture. There was significant difference in cell proliferation between PDLLA-PCL and HA-PCL TES. PrestoBlue™ Cell Viability Reagent was used to determine cell proliferation. SEM images reviled (after 5 days) that BMSCs proliferated and resulted in formation of mineralized matrix. A consistent increase in the cell number was observed on HA-PCL TES which were comparatively higher than PDLLA-PCL TES. SEM images proved that cells grown on HA-PCL scaffolds enhanced biomineralized matrix than PDLLA-PCL TES. Moreover, the matrix was seemingly mimicking the orientation of natural bone's Haversian canals. From these results we can understand that BMSCs could differentiate better on HA-PCL TES compared to pure PDLLA-PCL.

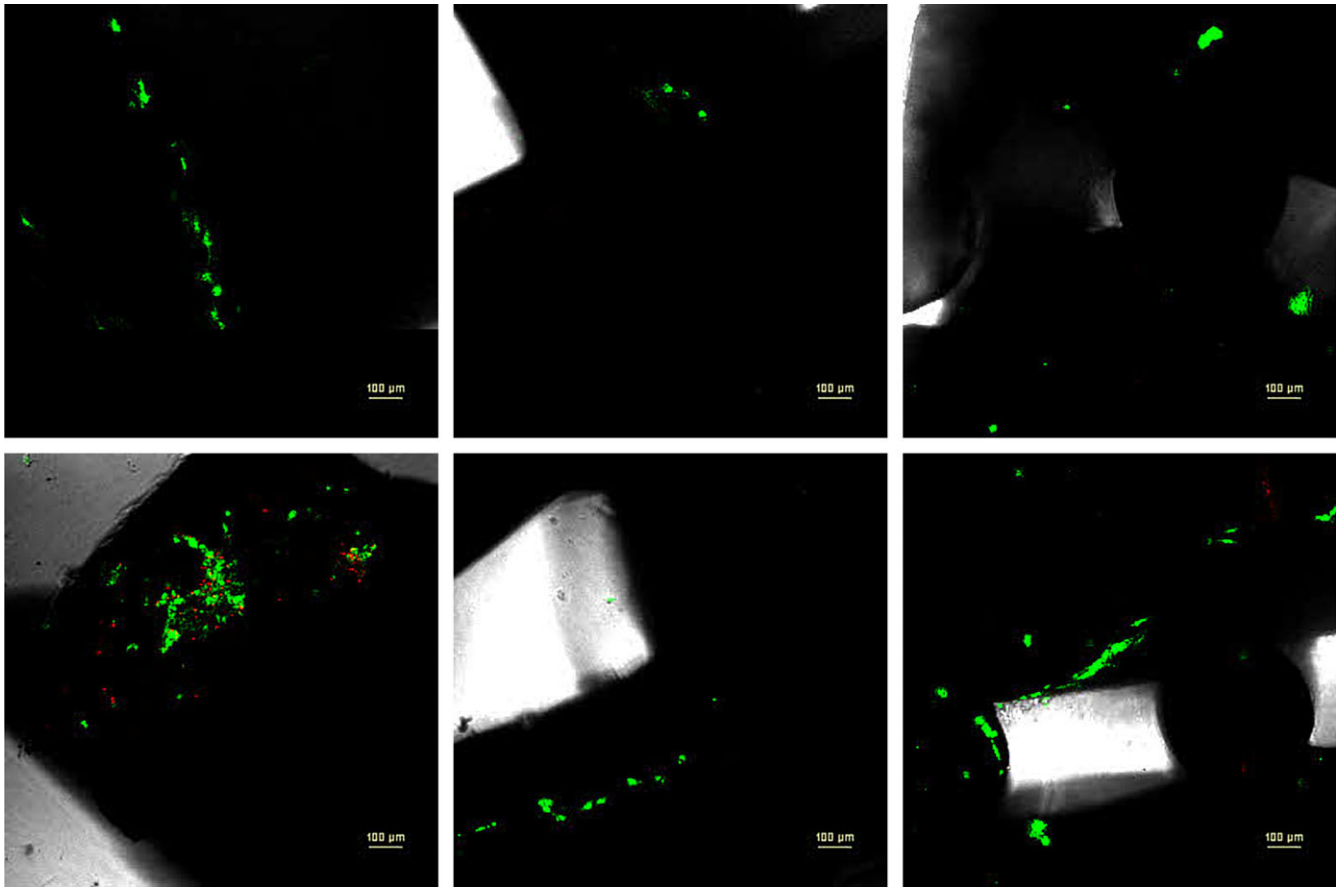

FIGURE 3 Confocal micrographs of osteoprogenitor stained with viability kits after 1, 3 and 5 d, on PDLLA-PCL and HA-PCL TES. (D: 1.0 mm, L: 1.5 mm, design architecture: 0-90) (Red: dead cell; green: live cells)

5 | CONCLUSIONS

In this study, novel combination of biomaterials was used to fabricate TES with enhanced biocompatibility using the BS3P technique. The competency of BS3P technique to fabricate HA blended TES was demonstrated here. The scaffolds exhibited well interconnected porous structure. This process opens new avenues in fabricating complex TES. Scaffolds exhibited excellent biocompatibility and osteogenic potential. CLM analyses showed cell adhesion, proliferation, and ECM was produced on the scaffolds. Interconnected porous structure along with HA as an osteogenic inducer enhanced via cell-to-cell interaction with production of ECM. Scaffolds fabricated with HA blended biomaterials have not been extensively explored in the field of 3D printed TES. Owing to these merits, future studies will be concentrated on investigating the effect of hybrid materials on other cell types in vitro and in vivo and improvement of PCL hydrophilicity.

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REFERENCES

1. Khan F, Tanaka M, Ahmad SR. Fabrication of polymeric biomaterials: a strategy for tissue engineering and medical devices. J Mater Chem B. 2015;3:8224–49.
2. Abdelaal OA, Darwish SM. Fabrication of tissue engineering scaffolds using rapid prototyping techniques. World Acad Sci Eng Technol Int Sci Index 2011;59(11):1325–33.
3. Qu Y, Wang B, Chu B, Liu C, Rong X, Chen H. Injectable and thermosensitive hydrogel and PDLLA electrospun nanofiber membrane composites for guided spinal fusion. ACS Appl Mater Interfaces. 2018;10:4462–70.
4. Fu SZ, Ni PY, Wang BY, Chu BY, Peng JR, Zheng L. In vivo biocompatibility and osteogenesis of electrospun poly(ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone)/nano-hydroxyapatite composite scaffold. Biomaterials. 2012;33(33):8363–71.
5. Kim JY, Cho DW. Blended PCL/PLGA scaffold fabrication using multi-head deposition system. Microelectron Eng. 2009;86:1447–50.
6. Butscher A, Bohner M, Hofmann S, Gauckler L, Muller R. Structural and material approaches to bone tissue engineering in powder-based three-dimensional printing. Acta Biomater. 2011;7:907–20.
7. Hoque ME, Meng TTH, Chuan YL, Chowdhury M, Prasad RGSV. Fabrication and characterization of hybrid PCL/PEG 3D scaffolds for potential tissues engineering applications. Mater Lett. 2014;131:255–8.

8. Nemati HA, Hosseinalipour SM, Rezaie HR, Shokrgozar MA. Characterization of poly(3-hydroxybutyrate)/nano-hydroxyapatite composite scaffolds fabricated without the use of organic solvents for bone tissue engineering applications. Mater Sci Eng C. 2011;32:416–22.
9. Asti A, Gioglio L. Natural and synthetic biodegradable polymers: different scaffolds for cell expansion and tissue formation. Int J Artif Organs. 2014;37(3):187–205.
10. Senatov FS, Niaza KV, Zadorozhnyy MY, Maksimkin AV, Kaloshkin SD, Estrin YZ. Mechanical properties and shape memory effect of 3D-printed PLA-based porous scaffolds. J Mech Behav Biomed Mater. 2016;57:139–48.
11. Galloway DA, Laimins LA. Human papillomaviruses: shared and distinct pathways for pathogenesis. Curr Opin Virol. 2015;14:87–92.
12. Wang Q, Xu JX, Jin HM, Zheng WH, Zhang XL, Huang YX, et al. Artificial periosteum in bone defect repair—A review. Chin Chem Lett. 2017;28:1801–7.
13. Chern MJ, Liang YY, Shen YK, Hung JH. 3D scaffold with PCL combined biomedical ceramic materials for bone tissue regeneration. Int J Precis Eng Manuf. 2013;14(12):2201–7.
14. Patricio T, Gloria A, Bartolo P. Mechanical and biological behaviour of PCL and PCL/PLA scaffolds for tissue engineering applications. Chem Eng. 2013;32:1645–50.
15. Williams JM, Adewunmi A, Schek RM, Flanagan CL, Krebsbach PH, Feinberg SE, et al. Bone tissue engineering using polycaprolactone scaffolds fabricated via selective laser sintering. Biomaterials. 2005;26(23):4817–27.
16. Yeong WY, Sudarmadji N, Yu HY, Chua CK, Leong KF, Venkatraman SS, et al. Porous polycaprolactone scaffold for cardiac tissue engineering fabricated by selective laser sintering. Acta Biomater. 2010;6(6):2028–34.
17. Hoque ME, Nurul S, Chuan YL. Synthesis and characterization of hydroxyapatite bioceramic. Int J Sci Eng Technol. 2014;3(5):458–62.
18. Hutmacher DW, Hoque ME, Wong YS. Design, Fabrication and Physical Characterization of Scaffolds Made from Biodegradable Synthetic Polymers in combination with RP Systems based on Melt Extrusion. In: *Virtual prototyping and bio manufacturing in medical applications*. Bopaya B, Paulo B (eds). USA: Springer; 2008: pp. 261–92.
19. Hoque ME, Chuan YL. Desktop robot based rapid prototyping system: an advanced extrusion based processing of biopolymers into 3D tissue engineering scaffolds. In: *Rapid prototyping technology - Principles and functional requirements*. Hoque MD (ed). London, UK: InTech Open; 2011: pp. 105–34.
20. Patel KD, Singh RK, Mahapatra C, Lee EJ, Kim HW. Nanohybrid electro-coatings toward therapeutic implants with controlled drug delivery potential for bone regeneration. J Biomed Nanotechnol. 2016;12(10):1876–89.
21. Zhao X, Komatsu DE, Hadjiargyrou M. Delivery of rhBMP-2 plasmid DNA complexes via a PLLA/collagen electrospun scaffold induces ectopic bone formation. J Biomed Nanotechnol. 2016;12(6):1285–96.
22. Gómez-Lizárraga KK, Morales CF, Prado-Audelo MLD, Pérez MAA, Piña-Barba MC, Escobedo C. Polycaprolactone- and polycaprolactone/ceramic-based 3D-bioplotted porous scaffolds for bone regeneration: a comparative study. Mater Sci Eng C. 2017;79:326–35.

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