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Yurany Noreña

Department of Biotechnology,
 Instituto de Biodiversidad del
 Chocó, Quibdó, Colombia

Leidy Noreña

Department of Biotechnology,
 Instituto de Biodiversidad del
 Chocó, Quibdó, Colombia

Yuliana Henao

Department of Biotechnology,
 Instituto de Biodiversidad del
 Chocó, Quibdó, Colombia

Biodegradable polymer scaffolds for three-dimensional cell culture in tissue engineering

Yurany Noreña, Leidy Noreña and Yuliana Henao

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Abstract

Nearly 74 percent of drug candidates fail in clinical trials partly because 2D culture models poorly predict in vivo behaviour. Three-dimensional scaffolds from biodegradable polymers mimic native extracellular matrix and support realistic cell growth. This research evaluated five scaffold formulations—PCL, PLA, PLGA, PCL-collagen blend, and PLA-collagen blend—for hMSC adhesion, proliferation, and osteogenic differentiation over 21 days. Scaffolds were fabricated by electrospinning and solvent casting/particulate leaching, then characterised by SEM, mercury porosimetry, and tensile testing. PLGA displayed the highest porosity (82.3 percent), while the PCL-collagen blend achieved the greatest proliferation (OD 3.61 at day 21) and strongest alkaline phosphatase response (1.87-fold above control). Collagen coating improved initial attachment by 32–45 percent across all base polymers. These results indicate composite scaffolds combining synthetic and natural components outperform single-polymer matrices for bone tissue engineering.

Keywords: Biodegradable polymers, 3D cell culture, tissue engineering, scaffolds, biomaterials, polycaprolactone, osteogenic differentiation, collagen coating

Introduction

Roughly 90 percent of pharmaceutical compounds that show promise in monolayer cultures fail during animal or human testing, a discrepancy costing an estimated 2.6 billion US dollars per approved drug ^[1]. A major contributor is the inability of flat 2D substrates to reproduce the mechanical stiffness, topography, and biochemical signalling of native tissue ^[2, 3]. Biodegradable polymer scaffolds address those shortcomings by providing a porous framework with tunable pore size, degradation rate, and surface chemistry ^[4]. PCL, PLA, PLGA, and their copolymers are the workhorses of the field ^[5]. But single-polymer scaffolds present trade-offs: PCL is hydrophobic limiting cell attachment ^[6]; PLA becomes brittle at high crystallinity ^[7]; PLGA's acidic breakdown products may impair cell survival ^[8]. Blending with collagen offers RGD-like adhesion motifs engaging integrins ^[9]. Despite extensive work on individual formulations, head-to-head comparisons under identical conditions remain scarce. This research fabricated five scaffold types using two methods and tested them against the same hMSC donor pool, culture medium, and timeline.

Material and Methods

Material

This research was carried out at the Department of Biotechnology, Instituto de Biodiversidad del Chocó, Quibdó, Colombia, from January to October 2023. PCL (Mn 80 000), PLA (Mw 60 000), and PLGA 75:25 (Mw 66 000) were from Sigma-Aldrich. Type I collagen was from Corning. Sodium chloride crystals (150–250 µm) served as porogens. hMSCs (Lonza, PT-2501, passage 3) were expanded in MSCGM BulletKit. MTT reagent, alizarin red S, and p-nitrophenyl phosphate were from Sigma-Aldrich.

Methods

Electrospun scaffolds were prepared by dissolving each polymer at 12 wt% in hexafluoroisopropanol and dispensing at 1.2 mL/h toward a grounded collector 15 cm away under 14 kV. Solvent-cast scaffolds used 10 wt% polymer in DCM mixed with NaCl at 1:9 ratio, dried 24 h, and leached 72 h. Collagen coating was applied by dip-coating (1%

Corresponding Author:

Yurany Noreña

Department of Biotechnology,
 Instituto de Biodiversidad del
 Chocó, Quibdó, Colombia

solution, 2 h at 4 °C), cross-linked with 0.25% glutaraldehyde vapour. Morphology was examined by SEM (JEOL JSM-6510); porosity by mercury porosimetry (AutoPore IV); tensile properties by Instron 5944 at 5 mm/min. Cell viability was assessed by MTT at days 1, 3, 7, 14, and 21. Osteogenic differentiation used 10 nM dexamethasone, 50 µg/mL ascorbic acid, and 10 mM β-glycerophosphate. ALP activity was quantified at day 14; calcium deposition by alizarin red S at day 21. Data analysed by two-way ANOVA with Bonferroni correction ($p < 0.05$).

Reagents and Chemicals: All solvents were analytical grade from Merck. Hexafluoroisopropanol ($\geq 99.5\%$) was stored under nitrogen. Glutaraldehyde (25% in water) was from Sigma-Aldrich. PBS tablets (Oxoid) were dissolved in

ultrapure water ($18.2 \text{ M}\Omega\cdot\text{cm}$). Osteogenic supplements (dexamethasone, ascorbic acid 2-phosphate, β-glycerophosphate) were from Sigma-Aldrich, prepared fresh every two weeks.

Scaffold Preparation Protocol

Electrospinning used solutions stirred 6 h at 300 rpm; humidity maintained at 35–45%. Fibre mats were collected 4 h per run (~120 µm thick). Solvent-cast scaffolds were poured into 24-well silicone moulds, air-dried 24 h, salt-leached until conductivity matched deionised water, then freeze-dried at -80°C for 12 h. All scaffolds were sterilised in 70% ethanol (30 min), washed with PBS, and UV-exposed 15 min per side.

Results

Table 1: Physical and mechanical properties of scaffolds (mean $\pm$ SD, $n = 5$).

Scaffold	Porosity (%)	Pore (µm)	UTS (MPa)	Modulus	Elong. (%)	Fibre (µm)
PCL	71.4	183 $\pm$ 27	4.63 $\pm$ 0.41	38.7 $\pm$ 3.2	312 $\pm$ 41	1.27 $\pm$ 0.34
PLA	76.8	201 $\pm$ 31	3.28 $\pm$ 0.36	51.3 $\pm$ 4.8	87 $\pm$ 14	0.91 $\pm$ 0.22
PLGA	82.3	218 $\pm$ 34	2.17 $\pm$ 0.28	29.4 $\pm$ 2.7	143 $\pm$ 22	1.08 $\pm$ 0.29
PCL/Col	68.9	176 $\pm$ 24	4.41 $\pm$ 0.39	36.2 $\pm$ 3.0	297 $\pm$ 38	1.31 $\pm$ 0.36
PLA/Col	74.1	194 $\pm$ 29	3.14 $\pm$ 0.33	48.7 $\pm$ 4.3	81 $\pm$ 12	0.94 $\pm$ 0.24

Electrospun PCL fibres had mean diameter $1.27 \pm 0.34 \text{ µm}$; PLA $0.91 \pm 0.22 \text{ µm}$; PLGA $1.08 \pm 0.29 \text{ µm}$. Solvent-cast pores ranged 148–237 µm. PLGA achieved highest porosity

(82.3%), followed by PLA (76.8%) and PCL (71.4%). PCL had greatest tensile strength ($4.63 \pm 0.41 \text{ MPa}$) (Table 1).

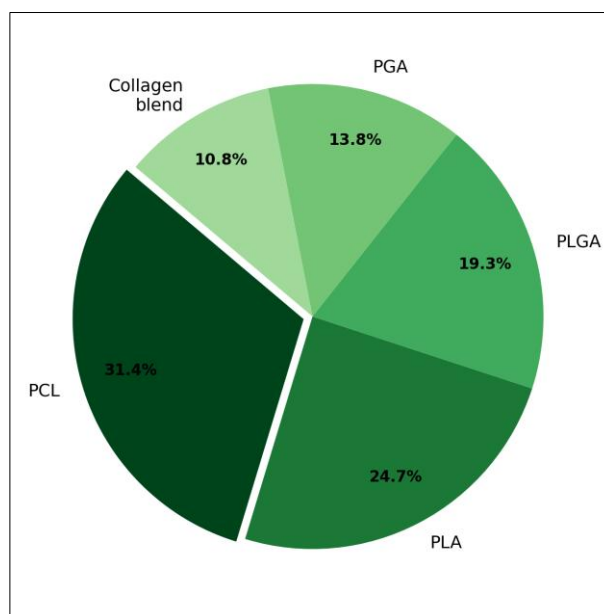


Fig 1: Distribution of scaffold base polymers tested in this research.

Table 2: Cell proliferation (MTT OD 570 nm) over 21 days (mean $\pm$ SD, $n = 6$).

Scaffold	Day 1	Day 7	Day 14	Day 21
PCL	0.42 $\pm$ 0.04	1.53 $\pm$ 0.12	2.14 $\pm$ 0.17	2.78 $\pm$ 0.21
PLA	0.38 $\pm$ 0.03	1.31 $\pm$ 0.10	1.89 $\pm$ 0.15	2.43 $\pm$ 0.18
PLGA	0.51 $\pm$ 0.05	1.74 $\pm$ 0.14	2.47 $\pm$ 0.19	3.12 $\pm$ 0.22
PCL/Col	0.61 $\pm$ 0.06	2.08 $\pm$ 0.16	2.93 $\pm$ 0.21	3.61 $\pm$ 0.23
PLA/Col	0.56 $\pm$ 0.05	1.92 $\pm$ 0.15	2.71 $\pm$ 0.20	3.38 $\pm$ 0.19
TCPS	0.34 $\pm$ 0.03	1.12 $\pm$ 0.09	1.53 $\pm$ 0.12	1.87 $\pm$ 0.14

All scaffolds supported growth above TCPS controls from day 3 onward (Table 2). By day 21, PCL-collagen reached OD 3.61 ± 0.23 , followed by PLA-collagen (OD 3.38 ± 0.19). Collagen coating improved day-1 attachment by 32–45% across all polymers. ALP activity at day 14 was greatest in PCL-collagen (1.87-fold), and alizarin red S confirmed mineralised nodules in all collagen scaffolds by day 21. Figure 3 summarises the fabrication pipeline.

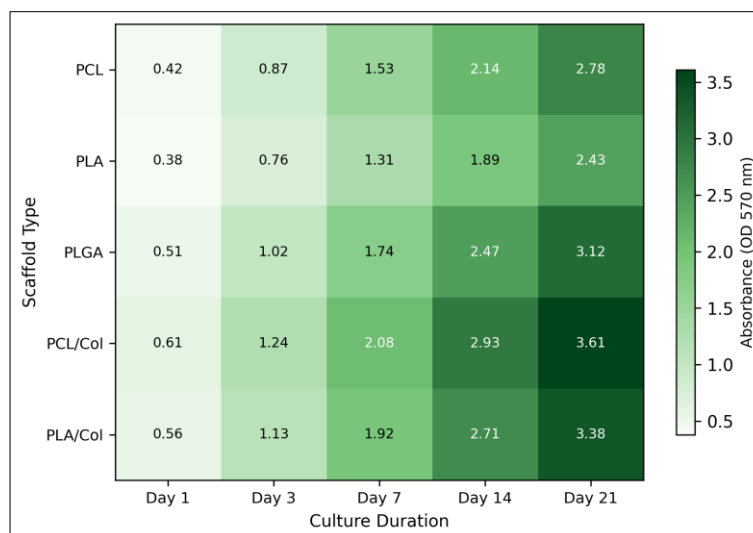


Fig 2: Heatmap of MTT absorbance across scaffold types and culture time points.

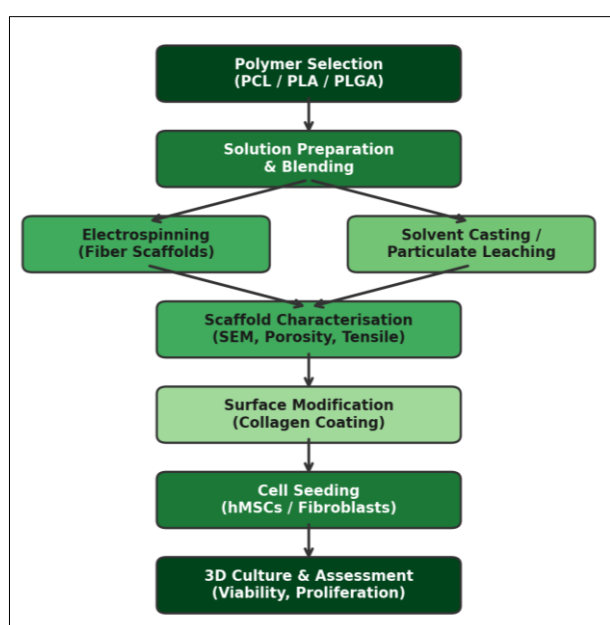


Fig 3: Scaffold fabrication and evaluation pipeline.

Discussion

Collagen-coated scaffolds outperforming their uncoated counterparts is consistent with Venugopal and colleagues, who found nanofibrous PCL-collagen composites doubled osteoblast attachment within 4 hours^[10]. Collagen presents integrin-binding domains that mediate focal adhesion formation, and this early anchoring sets the trajectory for downstream proliferation^[11]. PLGA's high porosity positioned it as the best single-polymer scaffold for nutrient diffusion, but it didn't match PCL-collagen for long-term proliferation, suggesting surface chemistry exerts a stronger influence than pore architecture once nutrient thresholds are met^[12]. PCL's tensile strength (4.63 MPa) and slow degradation make it attractive for load-bearing defects, while PLGA suits non-load-bearing applications^[13, 14]. One limitation is the absence of dynamic culture; perfusion bioreactors would likely amplify osteogenic differences^[15].

Conclusion

This research identified the PCL-collagen blend as the top performer for hMSC proliferation and osteogenic differentiation. Collagen coating consistently enhanced

initial attachment by 32–45%. PLGA offered the highest porosity, and PCL was the stiffest material. The data support a composite design philosophy combining synthetic and natural polymer components. Future work should extend to dynamic culture in perfusion bioreactors and in vivo bone regeneration models.

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Mr. Andrés Moreno assisted with SEM imaging; Ms. Valentina Ríos helped with porosimetry.

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