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Impact of the Hydroxyapatite Concentration on the Mechanical properties and accelerated degradation of PCL-based Scaffolds in the Bone Tissues Engineering.

Hussein Mishbak1*
1 Biomedical Engineering Dept., Collage of Engineering, The university of Thi Qar
Nassiriyia, Thi_Qar, Iraq
Email: Hussein.mishbak@utq.edu.iq

Abstract:

Polycaprolactone (PCL) has become one of the most prominent biomaterials for bone tissue engineering scaffolds due to its biocompatibility, FDA approval and durability of mechanical properties. However, pure PCL scaffolds have some inherent limitations such as high hydrophobicity and inadequate bioactivity. This study overcomes these limitations by incorporating hydroxyapatite (HA) nanoparticles in PCL based composite scaffolds at different concentrations (10% and 20% w/w). PCL/HA composite scaffolds and pure PCL controls were produced by the solvent casting and salt leaching method and fully characterized. The addition of HA improved both tensile and compressive mechanical properties of the composites in a concentration dependent manner. PCL/HA (20% w/w) scaffolds showed tensile strength of 16.5 MPa and compressive strength of 18.4 MPa which were 52.8% and 60.0% respectively higher than pure PCL. All scaffolds had well-interconnected porous architectures that are suitable for the infiltration of cells and the transport of nutrients. Accelerated degradation studies with 5.0 M NaOH solution showed that the effect of HA incorporation significantly accelerated degradation of the scaffold in a concentration-dependent manner with PCL/HA (20% w/w) showing 25% mass loss over five days compared to less than 4% for pure PCL. This accelerated degradation is attributed to the hydrophilic nature of HA particles to act as absorbances and to infiltrate the corrosive medium into the scaffold substance coupled with increased internal surface area due to HA-induced micropores on strut walls. These findings indicate that PCL/HA composite scaffolds provide an acceptable compromise between improved mechanical properties and tunable degradation behavior, and could be good candidates for load-bearing bone tissue engineering applications in which mechanical support and controlled tissue integration are important.

1. Introduction

Bone tissue engineering (BTE) has become a revolutionary clinical approach for the repair of large bone defects, especially large size critical bone defects caused by trauma, tumor resection, and congenital anomalies that fail to heal on their own (1–3). Conventional treatments such as autografts and allografts are plagued with limitations such as donor site morbidity, risk of disease transmission, risk of immune rejection and availability of these bone grafts, which highlights the urgent need for synthetic bone graft substitutes (4,5). The success of BTE depends on the designer of three-dimensional porous scaffolds as a temporary extracellular matrix. An ideal scaffold should be able to provide mechanical support, guide cell attachment and proliferation and regenerate functional tissue (6). For this, scaffolds should be biocompatible, have mechanical properties similar to native bone, controlled biodegradability matched with new tissue formation, an interconnected porous architecture for infiltration and transport of nutrients and cells, and being osteoconductive to promote bone cell adhesion and differentiation (7–9).

Among the different synthetic polymers investigated as BTE, Polycaprolactone (PCL), a semi-crystalline and biodegradable aliphatic polyester, has attracted much attention (10). Due to its excellent biocompatibility, high mechanical strength compared to other polyesters, ease of processing into complex shapes and the fact that it is approved by the U.S. Food and Drug Administration (FDA) for the use in a variety of biomedical devices, it is a leading candidate (10–12). PCL's low degradation rate (2-3 year) is especially useful in the load-bearing application where long-term structural support is most important (13,14). However, pure PCL scaffolds have several inherent limitations which prevent their clinical functions (15). It has a strong hydrophobicity, which hinders the early cell binding and protein adsorption and its insensitivity to intrinsic bioactivity does not actively induce osteogenic signaling pathways (16). Furthermore, its mechanical modulus is too low for use in cortical bone, and its slow degradation is sometimes a drawback, which may delay the transfer of load to the newly formed tissue (17).

The potential of PCL-based composite scaffolds is well documented in the literature recently (14,18). Murugan, S., Parcha, S.R. (2021) have used 3D printing to produce PCL/HA scaffolds that have a high compressive strength and osteoblast proliferation rate than pure PCL (19). Similarly, Weihua Huang et al. (2024) showed that the PCL/bioactive glass composite scaffolds greatly induced the osteogenic differentiation and mineralization of mesenchymal stem cells (20). The other innovations are the production of functionally graded PCL/BG scaffolds to repair osteochondral (21). Some studies have even investigated tripartite systems demonstrating a synergistic effect of the incorporation of growth factors such as BMP-2 into PCL/HA scaffolds to promote faster in vivo bone formation (22). The accelerated degradation behavior is a very important characteristic to consider in the choice of the best filler for a given clinical indication, and is frequently not reported in comparative studies.

This study is intended to study the PCL-based composite scaffolds with various concentrations of HA by solvent casting and particulate leaching method. The goal of this study is to assess the effect of the incorporation of HA on scaffold mechanical characteristics and degradation behavior in physiological conditions. this direct comparative analysis, will offer useful information to guide the rational design and optimization of PCL-based composite scaffolds for the future bone tissue engineering applications.

2. Materials and Methods

2.1 Materials

Polycaprolactone (PCL) was bought from Sigma-Aldrich (UK). Hydroxyapatite nanoparticles (HA, < 200 nm) were purchased from Sigma-Aldrich (UK). Sodium chloride (NaCl, 250-450 µm) was used as porogen and was purchased from Merck (Germany). Chloroform ($CHCl_3$) was used as solvent and purchased from Fisher Scientific (UK). Phosphate-buffered saline (PBS, pH 7.4), lipase from Pseudomonas cepacia (≥ 30 U/mg) and all other reagents were of analytical grade and were purchased from Sigma-Aldrich (UK).

2.1.2 Scaffold Fabrication

PCL-based scaffolds were prepared by the solvent casting and salt leaching method. Three types of scaffolds were prepared: pure PCL, PCL/HA (10% w/w) and PCL/HA (20% w/w). Pure PCL scaffolds were prepared by dissolving 2 g of PCL in 20 mL of chloroform at room temperature under constant magnetic agitation for 2 h until the pellets were fully dissolved. For composite scaffolds, the necessary amount of HA powder was dispersed in the PCL solution by ultrasonic treatment (40 kHz, 200 W) for 30 minutes to obtain homogenous dispersion.

As depicted in Fig. **1.**

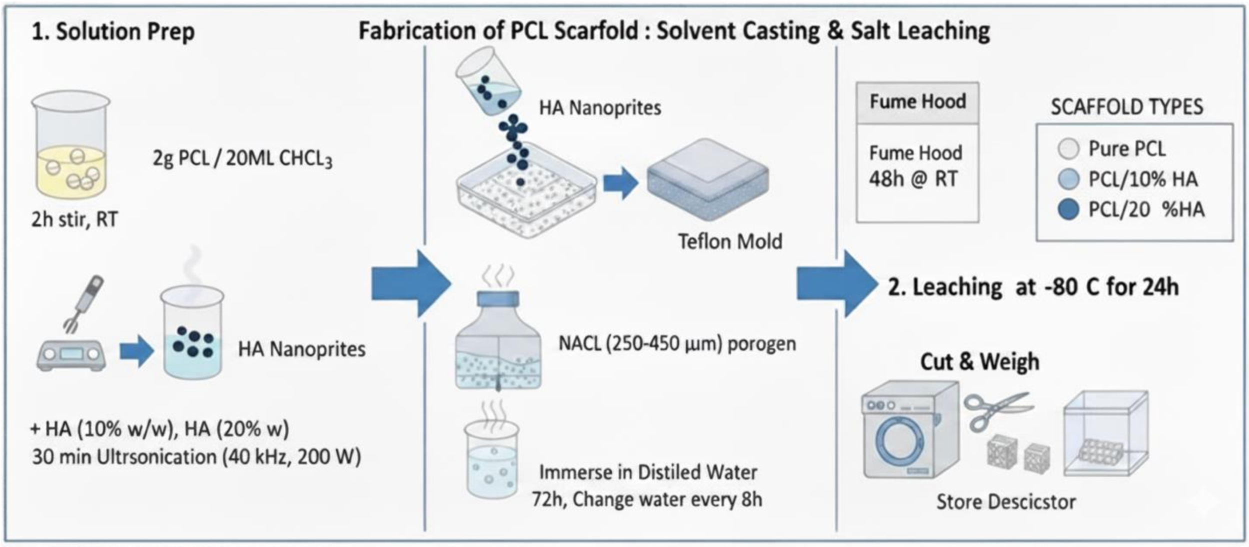

Fig. 1: Schematic representation of fabrication of PCL-based scaffold using Solvent Casting and Salt Leaching method.

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2.2 Mechanical Testing

2.2.1 Tensile Testing

Tensile properties were tested by using universal testing machine (Instron 5969, USA) with a load cell of 5 kN. Rectangular samples (50 mm x 10 mm x 3 mm, n = 5 per group) were tested according to ASTM D638 standard. The tests were conducted at room temperature (25 C) with a crosshead speed of 5 mm/min. Tensile strength, elongation at break and Young's modulus were determined from the stress-strain curves.

2.2.2 Compressive Testing

Compressive strength was determined with the same universal testing machine with a 50 kN load cell. Cylindrical samples (diameter = 10mm, height = 10mm, n = 5 per group) were compressed at crosshead speed of 1mm/min as per the standard ASTM D695. Compressive strength and compressive modulus were measured from the stress-strain curves.

2.3 Degradation studies

An accelerated degradation experiment based on the base-catalyzed hydrolysis was carried out to simulate long-term degradation. Alkaline degradation medium was prepared by 5.0 M sodium hydroxide (NaOH) solution in DI water. Prior to immersion, all scaffold specimens were dried in a vacuum oven to constant weight and this wet mass (W_0) was noted. After that, three replicates per group per time point (n = 3) were transferred to 20 mL sterile vials closed with rubber caps with 15 mL of 5.0 M NaOH solution. These vials were incubated in the incubator shaker at 37 °C for the duration of the experiment and samples were removed at different time points; 1, 2, 3, 4, and 5 days. Each scaffold was then immediately removed from NaOH solution and washed extensively with DI water until the final wash solution was neutral (pH ~ 7.0). After neutralization, the scaffolds were submerged in DI water for 1 hour to make sure that the residual salts were removed. Finally, the rinsed scaffolds were lyophilized (freeze-dried) for 24 hours to remove all the moisture completely for the final dry weight (W_f) for mass loss calculations.

2.4 Statistical Analysis

All quantitative data were reported as mean+SD. Statistical analysis was done by one way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons. A p-value of < 0.05 was considered statistically significant. All analyses were done by GraphPad Prism 9.0 software (GraphPad Software, USA).

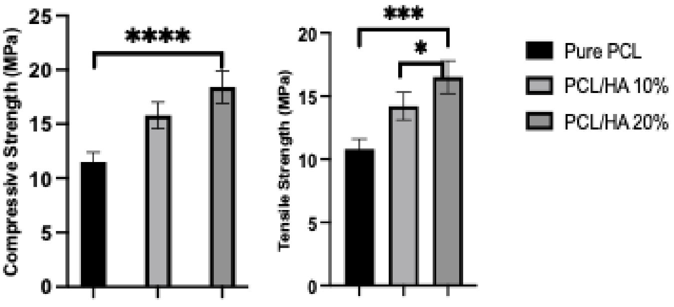
3. Results and Discussion

3.1 Scaffold Structure and Mechanical Properties

visual observation shows that all fabricated scaffolds had highly porous and interconnected three-dimensional structures, which are necessary for cell infiltration, nutrient transportation and ingrowth of tissue. Pure PCL scaffolds showed a smooth pore wall surface with well-defined pore architecture. The surface morphology of PCL/HA composite showed obvious changes after the HA was incorporated into the PCL matrix. PCL/HA composite scaffolds exhibited the existence of HA nanoparticles dispersed evenly in the polymer matrix and embedded on the pore walls. At higher HA concentrations (20% w/w) it was observed that some agglomeration of the particles occurred. As depicted in Fig.2.

Fig 2. a) Pure PCL b) PCL/10% HA, and c) PCL/20% HA

The interconnectivity of pores is one of the critical factors in scaffold performance, since it allows cell migration to occur throughout the entire scaffold volume, and allows for nutrient and waste exchange. Visual inspection of cross-sectional scaffolds showed that all scaffolds had well interconnected pore networks with multiple connections between neighboring pores. This interconnectivity was retained throughout all of the compositions, suggesting that the solvent casting and salt leaching method was able to produce scaffolds with appropriate architecture for tissue engineering applications.



Mechanical properties are of major importance for bone tissue engineering scaffolds, as they have to offer sufficient mechanical support during the regeneration process, and have to be similar to the mechanical properties of the native bone, to prevent stress shielding. The results of the mechanical testing are summarized in Fig

Fig. 2: A- Stress vs Strain curve B- Compressive modulus (kPa) C- Young's modulus (kPa)

The tensile strength of pure PCL scaffolds was 10.8 +- 0.8 MPa and Young's modulus was 350.5 +- 25.3 MPa. These values are consistent with previously reported data for the scaffolds based on porous PCL and are within the range of the properties of trabecular bone (tensile strength: 5-20 MPa, Young's modulus: 100-500 MPa). The use of ceramic fillers greatly improved the tensile properties of the scaffolds. PCL/HA composite scaffolds exhibited a concentration-dependent enhancement in tensile properties. PCL/HA (10%) showed a tensile strength of 14.2 +- 1.1 MPa and Young's modulus of 485.3 +- 32.5 MPa, which are 31.5% and 38.5% higher than those of pure PCL. Further increasing the HA content to 20% even higher values were obtained: tensile strength of 16.5 +- 1.3 MPa and Young's modulus of 562.8 +- 38.9 MPa (52.8% and 60.6% increases, respectively). These improvements can be attributed to the reinforcing effect of the stiff HA particles which act as stress transfer agents within the polymer matrix. The strong interaction between HA and PCL chains mediated by hydrogen bonding interaction of hydroxyl groups of HA and carbonyl groups of PCL improves the efficiency of load transfer.

The improvement in both tensile and compressive properties shows that the introduction of bioactive ceramics has not only an effect on the biological performance but also helps to maintain and even increase the mechanical integrity of PCL scaffolds. This is especially important for bone tissue engineering applications where mechanical support during the healing process is important.

3.2 Accelerated degradation

The simulated accelerated degradation study shows clear composition dependent patterns of scaffold degradation. The most important finding is that the rate of degradation is directly proportional to the hydroxyapatite (HA) content. It is most obvious from the percentage weight loss data in which the PCL/HA 20% scaffold showed the greatest weight loss of about 25% over 5 days. This was followed by the PCL/HA 10% scaffold at ~17.5% and Pure PCL scaffold was highly stable with a loss of less than 4% of its initial mass in the same time period. The rationale for these trends is the competing chemical properties of the components of the scaffold. The mechanism of degradation is fast, base-catalysed hydrolysis (saponification) of the ester bonds of the PCL, which is initiated by the 5M NaOH solution (23). PCL is an inherently hydrophobic polymer, i.e. it repels the aqueous NaOH solution, and it should naturally protect the internal structure (24). However, the HA filler is a hydrophilic (water-attracting). These HA particles act like "hydrophilic wicks" that actively suck the corrosive medium of degradation deep into the bulk of the scaffold (25). This action coupled with the fact that HA addition creates micropores on the strut walls (26), that creates a vastly larger internal surface area for the NaOH to attack the polymer. Therefore, the PCL/HA 20% scaffold degrades the quickest simply because it has the highest concentration of these "absorbing " sites, and therefore the most rapid and extensive infiltration of the degradation solution is possible. Fig.4

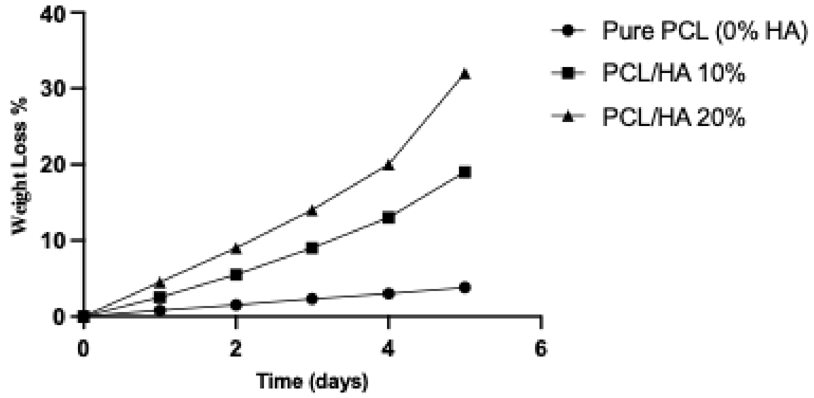


Fig 4. Accelerated degradation profile for pure PCL, PCL/10% HA and PCL/20% HA scaffolds

1. Conclusion

The paper has developed and produced polycaprolactone (PCL) composite scaffolds with 10% and 20% w/w hydroxyapatite (HA) in a solvent casting and salt leaching technique in order to address the natural disadvantages of pure PCL, including its hydrophobicity and slow erosion pace, in bone tissue engineering. The outcomes have shown that each scaffold had porous and interconnected structures that are good at cell infiltration. Addition of HA nanoparticles had a concentration dependent positive effect on the properties of the scaffolds. It is notable that the

PCL/HA (20%), group had an increase of tensile strength (16.5 MPa) and compressive strength (18.4 MPa) by 52.8 and 60.0 % respectively in comparison with pure PCL, which means that their mechanical properties are similar to those of trabecular bone and have the potential to be used in load-bearing applications. Moreover, rapid degradation experiment has shown that the rate of degradation was directly proportional to the content of HA. The PCL/HA (20%) scaffolds were found to lose 25% of its mass in five days in 5.0 M NaOH as opposed to less than 4 % of pure PCL. This increased degradation rate is due to the hydrophilicity of the HA particles that are considered as wicks that concentrate the corrosive medium within the bulk of the scaffold as well as the high internal surface area that is created by the HA generated micropores. PCL/HA composite scaffolds offer a good and tunable intermediate, not only enhancing mechanical integrity to support the mechanical structure, but also degrading faster, which validates them as good candidates to use in further bone tissue engineering.

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