Human & Veterinary Medicine
International Journal of the Bioflux Society HVM

OPEN ACCESS
Research Article

New scaffolds for guided bone regeneration

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Abstract. Objective: The aim of this study was the development and characterization of new scaffolds from polycaprolactone (PCL) loaded with nano-hydroxyapatite (nHAP) and metronidazole (MET) for guided bone regeneration. Material and Methods: The scaffolds with different compositions (PCL, PCL-5%MET, PCL-5%nHAP-5%MET) were obtained through electrospinning. The morphology, fiber size, and mechanical properties of the obtained scaffolds were analyzed and described. The obtained results showed scaffolds with the typical electrospun architecture of randomly continuous oriented bead-free fibers. The fibers with a size between 0.6 and 11 µm, formed a porous structure. The mechanical properties showed results situated between 2.2 and 5.2 N for the force at maximum load, and for the Young modulus, the results were registered between 7 and 28 MPa. The highest value for stiffness was registered for the PCL scaffolds and was evaluated at 6650 N/m and the lowest value was certified for the PCL-5%nHAP-5%MET scaffolds at 1990 N/m. The tensile strength was registered to be between 1.05 and 2.4 MPa. In conclusion, the addition of MET lowered the fiber size and the addition of nHAP increased the size of the fibers. The size of the fiber affected the mechanical properties of the scaffolds. The obtained scaffolds could be promising in the field of guided bone regeneration, but further tests are necessary to prove their biological and antibacterial properties.

Key Words: electrospinning, metronidazole, guided bone regeneration, mechanical properties

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Introduction

Periodontitis is a gum disease associated with gram-negative, anaerobic microflora, which is characterized by pocket formation, loss of periodontal ligament, and tooth loss (Brogden & Guthmiller 2002). There are some well-established risk factors like diabetes mellitus (Lalla & Papapanou 2011), smoking (Albandar et al 2000), psychological stress, host immune response, genetic susceptibility, osteoporosis, and aging (Guiglia et al 2013), which make the treatment highly challenging (Joshi et al 2016). Metronidazole (MET) is used for a long period, in the treatment of anaerobic infections, involved in the periodontal disease (Joshi et al 2016), but it requires long periods of intake to be efficient and commonly shows side effects like metallic taste, nausea, and loss of appetite (Joshi et al 2016). All these many disadvantages require a new administration method, which involves local drug delivery (Bailey 1997).

Tissue engineering targets the restoring of damaged tissues by promoting substitutes, like scaffolds (Langer 2009). The scaffolds must provide a cell-friendly habitat from micro- to nanoscale to allow cells to grow and develop their function. Because of this, many methods were investigated to design a scaffold that mimics the environment of the natural tissue (Langer 2009). Electrospinning is a simple, versatile (Xue et al 2019) and popular method for fabricating scaffolds, with long and continuous ultrathin polymeric fibers (Mujica-Garcia et al 2014), in the range of micro/nanofibers (Mercante et al 2017). The reduced size of the fibers provides a great surface-area-to-volume ratio, which can improve cellular activities, like cell attachment, proliferation, and differentiation (Chronakis 2005). Also, these types of electrospun scaffolds mimic the native structure of the extracellular matrix, which provides an important role in cell functions (Braghirolli et al 2014). The ideal scaffold must have mechanical properties similar to the replaced tissue (Shuai et al 2020). The capacity of incorporating different drugs in the fibers can give different biomedical applications to the developed scaffolds (Liu et al 2020). The incorporation of MET makes the scaffolds proper in the treatment of periodontal disease (Joshi et al 2016), avoiding all the side effects from the systemic administration (Bailey 1997).

Hydroxyapatite (HAP) poses excellent biocompatibility for soft tissues, proposing it as an excellent alternative for different cavities (dentin, enamel, and cementum) but also for pulp, and periodontal ligament (Pinheiro et al 2009). Because the major content in the bone is the HAP nanoparticles, usually the scaffolds designed for bone regeneration, are reinforced with an inorganic substance such as HAP (Singh & Pramanik 2017). The use of HAP in the nano size (nHAP) brings additional advantages like high surface area, better wettability, and the ability to form a stronger and thinner layer with the enamel (Pinheiro et al 2009). Polycaprolactone (PCL) is a semi-crystalline, biodegradable, and biocompatible linear aliphatic polyester, with a unique combination of polyolefin-like mechanical properties (Peponi et al 2012). PCL is also acknowledged to be safe by the Food and Drug Administration (FDA) and provides high interest in the medical sector (Malikmammadov et al 2018).

The literature describes different types of biomaterials obtained through electrospinning loaded with different drugs like amoxicillin (Furtos et al 2017), ciprofloxacin (Aytac et al 2019), or gentamicin (Coimbra et al 2019). But over time also different scaffolds, with MET content were developed and characterized to treat different anaerobic infections (Tuğcu-Demiröz et al 2020; Celebioglu & Uyar 2019; He et al 2017).

The aim of this study was the development of new scaffolds from PCL loaded with nHAP and MET for the treatment of periodontal disease. The structure of the new scaffolds was evaluated on SEM imagines by measuring the diameter of the fibers. The mechanical properties were analyzed by calculating the Young modulus, the stiffness, the load at maximum load, and the tensile strength.

Materials and Methods

Materials

PCL (M.W. 80000 g·mol^{-1}), MET, dichloromethane (DCM)/dimethylformamide (DMF), poly(vinyl alcohol) (PVA), calcium nitrate tetrahydrate ($Ca(NO_3)_2 \cdot 4H_2O$), diammonium hydrogen phosphate ($(NH_4)_2HPO_4$), and ammonium hydroxide solution (NH_4OH) were obtained from Sigma-Aldrich, Germany. Darvan 821A was purchased from R. T. Vanderbilt, Norwalk, CT, USA. All commercial materials were used without any purification. The nHAP synthesis for the scaffolds took place in the lab of the Department of Dental Materials, Babes-Bolyai University-Raluca Ripan, Institute of Research in Chemistry, Cluj-Napoca, Romania. nHAP was obtained by a chemical method, from Ca and P precursors. Two solutions of 1L were prepared in two beaker glasses (2L). The solutions of calcium nitrate and ammonium hydrogen phosphate were obtained by mixing and strong stirring of Ca and P with double distilled water at ambient temperature. In both solutions, the dispersing agent of 0.2 vol.% of 1:1 Darvan 821A/PVA was added. The pH of the solution was adjusted with 25% NH_4OH to keep a pH of 10.5. In the end, both solutions were mixed according to the standard stoichiometry for pure HAP at a Ca/P ratio of 1.67.

Preparation of experimental scaffolds

Three types of different scaffolds were proposed to be obtained for this study (Table 1). For all the experimental realized scaffolds, PCL was used in an equal quantity of 2g, to get a close thickness of the scaffolds. The quantity (% wt) of nHAP/MET was added according to Table 1. The obtaining mechanism was described in detail in another paper (Mirica et al 2021).

Table 1. The composition of experimental scaffolds

Nr.	Code	Composition of experimental scaffolds		
		PCL (%wt.)	**nHAP (%wt.)**	**MET (%wt.)**
1	PCL	100	0	0
2	PCL-5%MET	95	0	5
3	PCL-5%nHAP-5%MET	90	5	5

Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM)

To evaluate the size and shape of the obtained nHAP particles, the nHAP powder was investigated by TEM (H-7650 120kV automatic microscope, Hitachi, Japan) using settings at 80KV high voltage and 20x magnification. The measurements of the diameter of the used nHAP were made using Image J software by calculating the mean diameter, and standard deviation (SD). The morphology of the scaffolds was analyzed by scanning electron microscopy (SEM Inspect S, FEI, Netherlands) using high vacuum, 15KW, 2000 magnification, and a working distance between 10.7 and 13.9 mm. The diameter of the fibers was measured using Image J software at different random locations for each scaffold type. The mean diameter and standard deviation (SD) were calculated and translated on the graphs.

Mechanical Properties

The samples (n=5) with a rectangular shape (width=6 mm, length=8 mm) were tested in dry condition using a mechanical testing machine (LR5K Plus, Lloyd instruments. Ltd., England) at a loading rate of 1 mm/min-1. The investigated parameters were: the Young modulus, the force at maximum load, the tensile strength, and the stiffness. The Young modulus of the specimens was measured from the slope of the linear portion of the stress-strain curve. The stiffness (S) was determined using equation 1.

$$S = \frac{F}{\delta} \quad (N/m) \qquad (1)$$

where: F is the force on the body; δ is the displacement produced by the force along the same degree of freedom.

The tensile strength (TS) was analyzed using equation 2.

$$TS = \frac{F}{A} \quad (MPa) \qquad (2)$$

where: TS is the tensile strength (MPa), F is the force on the cross-section of the specimen at final tension (N); A is the nominal cross-sectional area of the sample (mm2).

Statistical analysis

The quantitative results were statistically determined using the one-way analysis of variance (ANOVA) and the Tukey's test (SPSS version 11.5, SPSS Inc., USA). The level of significance set at 0.05 was considered to be statistically significant.

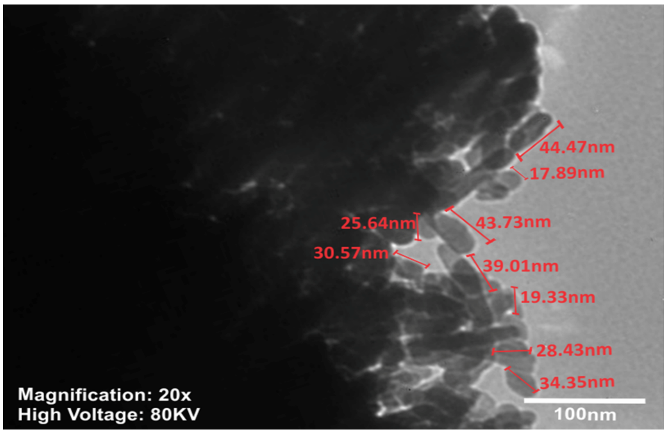

Fig. 1. TEM micrographs of the synthesized nHAP powder

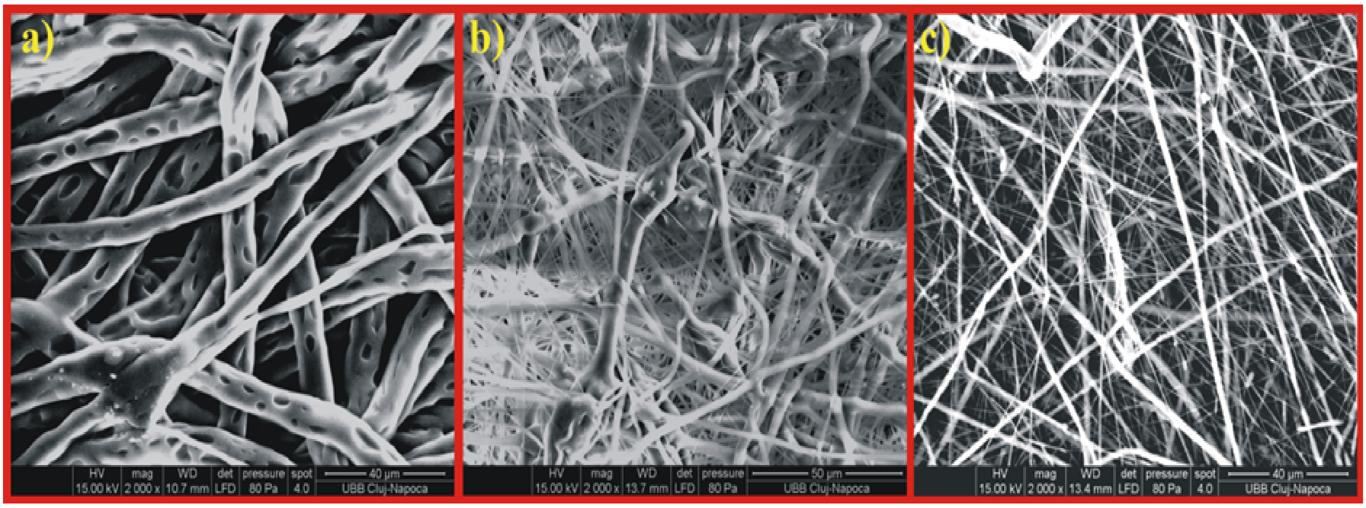

Fig. 2. SEM imagines of the obtained scaffolds. a) PCL scaffold; b) PCL-5%nHAP-5%MET scaffold; c) PCL-5%MET scaffold

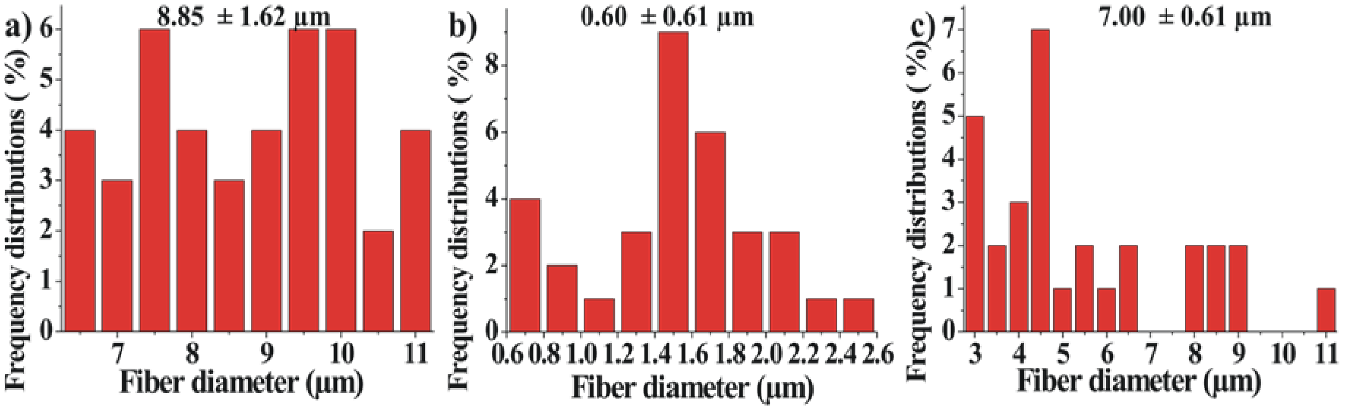

Fig. 3. Fiber distribution of the obtained scaffolds: a) PCL; b) PCL-5%MET; c) PCL-5%nHAP-5%MET

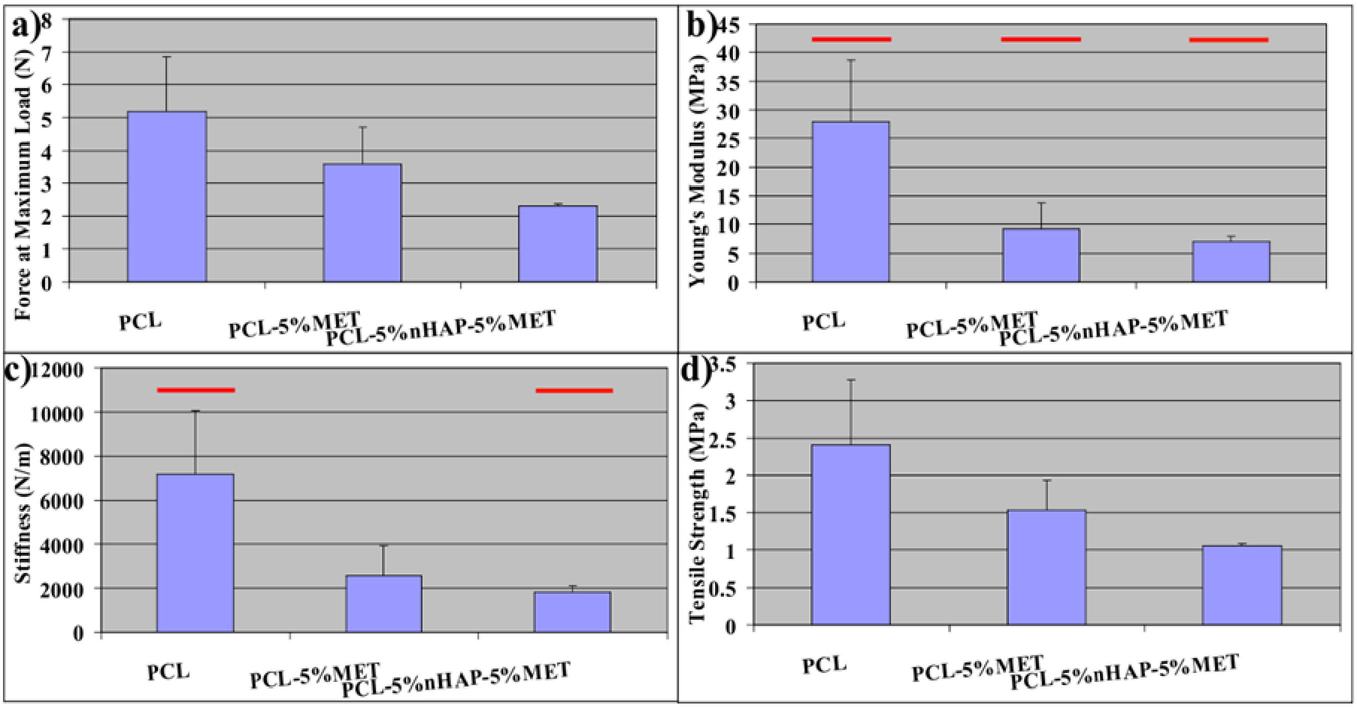

Fig. 4. Mechanical properties of the developed scaffolds: a) force at maximum load (N); b) Young modulus (MPa); c) stiffness (N/m); d) tensile strength (MPa) (red horizontal bars underline the results, statistically significant different from each other compared using Tukey's test)

Results

TEM micrographs (Fig. 1) of crystals of nHAP rod particles showed a mean length of 31.49 nm (±9.75 SD). The SEM analysis showed typical electrospun architecture of randomly continuous oriented bead-free fibers. The interconnected fibers build macro pores distributed in the whole structure as is shown in Fig. 2. The size of the fibers ranged between 6.5 and 11 μm for the PCL scaffolds (Fig. 2a), for the PCL-5%MET the fiber size ranged between 0.6 and 2.5 μm (Fig. 2b), and for the PCL-5%nHAP-5%MET scaffold the size of the fiber ranged between 3 and 11 μm (Fig. 2c). The distribution of the fiber diameter frequency is shown in Fig. 3.

The tests run to evaluate the mechanical properties of the scaffolds showed results situated between 2.2 and 5.2 N for the force at maximum load (Fig. 4a). The results for the Young modulus were registered between 7 and 28 MPa (Fig. 4b). The highest value for stiffness was registered for the PCL scaffold and was evaluated at 6.650 N/m and the lowest value was certified for the PCL-5%nHAP-5%MET scaffold at 1.990 N/m (Fig. 4c). The tensile strength was registered to be between 1.05 and 2.4 MPa (Fig. 4d).

Discussion

According to the World Health Organization (WHO), around 10.8% of adults worldwide present severe periodontitis (Petersen & Ogawa 2000), which is described to be the sixth most prevalent condition in the world (Kassebaum et al 2014). In the last period, several regenerative-based strategies were proposed to treat periodontal disease by reconstruction of the periodontal tissue (Chiu et al 2013), but the ideal scaffold is still to be found. Electrospinning is a process, which enhances the plasticity of the scaffolds, improving flexibility without compromising their lasting in time. The orientation of the nanofibers in the scaffolds is tuning the mechanical properties (Ghosal et al 2018).

The scaffolds obtained in our research gave promising results from the point of view of morphology and mechanical properties. The morphology of the continued nanofibers was given by the strength of the compound jet, which was affected by the physical properties of the compounds (PCL, MET, DCM, DMF, nHAP), as well as the electrospinning parameters (temperature, applied voltage, and humidity) (Díaz et al 2006). After optimizing the electrospinning parameters, the obtained nanofibers showed diameters influenced by their compositions. It was noticed that the addition of MET is lowering the diameter of the fibers, the PCL-5%MET scaffolds showed the fibers with the smallest diameter, around 0.6 μm (Fig. 2c). The addition of nHAP is increasing the diameter of the nanofiber to 7 μm but under the diameter of the unloaded scaffold (PCL) which was situated around 8.85 μm. Other studies (Mirica et al 2021) showed a similar trend. The mechanical properties of the developed scaffolds were dependent on the morphology of the fibers (Cork et al 2017). The inclusion of MET decreased very much the fiber diameter (Fig. 3c), reflected in the poor mechanical behavior (Fig. 4). A higher diameter of the nanofibers in our study explained the increased mechanical properties (Fig. 4), finding in concordance with other studies (Furtos et al 2017; Mirica et al 2021). The stiffness decreased by around 71% after adding MET and after the addition of MET and nHAP, these properties decreased by another 4 % (Fig. 4c). Our results were in concordance with the study of Rowe (Rowe et al 2016), who developed and tested in his research scaffolds with borate bioactive glass. An explanation for this can be given by the fact, that the interfacial area between the PCL matrix and the other compounds (MET, nHAP) was dramatically reduced (Grady 2010). The force at maximum load decreased in the following order: PCL> PCL-5%MET> PCL-5%MET-5%nHAP and was in concordance with other studies (Mirica et al 2021).

The Young modulus indicates the property of the material to resist mechanical deformation (Wang et al 2018). The results of our developed scaffolds showed a lowering of this property with 75% when MET was added together with nHAP but was higher than in other studies (Gazquez et al 2016). The tensile strength is a very important parameter, which shows how long the integrity of the formulation will last (Deepak* et al 2018). In our study, the tensile strength decreased by 37.5 % when MET was added and by 43.75 % when both compounds were added. This fact was explained by Hivechi (Hivechi et al 2019) due to the agglomeration of the compounds, which introduces weak positions in the nanofibrous mats, and forms stress concentration points. Although the addition of MET decreased the mechanical properties of the developed scaffolds, this compound gives the principal characteristic of the proposed developed scaffolds, the antibacterial effect (Deepak et al 2018).

Conclusion

The experimentally developed scaffolds showed typical electrospun bead-free fibers, which formed macropores in the whole structure of the sample. The incorporation of MET lowered the fiber size and the addition of nHAP increased the diameter of the fibers. The size of the fiber affected the mechanical properties of the scaffolds. A smaller size lowered the mechanical properties and a larger size increased them. Further tests (antibacterial properties, cytotoxicity, and biomineralization assays) are needed to prove their use in the treatment of periodontal disease.

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Citation	Mirica IC, Furtos G, Lucaciu O, Moldovan M, Campian RS. New scaffolds for guided bone regeneration. HVM Bioflux 2021;13(2):88-93.
Editor	Antonia Macarie
Received	6 April 2021
Accepted	9 May 2021
Published Online	30 June 2021
Funding	None reported
Conflicts/ Competing Interests	None reported