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Study on Polycaprolactone Coated Hierarchical Meso/ Macroporous Titania Scaffolds for Bone Tissue Engineering

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ABSTRACT

In this study, the effect of polycaprolactone (PCL) coating on the mechanical strength, cell behavior and cell attachment of the hierarchical meso/macroporous Titania scaffold were investigated. Titania scaffold as the substrate was fabricated through the evaporation-induced self-assembly coupled with the foamy method. Then prepared scaffolds were coated by polycaprolactone solution with three different weight percentages by the dip-coating method. SAXS, WAXRD, SEM, compressive strength, MTT and cell attachment test were applied to characterized the samples. Based on XRD results, as polycaprolactone concentration increased, the intensity of the crystalline polycaprolactone phase increased while the TiO_2 peak intensity decreased due to the covering of mesoporous titania by polycaprolactone. Compressive strength showed that by increasing polycaprolactone percent, the porosity decrease from 89.5 to 73.8 % which caused increasing strength from 0.2 to 0.79 MPa. The SEM results illustrated that by increasing polycaprolactone concentration from 1.2 to 1.5 wt%, the macrospores were filled by polycaprolactone. In this regard, The sample containing 1wt% polycaprolactone was choosen as the selective sample. Also, the MTT test reported a small trace of cytotoxicity in contact with the L929 mouse fibroblast cells. The cell attachment test that was performed by using MG63 cells, showed that the coated samples provided the suitable substrate for cells to attach and also showed cell viability on the surface of the coated substrate. Overall, according to the results, the hierarchical meso/macroporous Titania scaffold coated with 1 wt% polycaprolactone, could have good potential to be used in tissue engineering.

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1. INTRODUCTION

The natural bone is an alive complex structure made of organic/inorganic hierarchical porous composites that provide the metabolism and mechanical strength of the bone [1-3]. Bone injuries would be happened due to old age, accidents, and mechanical strikes altogether have made the researchers use bone grafts and artificial bone tissue engineering devices. In this way, bone tissue engineering scaffolds have good potential as a response to these challenges [4-8]. For this purpose, biomimetic ceramic-polymer composite which has controllable hierarchical porous could mimic the structure and function of natural bone and have positive interactions with cells of this tissue [9, 10]. Improvement of mechanical strength, increasing specific surface area, the possibility of collateral cell growth, and the potential of releasing biological agents and drugs are the positive point of this type of structure [11-13]. Recently, bio-glasses mesoporous structure, silica, and Titania that have bioactive features caused to showed a new approach in bone tissue engineering [13-17]. Titanium dioxide, with the ability to adsorb proteins and hydroxyapatite, can bone attachment. These results were considered in the in-vitro condition which showed a positive effect in the in-vivo condition [18-23]. The hierarchical porous titanium dioxide provides surface activity, nano roughness, and appropriate space for loading cellular and biological agents [24].

Polycaprolactone (PCL) is an organic component because of its adaptability and biodegradability has been considered much in tissue engineering applications [25].

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Hybrid structures containing PCL and titanium dioxide can increase the corrosion resistance of biodegradable alloys by coating them [26, 27] or to be used in drug release applications [28]. Some investigations also have focused on the use of PCL as an inorganic and titanium oxide with various designs as an inorganic component of the scaffolds for bone tissue repairing and regeneration. Some of them are mentioned in the following paragraph. Khoshroo et al. [29] designed and produced a scaffold for bone tissue engineering by exploiting the properties of PCL and combining it with titanium oxide nanotubes. De Santis et al. [30] investigated the cell compatibility and some features of the polycaprolactone/ hybrid titanium dioxide. Catauro et al. [31] studied the TiO_2/PCL hybrid layers through sol-gel on the surface of the titanium by deep coating. They investigated the characterization and biological features of this hybrid that shows it's in vitro bioactivity of it. Hierarchical meso/macroporous structure provides suitable bio-inspired geometry structure for scaffolds. Also by literature survey, it could be concluded that by polymer coating of mentioned scaffolds, the biocompatibility improved. Also, by improvement of biological behavior, it could be potentially suitable for the targeted control of biological agents, which could prevent the body's defensive response and reject of scaffold which provides a appropriate cell differentiation. In another word, using polycaprolactone in the composition of the scaffold provides a better possibility for the formation of calcium phosphates [32].

So far, no studies have been performed on a hierarchical porous titanium oxide (titania) coated with PCL, which has been considered in the present work. For this purpose, a hierarchical porous Titania scaffold fabricated by EISA along with the foamy method [33] were coated with polycaprolactone polymer to enhance the mechanical strength and make the structure susceptible to the support of bioactive agents for bone tissue engineering applications.

2. MATERIALS AND METHODS

2. 1. Sample Preparation The hierarchical meso/macroporous Titania scaffolds were synthesized as the substrate according to our previous studies [24, 30]. Briefly, Titanium (IV) butoxide ($C_{16}H_{36}O_4Ti$, 97%, Sigma Aldrich) is the precursor, the tri-block F127 copolymer (99.5%, Sigma Aldrich) as the template, and anhydrous ethanol (C_2H_6O, 99.5%, Sigma Aldrich), hydrochloric acid (HCl, 38 wt.%) and acetylacetone ($C_5H_8O_2$, 99.5%, Sigma Aldrich) were used as the solvent and restrain the speed of hydrolysis-condensation. The sol-gel process according to Catauro et al. [34] and Li et al. [35] was used. In this regard, the mass ratio of F127/TBT/HCl/EtOH/AcAc was kept to 3/100/8/5/2, respectively and then, aged for 48h at room temperature and 40% humidity, the pre-cut polyurethane foam blocks (60 ppi) in size of $1*1*1cm^3$ were soaked in colloid for 2 minutes. Then the samples were squeezed to remove the extra solution and dried at room temperature for 72h. Finally, the samples were calcined in 550 ^{0}C for 2h with a rate of 4^{0}C/min.

To prepare the coating solution 1, 1.2, and 1.5wt% polycaprolactone (Sigma-Aldrich 80000 Mn) and chloroform (99% purity) were made in a container and ceramic scaffolds were immersed in it for 3 minutes. After that scaffolds were dried for 72h at room temperature. Table 1 summarized the sample designations, where the number before PCL represents the percentage of PCL.

2. 2. Invitro Cell Viability To evaluate the in-vitro cell viability test, the fibroblast mouse cell (Mouse C34/connective tissue-L929) from the cell bank of Pasture Institue of Iran was provided. In this way, the massive cells were cultured in RPMI-1640 medium containing 50 unit penicillins, 50 μg/ mL streptomycin, and 10% fetal bovine serum in an incubation flask with 5% carbonic gas and 85% humidity at 37 °C. After 3 to 4 days (which cell layer formed), the cells were removed by trypsin enzyme (0.25%) from the flask surface. Then a suspension with 20000 cells/mL concentration was prepared.

The prepared specimens (5 ×5 mm) were sterilized by UV for 1 h. Then the samples were put in a 24-well (culture) plate, in which for each sample 3 separated wells were considered also 3 wells were considered for the control sample. In this way, 1 mL cellular suspension was added to each well and was put in the incubator. In each well, 20000 cells in a culture medium (RPMI-1640) containing 10% fetal bovine serum (FBS) were added. After 48 hours, 100 μL of MTT stain with 5 mg/mL concentration was added to the cell medium culture and incubated at 37 °C for 48 h. Then the medium culture on the cells was removed by phosphate-buffered saline (PBS), in the following, 0.5 mL of DMSO solution was added to each well. After dissolving the purple color in the samples, they were transferred to an ELISA plate and the absorbance of the samples was reported at 570 nm. Three wells were considered from each sample to determine the mean absorbance values.

TABLE 1. Titania scaffolds designations with PCL coating

Sample	Amount of pcl (wt%) in the coating solutions
0PCL	Without any coating
1PCL	1
1.2PCL	1.2
1.5PCL	1.5

2. 3. Cell Attachment Assay The cell attachment test was considered in sample 1PCL, in this regard; Human osteosarcoma bone cell (MG63) was obtained from Pasture Institue of Iran cell bank. The massive cells were initially cultured in a cultured media containing 50 units of penicillin and 50 µg/mL streptomycin supplemented with 10% fetal bovine serum in incubation flasks with 5% CO_2 and 85% humidity at 37 °C. After 3 to 4 days (which cell layer formed), the cells were removed by trypsin enzyme (0.25%) from the flask surface. Then a suspension with 40000 cells/mL concentration was used. Both sides of the prepared samples were sterilized by UV for 1 h. Then the samples were put in a 24-well (culture) plate (each sample individually in one well) and a non-sample well was considered as a control. Then 1 mL of cell suspension was added to samples and placed in an incubator, After 24 and 48h incubation, the sample (1PCL) was evaluated qualitatively by an inverted microscope (Nikon TE-100). In order to stabilize the cells, the samples were washed three times with PBS. Then the sample was placed in glutaraldehyde solution (2.5%) for 2h after 2h washed it again with PBS. In order to dehydrate the sample, different concentrations of alcohol and water were used (by the concentration of 50, 60, 70, 80, 90, and 100) for each concentration washed for 5 min. finally, the prepared sample was dried at room temperature and the cell attachment was examined by using an FEI- ESEM Quanta 200 scanning electron microscope.

2. 4. Characterization Coating of mesoporous with polycaprolactone was studied by small-angle X-ray diffraction (SAXS) by an Asenware AW-DX300 diffractometer with Cu Kα radiation (λ = 1.54184 Aº) in the 2θ range 0.5-10º) and Wide-angle X-ray diffraction (WAXRD) was also applied to evaluate the crystalline phase of scaffolds using the same machine in the 2θ range 10 -100º.SEM investigation was used to investigate the morphology and macroporous structure coated with polymer (Zeiss SEM, Germany, on gold-coated samples) also in order to investigate the morphology of the cell attachment of coated samples was examined at room temperature using an FEI- ESEM Quanta 200 scanning electron microscope. Compressive strength of Titania scaffolds and Titania scaffolds coated by polycaprolactone polymer were tested using (AG-400NL, SHIMADZU Co., JAPAN) with an overhead speed of 0.5 mm/min.

An ethanol immersion test also was performed for calculating of porosity percentages of the samples.

2. 5. Statistical Analysis All data were reported as mean values and standard deviation using SPSS software. Statistical analysis of the results was performed using ANOVA test. P-values less than 0.05 were considered statistically significant.

3. RESULTS AND DISCUSSIONS

3. 1. X-ray Diffraction Figure 1a. shows the low-angle X-ray diffraction pattern of samples. As can be seen in this figure, by increasing the weight percent of polycaprolactone, the peak intensity at about 2θ=0.7 which is representative of the mesoporous structure decreased sharply at small angles, which indicated that the mesoporous structure decreased due to filling the porosity by polycaprolactone .

Also, Wide-angle diffraction (WAXRD) approved the presence of crystalline and amorphous anatase phases and crystalline polycaprolactone. In this way Sownthari and Suthanthiraraj [36] reported that pure PCL has 3 strong diffraction peaks at 2θ=21.4, 22 and 23.7 that these peaks were related to (110) (111) and (200) orthorhombic plans, which the XRD results of our obtained data had a good agreement with the reports and had both 2θ=21.4 and 23.7. As the concentration of the polycaprolactone coating solution increased, the corresponding peak of polycaprolactone mentioned above was sharply increased and at the same time, the TiO_2 peak intensity decreased (see Figure 1b).

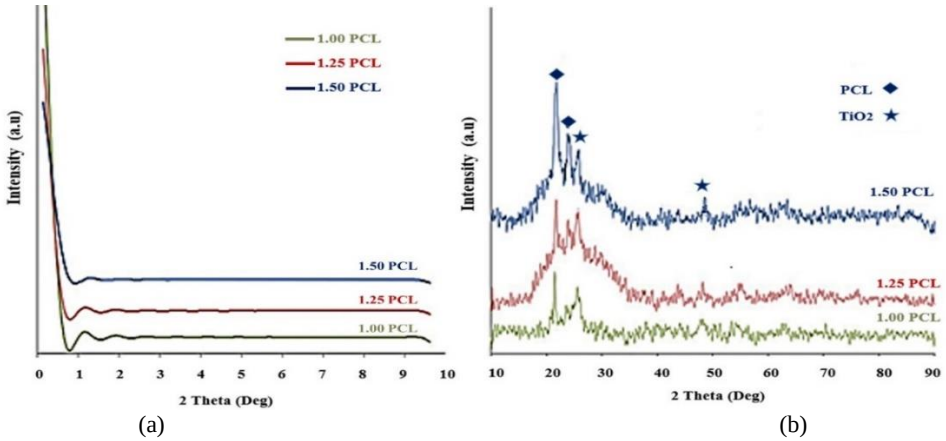

Figure 1. XRD patterns of sample 1PCL, 1.2PCL, 1.5 PCL a) small-angle XRD (SAXS) and b) wide-angle XRD (WAXRD)

As porous ceramics have low mechanical strength, the coating of these materials by polymers could be an appropriate solution to solve this problem. Also at the same time decreasing the porosity could the other point which caused to increase in the mechanical strength of the titania scaffold in the presence of PCL coating [12].

3. 2. Scanning Electron Microscopy Figure 2 shows the SEM micrograph of samples 1.2 PCL and 1.5 PCL at 50 and 300 × magnifications. As could be seen in this figure by increasing the PCL concentration, the vesicular macroporous were filled by PCL and caused limited interconnections of the macroporous network for vascularization. In sum, although by increasing the concentration of PCL, the mechanical strength increased, but due to decreasing the interconnection of macroporous, the sample 1PCL was selected as an optimized sample, and additional investigation was considered in this sample.

In this regard, the microstructure of sample 0PCL was compared with sample 1PCL. Figure 3(a) shows the microstructure of sample 0PCL, by investigation of this micrograph it could be concluded that the 0PCL macroporous sample had an integrated structure without any cracks. Also, macroporous sizes of about 300 μm and vesicular porous made this macroporous structure a suitable scaffold for the cell growth. But despite all of these positive features and according to mechanical strength, the low strength of these scaffolds caused to protect them with PCL polymer (see Figure 3(a)).

Figure 3b shows the 1PCL sample, results showed the presence of PCL on the macroporous walls which had no negative effect on limiting macroporous interconnection and the integrated structure of this sample had been preserved. So we have a sample of the same positive features that have higher strength as it showed in Table 2. Also, a higher magnification of sample 1PCL is shown in Figures 3(c) and 3(d). Figure 3(c) shows a porous that is covered by the integrated PCL polymer coating and Figure 3d illustrates a polymer cover on the macroporous arm. It

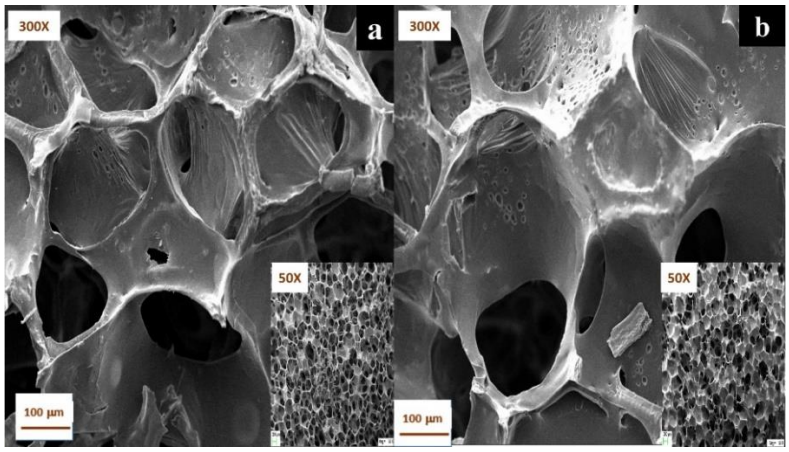

Figure 2. SEM micrograph of (a) sample 1.2 PCL (b) sample 1.5 PCL at 50 and 300× magnifications

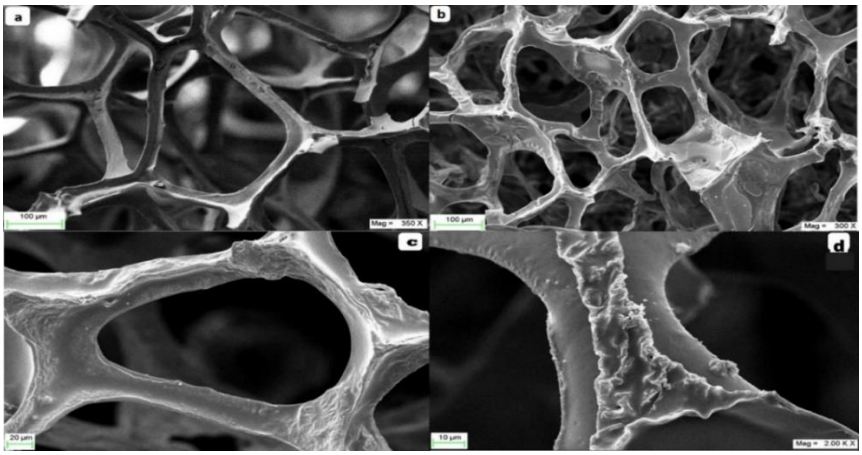

Figure 3. SEM micrograph of a) sample 0PCL b) sample 1PCL with the magnification of 300 c) sample 1PCL with the magnification 800 d) sample 1PCL with the magnification of 2000

relates to the appropriate concentration of the polymer solution and the dip-coating technique that was used to coat titania with PCL.

The technique had been used before in the formation of a thin polymer film on other macroporous ceramics such as alumina minimizing intrusion into the support pores [37].

3. 3. Mechanical Strength Test The compressive strength of uncoated Titania scaffolds which were measured and compared with coated samples (PCL 1, PCL 1.2, PCL 1.5) are summarized in Table 2.

Results showed that the uncoated sample had 89.5 % porosity by coating this scaffold with PCL the porosity decreased to 73.8 % with the addition of 1.5 % PCL. That the strength contrariwise effects with porosity and as porosity decreased, the strength increased from 0.29 MPa of uncoated sample to 0.79 MPa for the sample coated by 1.5% PCL.

Also, these results were approved by Kim et al. [38, 39] for the hydroxyapatite scaffold, he reported that a porous hydroxyapatite scaffold (with 8% porosity) synthesized through the inversion foam method showed 0.21 MPa compressive strength, as compositing with polycaprolactone the compressive strength increased to 0.45 MPa.

Taking everything into account, the macroporous titania which covered by 1 % PCL had suitable microstructure and mechanical strength in order to use it as a biomaterial.

3. 4. The Cytotoxicity Assay The cytotoxicity assay was performed using L929 fibroblast cells was used to compare samples 0PCL and 1PCL with a control sample. The results are shown in Figure 4. As could be seen in this figure the cell viability for the control sample was about 70.53% and this percentage decreased to 61.33% for sample 0PCL and 65.06% for sample 1PCL, that these results showed that all samples had good viability and no cytotoxicity was observed in these samples. In this way, the sample 1PCL which was coated by PCL showed better cell viability. The literature survey showed that The polymeric coating formed on the scaffold can enhance the mechanical strength and also can be considered as a carrier and a potential for sustained releasing of drugs and biological agents [34]. Khoshroo et al. [29] had pointed out that using PCL with TiO_2 could improve biological behavior for bone tissue engineering applications.

TABLE 2. Compressive strength and porosity of the samples

Sample	Mean Porosity %	Maximum compressive strength (MPa)
0PCL	89.5 ± 0.3	0.29 ± 0.04
1PCL	86.2 ± 0.2	0.69 ± 0.03
1.2PCL	79.3 ± 0.2	0.72 ± 0.02
1.5PCL	87.3± 0.3	0.79 ± 0.02

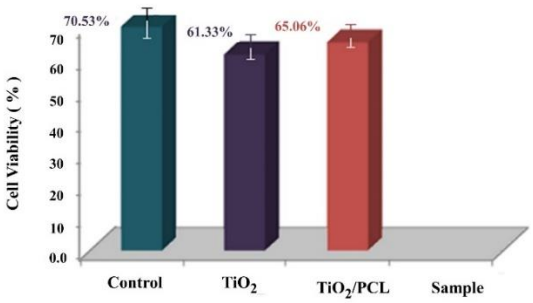

Figure 4. The bar chart of cell viability percentage (fibroblasts (L929) at 570 nm wavelength absorbance in control samples (without scaffold), of sample 0PCL and 1PCL during 48 h

In other words, the polymeric coating has improved the cell viability and a small trace of cytotoxicity was observed in these samples.

3. 5.The Cell Attachment Assay To the above results, it could be concluded that sample 1PCL had better potential to use as a biomaterial, so for the cell attachment assay, sample 1PCL was observed after 48 h immersion in a culture medium containing human osteosarcoma bone marrow (MG63) by using FEI ESEM Quanta 200 scanning electron microscope (see Figure 5). In this regard, Figures 5(a) and 5(b) show a cell that speared on the surface of the macroporous arm. Due to well cell attachment, 2 characteristics are important: cell spreading and cell adhesion, this sample shows both characteristics, so it showed a good cell attachment.

On the other hand, the cell had a spindle shape with pseudopodia of the osteosarcoma cell which caused better cell attachment in the arms of macroporous.

The higher magnification of sample 1PCL is shown in Figures 5(c) and 5(d). which Figure 5(c) shows the large number of cells attached to the macroporous arms. Also, Figure 5d illustrates the spindle shape of a cell attached by its pseudopodia of the osteosarcoma cell on the surface of macroporous which could provide cell proliferation.

Taking everything into account, sample 1PCL, simultaneously showed good strength and biological properties to use it as a scaffold in tissue engineering.

4. CONCLUSION

In this study, the effect of PCL coating on the mechanical strength, cell viability, and cell attachment of hierarchical meso/ macroporous titania scaffold for bone tissue engineering were reported. The mechanical strength of these samples showed that by coating hierarchical meso/ macroporous titania scaffold with PCL, the mechanical strength increased from 0.29 MPa to 0.79 MPa by coating 1.5% PCL. But in the same way, microstructure

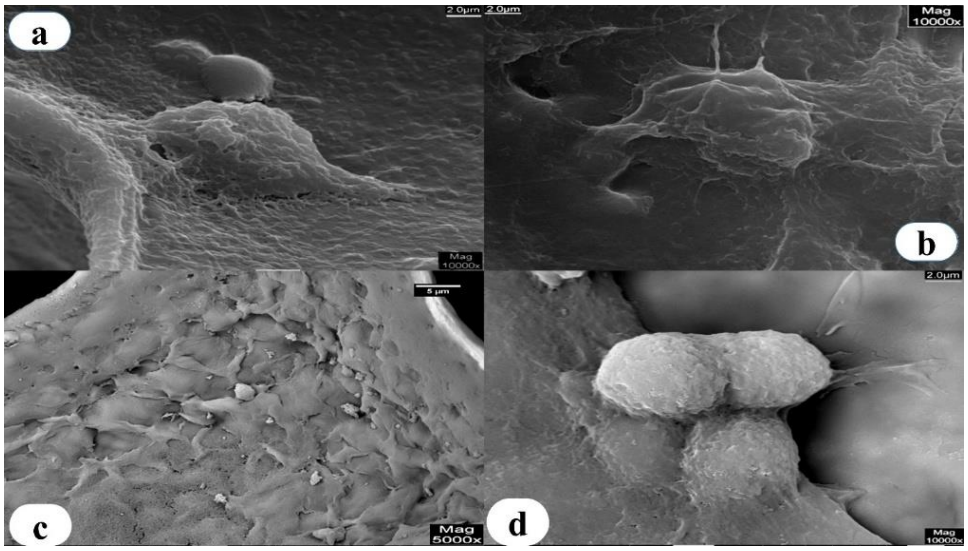

Figure 5. SEM micrograph of cell attachment of sample 1PCL at different magnification

investigation showed that by increasing polycaprolactone concentration from 1.2 to 1.5 wt%, the macrospores were filled with polycaprolactone and caused to decrease interconnection of pores. So the sample coated with 1% PCL was considered to evaluate the cytotoxicity and cell viability. Cell viability results showed that both hierarchical meso/ macroporous titania scaffold and hierarchical meso/ macroporous titania scaffold coated by 1% PCL had good cell viability, but the coated sample showed less cytotoxicity. So cell attachment of 1% PCL was evaluated and results showed cell spreading and cell adhesion on the surface of the macroporous arms which could provide cell proliferation.

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Persian Abstract

چکیده

در این مطالعه، اثر پوشش PCL بر استحکام مکانیکی، رفتار سلولی و اتصال سلولی به داربست مزو/ ماکرو متخلخل تیتانیا با ساختار مرتبه ای مورد بررسی قرار گرفت. داربست تیتانیا به عنوان بستر از طریق خودآرایی ناشی از تبخیر همراه با روش فومی ساخته شد. سپس داربست های آماده شده با محلول پلی کاپرولاکتون با سه درصد وزنی مختلف به روش غوطه وری پوشش داده شدند. آزمون SAXS، WAXRD، SEM، مقاومت فشاری، MTT و چسبندگی سلولی برای مشخصه یابی نمونه‌ها اعمال شد. بر اساس نتایج XRD، با افزایش غلظت پلی‌کاپرولاکتون، شدت فاز پلی‌کاپرولاکتون کریستالی افزایش یافت در حالی که شدت پیک TiO_2 به دلیل پوشاندن تیتانیا مزوپور توسط پلی‌کاپرولاکتون کاهش یافت. مقاومت فشاری نشان داد که با افزایش درصد پلی‌کاپرولاکتون، تخلخل از ۸۹/۵ به ۷۳/۸ درصد کاهش می‌یابد که باعث افزایش مقاومت از ۰/۲ به ۰/۷۹ مگاپاسکال می‌شود. یکی از پارامترهای یک داربست ایده آل برای مهندسی بافت، شبکه ماکرو متخلخل به هم پیوسته برای رگزایی، نفوذ بافت و تحویل مواد مغذی است، به این ترتیب نتایج SEM نشان می دهد که با افزایش غلظت پلی کاپرولاکتون از ۱.۲ به ۱.۵ درصد وزنی، حفره های ماکرو با پلی کاپرولاکتون پر شدند و باعث کاهش اتصال منافذ می شود. در این راستا، اگرچه با افزایش درصد پلی‌کاپرولاکتون، استحکام افزایش یافت، اما کاهش شبکه ماکرو متخلخل به هم پیوسته باعث شد که نمونه‌ی حاوی ۱ درصد وزنی پلی‌کاپرولاکتون به عنوان نمونه انتخابی انتخاب شود. همچنین، آزمایش MTT سمیت سلولی کم را در تماس با سلول های فیبروبلاست موش L929 گزارش کرد. آزمایش اتصال سلولی که با استفاده از سلول‌های MG63 انجام شد، نشان داد که نمونه‌های پوشش‌داده‌شده بستر مناسبی را برای اتصال سلول‌ها فراهم می‌کنند و همچنین زنده‌مانی سلولی را در سطح بستر پوشش‌داده شده نشان می‌دهند. به طور کلی، طبق نتایج، داربست سلسله مراتبی مزو متخلخل تیتانیا با پوشش ۱ درصد وزنی پلی کاپرولاکتون، می تواند پتانسیل خوبی برای استفاده در مهندسی بافت داشته باشد.