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Preparation and characterization of 3D printed bone scaffold for ibuprofen delivery

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Abstract

In this work, a blend of gelatin A (GA) and polyvinylpyrrolidone (PVP K30) was used for semi-solid 3D printing of bone scaffold for ibuprofen (IBU) delivery. The cross-linking of the obtained scaffold was performed with a 1% glutaraldehyde (GTA) solution, followed by lyophilization. The thermal and mechanical properties, as well as drug release profiles, and drug kinetics of prepared scaffolds were investigated. The cross-linked and lyophilized scaffold has shown good thermal stability, mechanical properties, and prolonged release of IBU following the Fickian diffusion process.

Key words: semi-solid extrusion 3D printing, gelatin-based bone scaffold, *in vitro* ibuprofen release and kinetics, microindentation, hardness

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Introduction

Drug delivery scaffolds are advanced formulations that allow controlled and targeted release of active pharmaceutical ingredients (API). In modern research, many approaches for the processing of scaffolds have emerged through blending natural and synthetic polymers (1). The development of these scaffolds combines materials science, pharmacy, and biomedicine principles in order to achieve regeneration and healing of damaged tissue. The polymeric scaffolds as a drug delivery system have potential in the development of smart therapies with combined effects on the bone tissue regeneration, as well as in treating illnesses and injuries (1). They should possess the following properties: biocompatibility, structural design, biodegradability and optimal porosity and mechanical properties (1, 2).

3D printing is a novel technology for the preparation of drug delivery scaffolds (3). It enables the fabrication of digital models, with a predesigned structure and shape, through layer-by-layer addition of material. 3D printing is an attractive processing method because it facilitates the personalization of patients' treatment and therapy (3). There are many 3D printing methods, such as fused deposition modelling (FDM), semi-solid extrusion (SSE), inkjet-based, digital light processing (DLP), selective laser sintering (SLS), and stereolithography (SLA) (4). SSE 3D printing uses paste/gel as feedstock material that is extruded through the print nozzle. The benefit of SSE is that it employs low temperature, commonly used solvents, and excipients such as polymers, plasticizers or inorganic/organic reinforcements mixed with API to prepare paste/gel (5, 6).

Gelatin A (GA) is a multipurpose natural polymer that has been used in pharmacy, medicine, cosmetics, food, and other industries. Gelatin has been known for its characteristics, such as biodegradability, biocompatibility, low antigenicity, affordability, and adhesiveness (7, 8). On the other hand, a disadvantage of gelatin use in bone tissue engineering are its poor mechanical properties (8). To overcome this problem, gelatin is often blended with other polymers (7, 9) or cross-linked (7, 10, 11). Polyvinylpyrrolidone (PVP) has great potential for blending with gelatin and application in drug delivery and tissue engineering (7, 12). PVP has good water solubility and biocompatibility, and it is a nontoxic polymer used in the pharmaceutical field for different formulations: tablets (13), buccal films (5), nanofibers (14) and hydrogels (15).

Scaffolds based on natural and synthetic polymers loaded with API can be used for various treatments and drug delivery (1). In cases of damaged bones, scaffolds with drug delivery function, beside tissue regeneration and mechanical support, have been developed as an attractive approach in bone tissue engineering (16-19). The recovery period after a bone tissue injury (mechanically or after disease) is often followed by patients' pain and non-steroidal anti-inflammatory drugs (NSAIDs) administration. These drugs are used for various therapeutic indications, such as acute or chronic pain, inflammation, and antipyresis (20). One of the most used NSAIDs is ibuprofen (IBU) (21). However, when taken orally, especially over an extended period or in higher doses,

IBU can cause side effects and gastrointestinal problems (stomach pain, nausea, ulcer, haemorrhage). The incorporation of IBU in a polymeric scaffold for drug delivery is an excellent option to avoid these problems. (22). After bone scaffold implantation, IBU release from the scaffolds could provide adequate treatment through local or targeted drug delivery strategies that allow bone tissue regeneration with reduced acute pain and inflammation (21). Various studies have been performed with *in vitro* drug release testing in simulated body fluid (SBF), and *in vivo* investigation of local delivery system for eliminating infection and inflammation (17, 19, 23).

In this paper, gelatin-PVP bone scaffolds loaded with IBU were processed by SSE 3D printing. Our choice was the composition of a scaffold with equal amounts of gelatin and PVP, because this promising material has been already successfully synthesized (7). The *in ovo* testing confirmed the biocompatibility of this scaffold, while *in vitro* testing showed the ability for proliferation and migration by using C3H10t1/2 cells (7). The aim of this work was to incorporate IBU, which would be additional advantage of this scaffold. The obtained scaffold was cross-linked to get better mechanical properties and lyophilized to achieve porosity. Each phase of scaffold development was followed by proper characterization. Based on the obtained results, it is possible to correlate the composition and structure of the final scaffold with drug release profile and mechanical behaviour.

Experimental

Materials

In the experiments, the following materials were used: type A gelatin from porcine skin (~300 g Bloom) (GA), polyvinylpyrrolidone (K30) (PVP), phosphate buffered saline tablets and 25% glutaraldehyde aqueous solution (Sigma-Aldrich Co., St. Louis, MO, USA). Glycerol 85% (Zorka Pharma HEMIJA d.o.o., Sabac, Serbia) was used for better paste printability. Ibuprofen (IBU) (Galenika a.d., Belgrade, Serbia) was Ph. Eur. 10 grade and was used as an active pharmaceutical ingredient (API). Deionized water (DI) (resistance of 18 MΩ cm) was used for experiments to prepare the solutions.

Methods

Semi-solid extrusion 3D printing of scaffolds

Gelatin and gelatin-PVP solutions with glycerol were prepared for 3D printing, as in our previous research (5). 5% w/w ibuprofen was added to the polymer solutions for the drug-loaded scaffolds and mixed on a magnetic stirrer for 2 hours at 50 °C to obtain a clear solution. After that, the syringes filled with mixtures were left for gelation at 36 °C for 12 hours to obtain good printability (smooth surface and good appearance of extruded filaments) (5, 24).

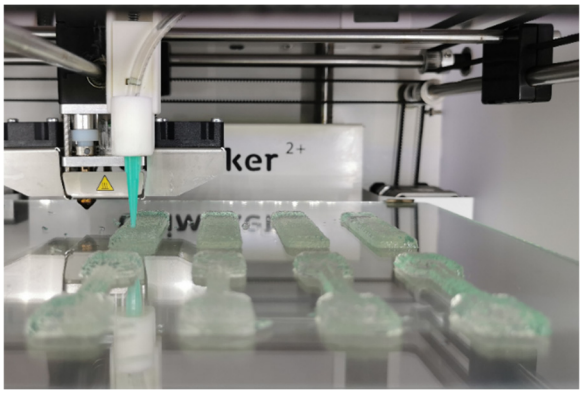


Figure 1. Semi-solid extrusion 3D printing set up
Slika 1. Proces 3D štampe ekstruzijom iz paste

The scaffolds were printed using a FDM 3D printer modified with a semi-solid extruder at 32 °C (Figure 1) (5). The shape of printed scaffolds was 60 mm × 15 mm × 0.8 mm strips. The printed scaffolds with IBU were cross-linked with 1% glutaraldehyde solution and rinsed with distilled water. The cross-linked scaffolds were then lyophilized for 24 h at -55 ° C and 0.021 mbar in a Christ Beta 2–8 LD plus freeze-dryer (Martin Christ Gefriertrocknungsanlagen GmbH, Germany) (7). The composition of the samples is presented in Table I.

Table I Composition of processed samples
Tabela I Sastav dobijenih uzoraka

Samples	GA, wt.%	PVP K30, wt.%	IBU, wt. %
S1	100	0	0
S2	50	50	0
S3	95	0	5
S4	47,5	47,5	5
SCL*	47,5	47,5	5

*cross-linked and lyophilized scaffold

Characterization

Fourier-Transform Infrared Spectroscopy (FTIR)

The characterization was performed by FTIR to follow the establishment of chemical bonding during processing; a Nicolet 6700 spectrometer (Thermo Fisher Scientific, Waltham, MA, USA) in the attenuated total reflectance (ATR) mode was used.

Differential Scanning Calorimetry (DSC)

The thermal properties of samples were followed by DSC analysis; equipment Q10, TA Instruments, Crawley, UK, was used with the setup: temperature range from 30 °C to 200 °C and a heating rate of 10 °C/min under nitrogen flow of 50 mL/min. The characteristic temperatures were determined in the accompanying TA Universal Analysis software (25).

Field Emission Scanning Electron Microscope (FESEM)

The morphology and microstructure of printed scaffolds were analysed by FESEM TESCAN MIRA 3 (Tescan Orsay Holding, a.s., Brno-Kohoutovice, Czech Republic) (5, 25).

Microindentation

Mechanical testing was performed through microindentation by a 4 mm diameter indenter and programmed loading-unloading conditions (5). The hardness (H) and the reduced elastic modulus (E_r) were calculated by the Oliver-Phar methodology (25, 26). The measurements were performed in both a dry and a wet state.

In vitro drug release test

An *in vitro* drug release test was performed as in our previous work (5), for 8h in an incubator at 37 °C using the shaker platform at 150 rpm (27). The determined ibuprofen loading in scaffolds was 5 mg per sample (25). The dissolution medium was 100 ml of PBS (pH 7.4; 0.01 M phosphate buffer, 0.0027 M potassium chloride and 0.137 M sodium chloride, data from manufacturer) (20, 27). Small amounts (3 ml) were sampled at a specified time interval (5, 10, 15, 30, 45, 60, 90, 120, 150, 180, 330, and 480 min) and replaced with the fresh medium (3 ml). Each sample was filtered with 0.45 μm membrane filter, and the amount of released IBU was determined at 221 nm by a UV–VIS spectrophotometer (5). The test was carried out in triplicate for every scaffold.

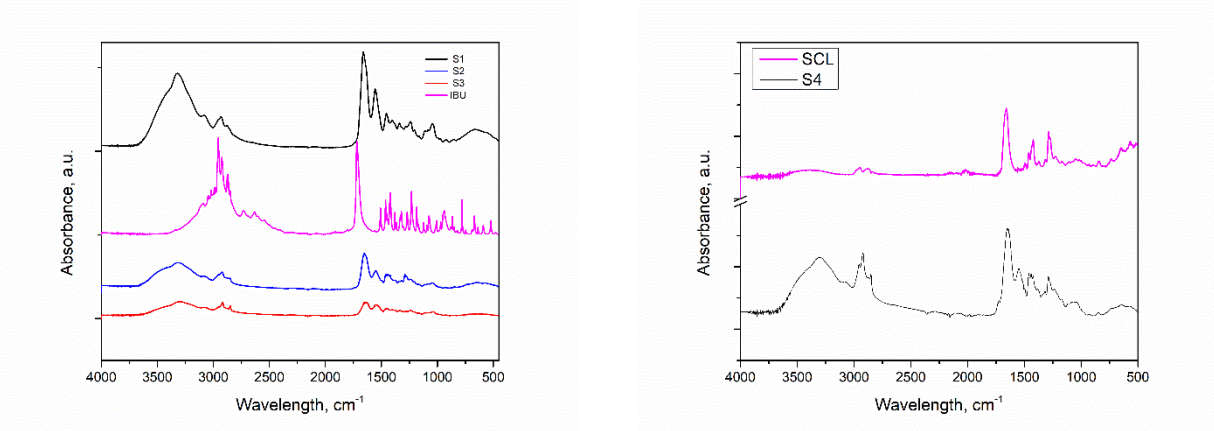
Drug release kinetics

The profiles of *in vitro* IBU release were used as input data in DDSolver software (28) to obtain drug release kinetics. The mathematical models applied for kinetics evaluation were: zero-order, first-order, Korsmeyer–Peppas and Higuchi (5). The best model for every scaffold was determined based on the highest values of the R^2 and the model selection criterion (MSC) value greater than two (5, 28).

Results and discussion

The results of FTIR analysis of starting materials, GA, PVP and IBU, through intermediate, S2, S3 and S4, and finally spectrums for SCL are presented in Figure 2. From the spectrum of S2, it could be seen that the hydrogen bond among PVP and GA was established, and better mechanical properties were obtained as a consequence (5). Moreover, the cross-linking with glutaraldehyde (GTA) was confirmed through shifting

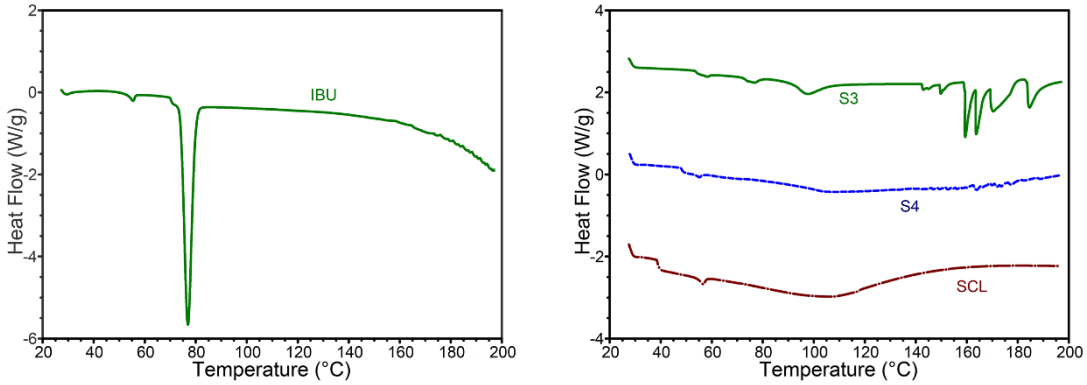
Amide II (1543 cm^{-1} to 1537 cm^{-1}) bands and the lowered intensity of peak at 3297 cm^{-1} attributed to Amide A (29, 30). A peak at 1717 cm^{-1} from -COOH group was obtained in spectrum of IBU. In the spectrum of S4, this peak was not observed, whereas the band at 1546 cm^{-1} from carboxylate ion COO^- was obtained. These results indicate that the deprotonation of the carboxylic acid group occurred during the processing of scaffolds (19).



a) b)

Figure 2. FTIR spectrums of a) S1, S2, S3 and IBU and b) S4 and SCL
Slika 2. FTIR spektri uzoraka: a) S1, S2, S3 i IBU I b) S4 i SCL

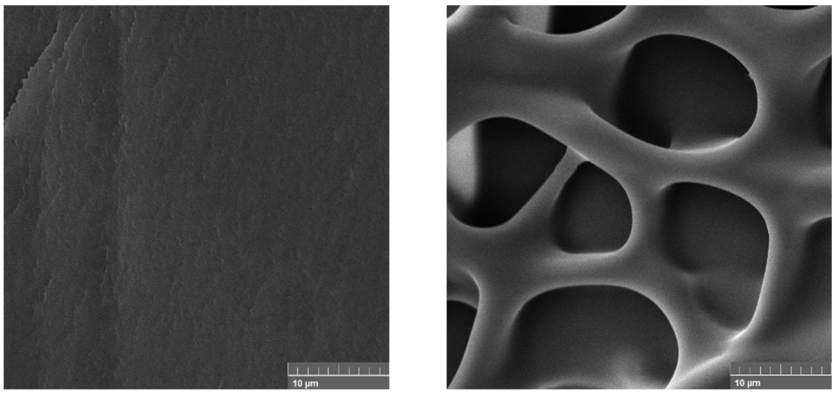
The thermal properties of scaffolds loaded with IBU during processing were followed by DSC analysis. The results are presented in Figure 3. On the thermogram for pure IBU, the melting temperature I of 77 °C was observed (31). In the thermal behaviour of gelatin, three characteristic temperatures can be distinguished: glass transition temperature (T_g), denaturation temperature (T_d), which corresponds to the melting behaviour of gelatin, and isomerization temperature (T_i), attributed to the stereoisomerism of the peptide bonds in GA (5, 25, 32). From the thermogram of S3 samples, characteristic temperatures for both IBU and gelatin were observed: T_m for IBU was at 79 °C, whereas T_m and T_d for gelatin were at 54 °C and 97 °C, respectively. The trans-cis isomerization region was obtained at around 160-180 °C. All characteristic temperatures could be observed for both scaffolds in the DSC curves of samples S4 and SCL. Interestingly, in thermograms for S4 and SCL there were no melting peaks for IBU around 79 °C, like in the thermogram for S3. It means that IBU was in crystalline form in S3 and in amorphous form in S4 and SCL. Furthermore, T_d increased with blending and cross-linking to 104 °C and 108 °C for S4 and SCL, respectively. The increase in T_d occurred because of the special features of peptide bonds and interchain hydrogen bonds established at the positions occupied by glycine (33).



a) b)

Figure 3. DSC analysis of a) IBU b) S3, S4 and SCL
Slika 3. DSC analiza uzoraka: a) IBU b) S3, S4 i SCL

The structure of S4 and SCL samples before and after cross-linking and lyophilization was investigated by FESEM analysis (Figure 4). The porous structure was obtained after lyophilization. This porosity is advantageous and promotes new tissue growth, due to better body fluids and cells flow through the scaffold (7, 17). Moreover, drug release is facilitated due to a larger active surface available. In the studies about the influence of porosity on the effectiveness of bone scaffolds with drug release, the results suggested that porosity of the scaffold closer to porosity of bone tissue led to better proliferation of osteoblast cells (17, 28, 29). Higher porosity provides higher swelling, allowing direct osteogenesis and extracellular matrix formation (17, 34, 35).

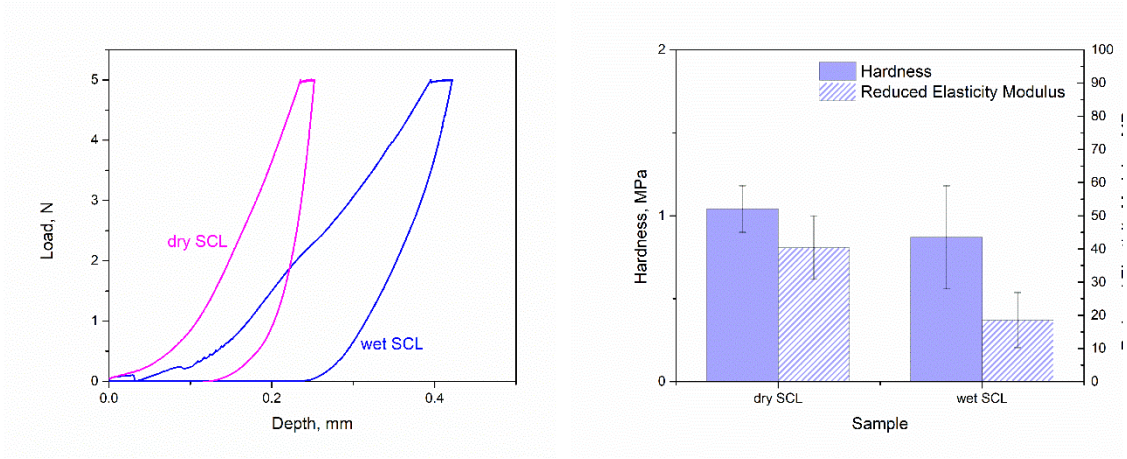


a) b)

Figure 4. SEM images of a) S4 and b) SCL
Slika 4. SEM uzoraka: a) S4 i b) SCL

A microindentation test can assess the mechanical behaviour of scaffolds during application. With this dynamical method, load, depth, and time data were collected. The

load-depth curves for dry and wet SCL scaffolds are presented in Figure 5a). The bar charts with calculated values of H and E_r (5) and standard deviation are presented in Figure 5b). The water molecules act as plasticizers in wet scaffolds, leading to a decrease of H and E_r. It should be noted that the presence of glycerol influences water absorption of gelatin and acts as plasticizers too, as it was described in our previous paper (5). In this case, the difference in mechanical properties between dry SCL and wet SCL is influenced by added PBS for rehydration. It is also a consequence of a reduction in the porosity of scaffolds (36, 37).



a) b)

Figure 5. Results of the microindentation test: a) Load-depth curves; b) Hardness and reduced elastic modulus histograms

Slika 5. Rezultati mikroindentacije: a) Kriva opterećenje-dubina; b) Histogrami za tvrdoću i redukovan modul elastičnosti

The IBU release from scaffolds is illustrated in Figure 6. In the case of pure GA (S3), drug release was immediate and it was the fastest, with more than 50% in the first 15 min. The scaffolds S4 and SCL have a modified drug release. The release profile is influenced by the degradation of scaffold or diffusion of the drug (7, 17, 34, 35). For the non-crosslinked gelatin, the IBU release process is influenced by partial degradation of the scaffold. The addition of PVP to gelatin leads to hydrogen and hydroxyl bonding between them (5). Therefore, the degradation of the scaffold was slower, and drug release was prolonged.

The cross-linking of the scaffold (SCL) resulted in an even more prolonged drug release in comparison to scaffolds S3 and S4. The diffusional force has a greater role in IBU release than the degradation of the scaffold SCL, as the longer diffusional path for the drug in this scaffold leads to prolonged release (10).

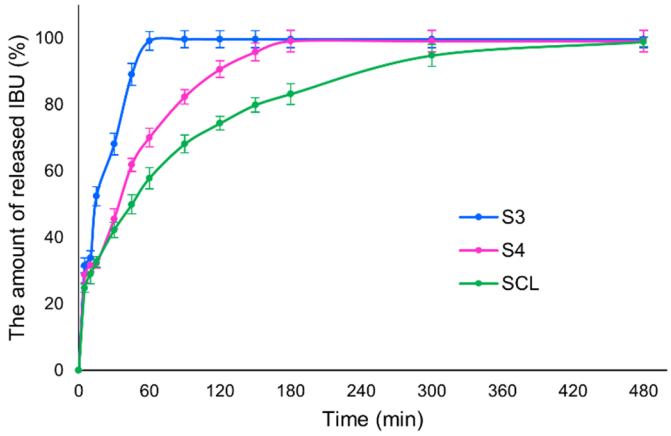


Figure 6. ***In vitro*** **release of ibuprofen**
Slika 6. ***In vitro*** **profil otpuštanja ibuprofena**

The release kinetics of IBU from scaffolds was determined and presented in Table II. The highest value of R^2 and MSC value greater than 2 were used to choose the best model that fits (5). The first-order kinetics was the best mathematical model for the scaffolds S3 and S4, meaning that the IBU release depends on concentration and is proportional to IBU remaining in the polymeric scaffold (5, 38). For SCL, the Korsmeyer–Peppas model resulted as the best fit. The release exponent (n) is <0.5, which suggests that the IBU release followed the process of Fickian diffusion (38).

Table II Results of ibuprofen release kinetics
Tabela II Rezultati kinetike oslobađanja ibuprofena

Model	Zero order		First order		Higuchi		Korsmeyer-Peppas		
Criteria / Scaffold	R^2	MSC	R^2	MSC	R^2	MSC	R^2	MSC	n
S3	0.4351	0.5316	0.9858	3.6104	0.2303	0.3799	0.8399	1.0367	0.199
S4	0.5531	0.9599	0.9607	2.7179	0.6580	0.5533	0.9113	1.8362	0.274
SCL	0.2300	0.7176	0.8899	1.6957	0.8136	1.1690	0.9848	3.6098	0.306

Conclusion

SSE 3D printing and characterization of gelatin-PVP bone scaffold loaded with IBU were performed. The gelatin/PVP blend, cross-linked with GTA, shows promise as a carrier with prolonged IBU release. It also overcomes the poor mechanical properties of gelatin. The lyophilization process made it possible to achieve good porosity of the scaffold. The presented results show that gelatin-PVP scaffolds have good potential in bone tissue engineering, enabling a synergic effect of tissue regeneration and targeted drug delivery. Besides delivery of the IBU, the porosity of cross-linked and lyophilized material could facilitate a good flow of body fluids and, in this way, optimal conditions for cell growth and tissue regeneration.

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3D štampa i karakterizacija nosača za dostavu ibuprofena u koštanom tkivu

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Kratak sadržaj

Nosač za dostavu ibuprofena (IBU) u koštanom tkivu dobijen je metodom 3D štampe ekstruzijom iz paste uz korišćenje smeše polimera želatina A (GA) i polivinilpirolidona (PVP K30). Dobijeni nosač je umrežen sa 1% rastvorom glutaraldehida (GTA), nakon čega je usledio proces liofilizacije uzoraka. Ispitivana su mehanička i termička svojstva, profili i kinetika oslobađanja ibuprofena iz dobijenih nosača. Umrežen i liofilizovan nosač pokazao je dobru termičku stabilnost i mehanička svojstva, kao i produženo oslobađanje IBU-a koje prati kinetiku po Fikovom zakonu difuzije.

Ključne reči: 3D štampa ekstruzijom iz paste, nosač lekova na bazi želatina, *in vitro* profil i kinetika otpuštanja ibuprofena, mikroindentacija, tvrdoća