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Ibuprofen controlled release from E-beam treated polycaprolactone electrospun scaffolds

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Abstract. Synthetic biodegradable polymers are considered to be a highly suitable materials for the targeted drug delivery devices creating. Especially promising is the use of the electrospinning technique, which makes it possible to obtain materials with a high surface-to-volume ratio that provides active diffusion of the drug into the body tissues. In order to control the rate of polymer degradation and drug release from polymer scaffolds surface modification techniques are widely used. This study was focused on the investigation of ibuprofen-loaded poly (ε-caprolactone) electrospun fibrous scaffolds and modification of theirs surface. Scaffolds with two ibuprofen concentrations were obtained: 5 wt./wt. % and 10 wt./wt.%. The modification was conducted by the pulsed electron beam irradiation. The sustained release of the model drug over a period of one day from both non-treated and treated samples was demonstrated. It was shown, that treatment leads to an increase in drug release rate and does not change surface morphology of scaffolds and fibers diameter distribution.

1. Introduction

Biodegradable polymers are now widely used in medicine as a means of targeted delivery and controlled release of drugs, as well as materials for regenerative medicine. Moreover, modern technologies for medical products and devices formation allow to obtain objects that can simultaneously work both as an extracellular matrix for the new tissues growth and as a means of local drug release. This combination is needed especially for perioperative diseases prevention, what is crucial in military regions, places with poor hygiene and healthcare system. E. M. Hetrick et al summarized current trends on designing new polymeric drug release systems for implant-related infections control and showed benefits of incorporating antibiotics into a polymeric coat for implants [1].

In particular, the method of electrospinning of polymer solutions is a promising approach. Electrospinning makes it possible to form highly porous sheet materials (scaffolds) with an extremely high surface-to-volume ratio from the polymeric solutions. This special structure provides better cell adhesion and proliferation, which increases materials biocompatibility. An important point is also the gradual destruction of the material and the resorption of the degradation products, which prevents the accumulation of foreign objects in the body after the damaged organs restoration.

Polycaprolactone was shown to be suitable material for drug delivery and controlled release formation [2]. It is used for long-term drug release, for example, in birth control implants and is

demonstrated to be a promising carrier for short-term releasing drugs as antibiotics [3], anti-inflammatory agents [4] and bone morphogenetic proteins [5].

The increased interest in scaffolds based on polycaprolactone is due, first of all, to good mechanical properties of the material at its affordable price. However, the main disadvantage of this material as a drug delivery agent is its hydrophobicity and slow degradation in the body, what leads to a week drug desorption and diffusion process. Degradation rate must not only correlate with a speed of tissue regeneration, moreover, degradation control is critical for drug release profile. A number of physico-chemical modification methods have been proposed to control the rate of degradation and drug release from polymer scaffolds [6]. One of the advanced methods is the pulsed electron beam treatment, which was shown to increase hydrophilic properties and degradation rate through decreasing the average molecular weight of the bulk polymer and pseudo-surface erosion [7].

In this study ibuprofen-loaded electrospun fibrous scaffolds were investigated and sustained release of the model drug over a period of one day was studied. Electron beam irradiation treatment in a pulsed mode was employed to increase polymer surface energy, reduce polymer molecular weight and subsequently modify the release kinetics of ibuprofen.

2. Materials and methods

2.1. Preparation of PCL fibers by electrospinning

Polycaprolactone (PCL) Mw~70–90 kDa (Sigma–Aldrich, Germany) was dissolved in hexafluoroisopropanole (HFIP) (Ekos-1, Russia) at a concentration of 7 wt.%. The ibuprofen substance was received from Shandong Xinhia Pharmaceutical (China). For the preparation of 5 wt./wt % and 10 wt./wt % (drug substance/dry polymer weight) ibuprofen-loaded PCL solutions, previously dissolved in HFIP ibuprofen powders were added to PCL granules and then refilled with the rest of the solvent. Mixtures were left for 30 hours at the room temperature in sealed glass containers until full homogenization. Before electrospinning solutions were stirred on the magnetic stirrer for 30 min.

Electrospinning of nanofibers was proceeding on NANON-01 (MECC CO., Japan) with a 200 mm diameter drum collector. The process parameters used in the current study are shown in Table 1.

Table 1. The process parameters optimized for preparation of PCL nanofibers.

Characteristics	Value
Voltage, kV	20
Feed rate, ml/h	5
Collector rotation speed, rpm	50
Needle	G 21

After fibers formation scaffolds were removed and placed into a custom made vacuum camera for 24 hours (5×10^{-3} Pa) to remove residual solvents.

2.2. Pulsed electron beam irradiation

Electron beam irradiation of PCL scaffolds was conducted using pulsed e-beam accelerator TEA-500 with range of absorbed dose of 25 kGy. The electron beam has diameter of 5 cm, beam kinetic energy was 350–400 keV, the beam current was 6–9 kA, duration of a pulse at half-maximum was 60 ns, and the electron beam energy was 90 J. The thickness of the titanium foil in the accelerator exit window was 50 μm.

2.3. Scanning electron microscopy (SEM)

SEM images were used to determine the average diameter of the nanofibers. Samples of each polymer scaffold were fixed onto metallic studs with a double-sided conductive tape. A thin gold film was sprayed onto samples in order to provide a contact of the material with the stub and to prevent the accumulation of a negative charge on the samples surface. The morphology of the sample was observed

with a scanning electron microscope VEGA3 TESCAN (Cheech Republic. France). One hundred randomly selected nanofibers were measured using ImageJ 1.44p software (National Institutes of Health, Bethesda, MD, USA) to calculate the average diameter of the nanofibers.

2.4. Gel permeation chromatography (GPC)

GPC was used to determine the relative molecular weight of polymer in obtained scaffolds samples. Samples were dissolved in chloroform to concentration 1.000 g/l and analyzed on Agilent 1200 LC system with refractive detector (Agilent technologies, USA). Flow rate was 1 mL/min, injection volume was 50 µL. As a value for comparison number average molecular weight (M_n) was chosen.

2.5. Drug release study

Untreated and e-beam treated electrospun PCL scaffolds, both with the incorporated drug, were immersed in Phosphate Buffer Saline (PBS, pH 7.4) at 25ºC with three replicates for each type of scaffold. The experiments were run in 2 ml of PBS without stirring, and the drug release results were found to be within one standard deviation to each other. At predetermined time points, a 1 mL aliquot was withdrawn for further analysis and replaced with an identical volume of the fresh medium. The amount of released ibuprofen was determined using UV-vis spectrometry (Specord 250 Plus, Analytik Jena AG, Germany), λ=225 nm.

3. Results and discussion

The results of scanning electron microscopy of ibuprofen-loaded PCL scaffolds are represented in figure 1.

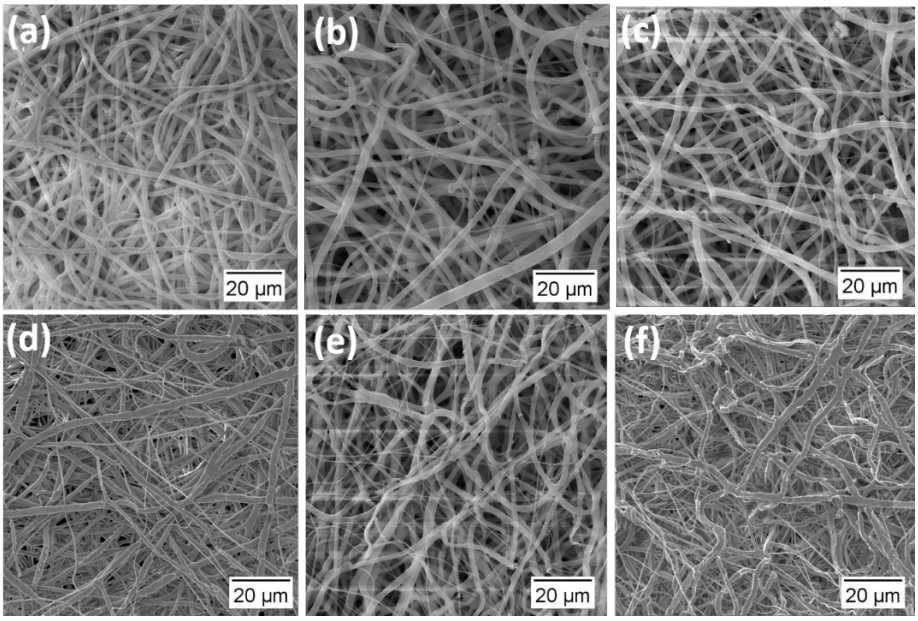


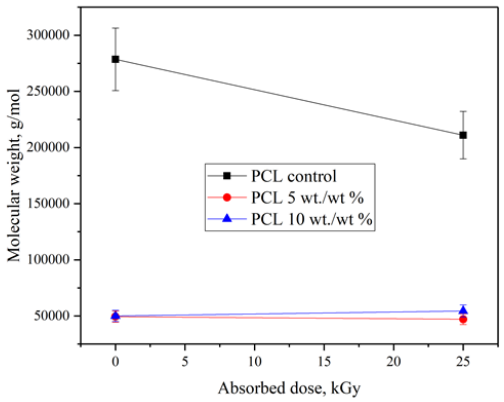
Figure 1. SEM images of untreated and e-beam treated control pure electrospun PCL nanofiber (a, b), PCL nanofibers loaded with 5 wt.% (c, d), 10 wt.% (e, f) ibuprofen respectively.

There are no significant changes in surface morphology of scaffolds and fibers diameter distribution after the e-beam irradiation. The electrospinning of PCL solutions under the chosen parameters (table 1) enabled the preparation of randomly oriented fibers. Drug loading does not affect the morphology of scaffolds, as shown in figure 1 and reported also in [3, 4]. SEM imaging of the prepared electrospun scaffolds with an incorporated drug revealed rounded, individual nanofibers with a smooth surface without visible crystals, what indicates full embedding of ibuprofen into nanofibers. At the same time, there is an enhancing tendency to fusion between fibers with increasing amount of a loaded drug.

Table 2. The mean diameters of PCL nanofibers before and after the e-beam irradiation.

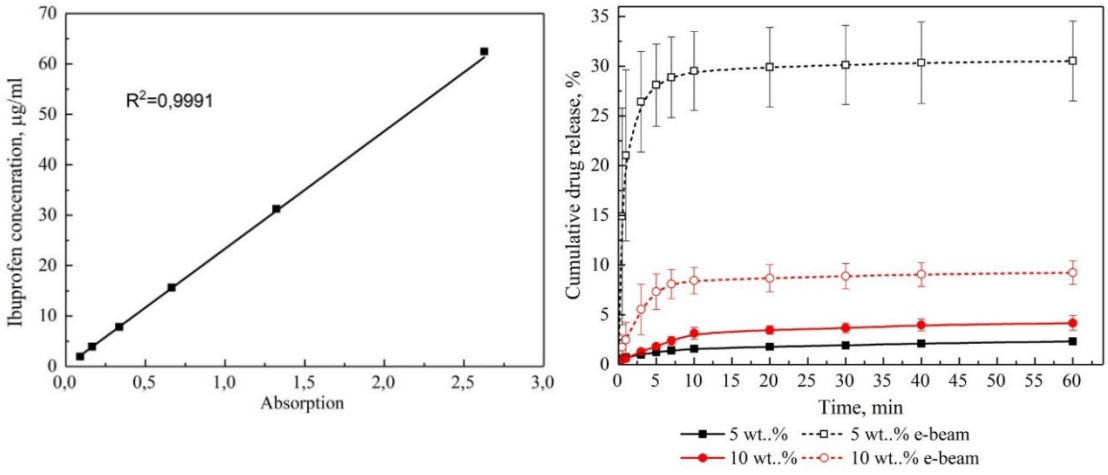
	Mean diameter, μm		
Samples	PCL	PCL 5% wt	PCL 10% wt
Before e-beam treatment	1.826±0.65	1.495±0.061	1.373±0.059
After e-beam treatment	1.869±0.053	1.397±0.060	1.447±0.060

Figure 2 shows the changes in molecular weight of the pulsed electron beam irradiated PCL samples. No significant decrease of molecular weight after e-beam treatment was observed. However, there was a decrease in M_n values for the ibuprofen-loaded PCL samples with 5 and 10 wt./wt. % for nonirradiated and irradiated samples. Between 5 and 10 wt./wt. % loaded PCL scaffolds no pronounced changes in molecular weight was observed. At the same time considerable fall in molecular weight was found in case of pure PCL scaffolds.



	Molecular weight, g/mol	
Samples	Before e-beam treatment	After e-beam treatment
PCL	$(27.85\pm2.79)\cdot10^4$	$(21.10\pm2.11)\cdot10^4$
PCL 5% wt	$(4{,}94\pm0.49)\cdot10^4$	$(4.71\pm0{,}47)\cdot10^4$
PCL 10% wt	$(5.01\pm0.50)\cdot10^4$	$(5.44\pm0{,}54)\cdot10^4$

Figure 2. Molecular weight of the pulsed electron beam irradiated PCL scaffolds samples.



(a) (b)

Figure 3. The calibration curve: correlation between ibuprofen concentration in PBS media and light absorption on the wavelength 225 nm (a) and the cumulative ibuprofen release from treated and untreated PCL scaffolds (b).

Calibration curve for description of amount of loaded drug was built on ten points, starting at 500 mkg/ml, with dilution twice, and shown in figure 3a. The treatment allowed for an increased drug amount to be delivered in a shorter time period compared to the released drug amount from the untreated samples. Release tests results demonstrated the significant rose in release rate of the loaded drug after treatment. Calibration curve as well as cumulative drug release is presented on the figure 3.

In case of 5 wt.% PCL scaffolds the cumulative amount of released ibuprofen after an hour of observation was only 2 wt.%. After scaffolds surface modification this value increased more than fourteen-fold up to 28 wt.%. The change of released drug amount in case of 10 wt.% ibuprofen samples in the PCL scaffolds was less than in 5 wt.% samples but still significant (from 4 wt.% before and 8.5 wt.% after the irradiation).

4. Conclusion

The properties of electron-beam treated ibuprofen-loaded PCL electrospun scaffolds had been investigated. It was shown, that:

1) The ibuprofen loading does not change mean fiber diameter as well as the surface morphology of PCL nanofibers.
2) The e-beam treatment with proposed parameters does not affect mean fiber diameter and surface morphology of the scaffolds.
3) The average molecular weight of polymer in the scaffold decreases with ibuprofen loading.
4) The results of GPC did not show significant changes of molecular weight after e-beam treatment.
5) The drug release rate has increased after the e-beam treatment of scaffolds.
6) The effect of drug release amplification depends on drug concentration: for the scaffolds with the lowest concentration the effect was more pronounced.

Thus, it has been demonstrated that the modification of ibuprofen-loaded PCL scaffolds by pulsed electron beam treatment leads to an increase of drug release rate and could be useful and effective method for controlling drug release from polymeric electrospun nanofibers.

5. Future outcome

The increase in the amount of released ibuprofen can be associated with increasing wettability of the polymer after the e-beam irradiation. In particular, it was shown in the paper [8] that the faster drug release corresponds to more hydrophilic surfaces of polymer matrix. It makes a significant contribution into the matt swelling and mass-transfer processes.

A more detailed study of the surface treatment on material properties will be carried out in the future, but it can be already declared that the pulsed e-beam irradiation is the promising method of non-destructive modification of polymeric drug delivery systems.

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