ELECTROSPUN POLY (ε-CAPROLACTONE) (PCL) NANOFIBERS FOR PARACETAMOL CONTROLLED RELEASE

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ПОЛУЧЕНИЕ МЕТОДОМ ЭЛЕКТОСПИННИНГА НАНОВОЛОКОН НА ОСНОВЕ ПОЛИКАПРОЛАКТОНА ДЛЯ КОНТРОЛИРУЕМОГО ВЫХОДА ПАРАЦЕТАМОЛА

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Аннотация. *Методом электроспиннинга были сформированы биоразлагаемые полимерные матриксы на основе поликапролактона и нерастворимого в воде лекарственного препарата – парацетамола с процентным соотношением полимер – парацетамол 8, 16 и 32 масс.%. На основе метода высокоэффективной жидкостной хроматографии разработана методика оценки кинетики десорбции лекарственного средства в фосфатно-солевой буфер. Выход парацетамола (16 масс.%) из матрикса за 1 час достигает 97%. Показано, что увеличение концентрации парацетамола мало влияет на средний диаметр волокон, но ухудшает волокнообразующие свойства прядильного раствора.*

The targeted delivery and controlled release of poorly water-soluble drugs present great current interest in nanomaterial researches. The main reason for this is, on the one hand, the necessity of fast and safe release, which is highly important when used for such patients as children and elderly, and, on the other hand, the necessity of high dosage connected with poor water-solubility. Synthetic polymer biodegradable PCL nanofibers seem to be very promising nanomaterials for this application [1, 2, 3]. They have already demonstrated good results with incorporation of ibuprofen and carvedilol [4]. The aim of our research is to make experimental samples of electrospun PCL nanofibers for paracetamol and to determine their potential as a novel delivery system for poorly water-soluble drugs.

For the preparation of polymer solutions polycaprolactone (PCL) Mw~70,000–90,000 g/mol (Sigma–Aldrich, Germany) and hexafluoroisopropanol (HFIP) (Ekos-1, Russia) were used. The paracetamol was received from Shandong Xinhia Pharmaceurical, China. Phosphate buffer solution (pH=7.4) was prepared by mixing 200 ml of distilled water with 2 tablets of phosphate buffer powder (Biolot, Russia).

The PCL solution (7 wt.%) was prepared by dissolving 4,5 g of PCL granules in 59,8 g of HFIP. For the preparation of (2 wt/%, 8 wt%, 16 wt%, 32 wt% based on the dry weight of the polymer) paracetamol-loaded

PCL solutions previously dissolved in HFIP paracetamol powders were added to 4,5 g of PCL granules and then refilled with the rest of the solvent (at the total rate 59,8 g). Mixtures were left for 30 h at the room temperature in sealed glass containers until full homogenization.

Table 1

The process parameters optimized for preparation of electrospun paracetamol-loaded PCL nanofibers

Characteristics	Amount	Characteristics	Amount
Voltage, kV	20	Scaffold width, mm	70
Feed rate, ml/h	5	Needle diameter, mm	1,2 (18G)
Collector rotation speed, rpm	50	Distance between needle and collector, mm	150
Solution volume, ml	8	Frequency/interval of cleaning, min	10/0

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.

The obtained scaffolds showed different adhesion to the collector that had been increasing with the increase of the drug amount. To remove drug-loaded scaffolds without damaging its structure isopropyl alcohol was used as a dampening agent. Then samples were placed into a custom made vacuum camera for 24 hours (5×10^{-3} Pa) to remove residual solvents.

To determine the average diameter of the nanofibers SEM images were used. Pieces of each polymer scaffold film 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 (Quanta 200 3D DualBeam, FEI Company, USA), using an accelerating voltage of 2000 kV and a LFD detector. 100 randomly selected nanofibers were measured using ImageJ 1.44p software (National Institutes of Health, Bethesda, MD, USA). According to the measurements, the average fiber diameter and its standard deviation (SD) were determined (Fig. 1).

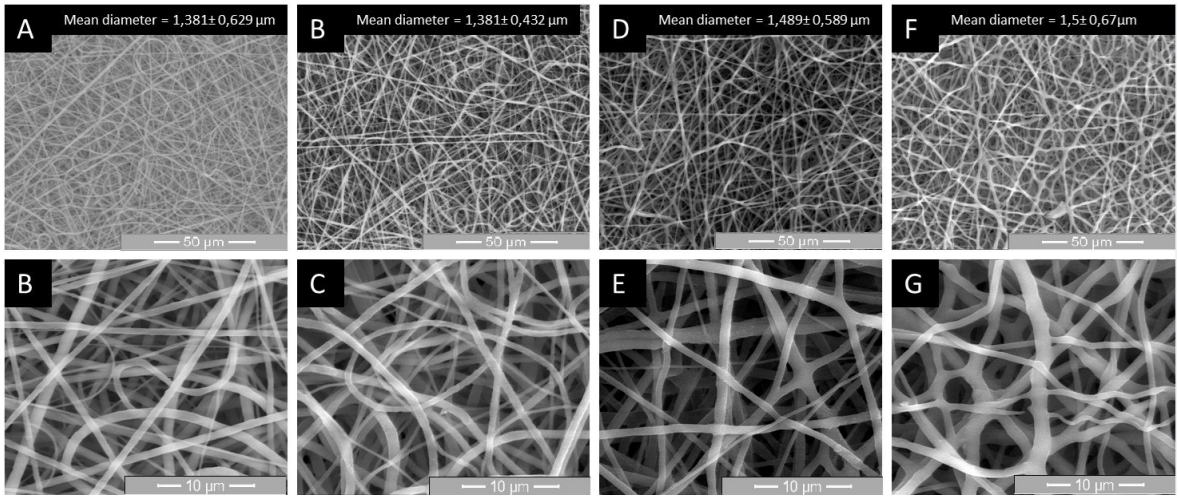

Fig. 1. SEM images of electrospun PCL nanofibers loaded with 8 wt.% (B,C), 16 wt.% (D (×1000),E (×20000)), 32 wt.% (F,G) ibuprofen (based on the weight of dry polymer) and control pure PCL nanofiber (A,B)

The electrospinning of PCL solutions under the chosen parameters (Table 1) enabled the preparation of randomly oriented fibers with the highly developed surface. Nanofibers with a very high paracetamol load were successfully prepared (Fig. 1 – F, G). A high drug load affects the morphology of scaffolds, as shown in Fig. 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 paracetamol into nanofibers. At the same time, there is an enhancing tendency to fusion between fibers with increasing amount of a loaded drug. This phenomenon also correlates with changing adhesion between a scaffold and a collector.

To do primal the analysis of the paracetamol dissolution rate a 16 wt. % mat was chosen. Four 35 mm^2 square samples were cut out from the mat and placed into four glass containers holding by a stainless steel carrier. Then 35 ml of phosphate buffer, pH 7.4, used as a dissolution medium, was added to each sample to fully cover its surface. The samples were stirred on a magnetic stirrer at the room temperature for two weeks. At the predetermined time points 200 µl of solution was withdrawn and replaced with fresh phosphate buffer. After centrifugation (3 min, 50000 rpm) the sample was analyzed by HPLC (Agilent 1200 Infinity, Agilent Technologies, USA). The paracetamol concentration was analyzed using a C18 column (5 µm, 500 mm × 50 mm; Milichrom, Russia) at 35 °C. The mobile phase consisted of acetonitrile and trifluoroacetic acid (TFA) in the ratio 90:10 (v/v). A constant flow rate of 0.2 ml/min was used and the drug was monitored using a diode array detector at 240 nm.

According to the obtained data a kinetic curve of paracetamol release was formed. The release from the PCL 16 wt/wt. % nanofiber scaffold was fast, reaching more than 97% of the total amount in the first hour.

The obtained results demonstrate that electrospinning can be used for the preparation of highly paracetamol-loaded PCL nanofibers. It is shown that incorporation of such poorly water-soluble drugs, as paracetamol in PCL nanofibrous material leads to their fast dissolution in pH-neutral medium. In conclusion, electrospinning is shown to be a promising approach to the delivery of poorly water-soluble drugs in order to control and enhance their release.

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