Study of the effects of the introduction of heparin on the mechanical properties of poly (glycolide-dl-lactide)

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Abstract. A technology has been developed for producing biodegradable films based on poly (glycolide-lactide) containing heparin. The obtained biodegradable films simulate the coatings of cava filters. The effect of the concentration of introduced heparin and the change in the molecular weight of poly (glycolide-lactide) on the strength and plastic properties, as well as on the thickness of the films obtained, is shown. The possibility of creating coatings with introduced heparin for cava filters with the required mechanical properties is shown.

1. Introduction

Deep venous thrombosis of the lower extremities (DVHC) and pulmonary thromboembolism (PE) are common diseases of the human cardiovascular system. Their prevention includes both pharmacotherapy and implantation of cava-filter medical devices. Cava filters are a device for capturing blood clots carried by blood. Currently, in medical practice, operations using these implants are widespread. There is a large number of different cava filters, differing in material of manufacture, construction, and other parameters, possessing both advantages and significant disadvantages. Therefore, there are numerous developments of new products that can minimize possible postoperative complications.

A promising direction is the combination in one device of the immediate function of capturing a thrombus with local pharmaceutical effects, which can be ensured by creating on the implant surface a system of local drug delivery. However, direct application to the surface of the implant leads to rapid washing out of the medicinal agent, which can be solved by using a biodegradable matrix. [1-4] When choosing a material for its creation, the following considerations are guided: the material must be chemically inert, not contain leached impurities, be easily synthesized, and in the case of hydrolysis (or resorption) do not form toxic compounds. These are silicone, polyurethane, polyethylene, polyethylene vinyl acetate. Developed new polymers used in medicine that meet the requirements that impose a decay rate and the physical characteristics of the delivery systems. The need to use biodegradable materials for this purpose led to the active development of biodegradable polymers of synthetic and natural origin, among which polyethers: polylactides, polylactideglycolides, polyethylene glycol, polyanhydrides, polyorthoesters, polysaccharum (starch, dextran, chitosan) were most developed. [5-8]
In this work, poly (glycolide-lactide) of various molecular weights was chosen as the biodegradable matrix. Polyglycolide is the simplest polyether, in which, due to the close location of the ester groups, intermolecular interactions are strongly pronounced, it has a high degree of crystallinity, a high melting point (~ 300 °C), and extreme hydrolytic instability. Polylactide aliphatic polyether, the monomer of which is lactic acid. It is biodegradable, biocompatible and thermoplastic. Using polylactide / polyglycolide copolymers, the bioresorption rate is varied depending on the type of polymer and its molecular weight [9]. Heparin was used as a drug. Heparin is an anticoagulant of direct action, that is, as a substance that prevents blood from clotting. It is used for the prevention and treatment of thromboembolic diseases, during operations on the heart and blood vessels. [10]

The type, concentration and method of introduction into the polymer matrix of a drug can significantly affect the properties of the resulting composite material, which must meet the requirements for the further development of medical implant coatings.

In this paper, the effect of heparin administration on the mechanical properties of poly (glycolide-lactide) of various molecular weights was investigated.

2. Materials and methods

To create films, weights of polymers weighing 2 g (± 0.01 g) were prepared. Chloroform with a volume of 200 ml was placed in a flask with a volume of 500 ml and heated to 800 °C on a magnetic stirrer.

Next, the obtained weights of the polymers were dissolved to a homogeneous state in chloroform at 800 °C for 1 hour with constant stirring using an electronic overhead stirrer.

In the resulting homogeneous solution, heparin is kneaded in an amount necessary to obtain 1, 2 or 3% solutions, at a solution temperature of 30 °C;

The resulting homogeneous solution is poured into a glass mold and set to dry in a thermostat at 37 °C for 48 hours.

At the end of drying, the films obtained were removed from the glass form.

The resulting samples were assigned ciphers using 2 digits (X.Y), used for independent research in the future.

The first digit “X” denotes the type of polymer from which the film is made:
1 - PGLA 45kDa; 2 - PGLA 90kDa; 3 - PSLA 180kDa. The second digit “Y” indicates the concentration of the drug. Values are given in mass percent relative to the weight of the polymer itself: 1 - 1%; 2 - 2%; 3 - 3%.

The main characteristic of this method of drug administration is low temperatures, allowing to preserve the integrity of the drug, obtaining a uniform, uniform structure of the material, as well as the possibility of drug administration without the use of ultraviolet radiation and the application of intermediate layers, which greatly simplifies the technology for producing films.

Strength tests of polymer films of poly (glycolide-lactide) were tested on a universal testing machine INSTRON 3382 with a loading rate of 10 mm / min. Samples of polymer films for testing were made according to GOST 14236-81, in the form of a double blade. The sample was fixed in the grips of the testing machine, which are evenly tightened to ensure that the sample does not slip during the test. Testing of polymer films with the determination of the relative elongation, yield strength and tensile strength was carried out according to GOST 14236-81. Processing of test results in determining the mechanical properties was carried out using the INSTRON Bluehill 2.0 software. The measurement error of the testing machine is less than 1%.

5 samples were tested per experimental point. The values of yield strength, tensile strength and relative elongation were determined.

3. Results and discussion

Table 1-2 presents the average results of mechanical testing of polymer films for each composition based on poly (glycolide-lactide) (PGLA) with different molecular weight and concentration of the drug.
From the obtained results, dependency graphs were built, which can be used to track the trend of changes in mechanical characteristics (Figure 1-3).

### Table 1. Mechanical properties of polymer films without drugs.

| Polymer and concentration | Deformation, % | Yield strength, MPa | Ultimate Strength, MPa | Thickness, μm |
|---------------------------|----------------|---------------------|------------------------|---------------|
| PGLA 45kDa                | 140±7          | 4.0±0.2             | 5.5±0.3                | 66±3          |
| PGLA 90kDa                | 262±13         | 2.4±0.1             | 5.2±0.3                | 63±3          |
| PGLA 180kDa               | 198±10         | 5.6±0.3             | 7.6±0.4                | 32±2          |

### Table 2. Mechanical properties of polymer films with heparin.

| Code | Polymer and concentration | Deformation, % | Yield strength, MPa | Ultimate Strength, MPa | Thickness, μm |
|------|---------------------------|----------------|---------------------|------------------------|---------------|
| 1.1  | PGLA 30/70 45kDa, 1% гепарина | 17,6±0,9 | 12,8±0,6             | 17,5±0,9                | 103±5         |
| 1.2  | PGLA 30/70 45kDa, 2% гепарина | 13,9±0,7 | 11,0±0,6             | 14,6±0,7                | 123±6         |
| 1.3  | PGLA 30/70 45kDa, 3% гепарина | 11,2±0,6 | 9,7±0,5              | 11,9±0,6                | 140±7         |
| 2.1  | PGLA 30/70 90kDa, 1% гепарина | 83,1±4,2 | 7,8±0,4              | 10,6±0,5                | 80±4          |
| 2.2  | PGLA 30/70 90kDa, 2% гепарина | 42,1±2,1 | 2,1±0,1              | 4,1±0,2                 | 83±4          |
| 2.3  | PGLA 30/70 90kDa, 3% гепарина | 99,4±5,0 | 4,2±0,2              | 4,6±0,2                 | 92±5          |
| 3.1  | PGLA 30/70 180kDa, 1% гепарина | 98,5±4,9 | 5,6±0,3              | 9,0±0,4                 | 98±5          |
| 3.2  | PGLA 30/70 180kDa, 2% гепарина | 28,3±1,4 | 5,8±0,3              | 8,7±0,4                 | 115±6         |
| 3.3  | PGLA 30/70 180kDa, 3% гепарина | 17,9±0,9 | 6,6±0,3              | 8,9±0,4                 | 135±7         |
**Figure 1.** Diagram of deformation depending on the concentration of heparin for PGLA

**Figure 2.** Diagram of the dependence of tensile strength on the concentration of heparin for PGLA
In Figures 1-3, one can observe the dependence of reducing the strength and plasticity, and increasing the film thickness with increasing drug concentration (heparin) in poly (glycolide-lactide) polymers (PGLA) for all molecular weights. The exception is point 2.3, which is explained by the uneven distribution of the drug in this film. Comparing the results of mechanical tests with a film without a drug, we can conclude that the plasticity of all samples decreases. So the relative elongation of the initial PGLA 30/70 180 kDa (without medication) is 198.32%. The addition of 1%, 2% and 3% heparin leads to a decrease in the relative elongation to 98.46%, 28.31% and 17.94%, i.e. the drop in performance was 50.4%, 85.7% and 90.9%, respectively. In all polymers there is an increase in strength. With increasing drug concentration strength characteristics decrease. The increase in strength is most likely due to the formation of a composite material in the form of a polymer, as a plastic base, with a strong filler in the form of small particles of a drug with high strength, and a decrease in strength is associated with the accumulation of a large number of these particles and the appearance of fragile zones.

4. Conclusions
Studies of the mechanical properties of polymeric composite films based on poly (glycolide-lactide) with introduced heparin were conducted, and the effect of the concentration of the drug and the molecular weight of poly (glycolide-lactide) on the thickness, strength and plastic properties of the resulting films was shown.

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References

[1] Giessen WV, Lincoff A, Schwartz R, Beusekom HV, Serruys P, Holmes D, et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. Circulation 1996;94(7):1690–7.

[2] Nasakina E. O., Sevostyanov M. A., Mikhailova A. B., Baikin A. S., Sergienko K. V., Leonov A. V., Kolmakov A. G. Formation of alpha and beta tantalum at the variation of magnetron sputtering conditions// IOP Conference Series-Materials Science and Engineering. 110 (2016) 012042 doi: 10.1088/1757-899X/110/1/012042.

[3] Sevost’yanov M.A., Nasakina E.O., Baikin A.S., Sergienko K.V., Konushkin S.V., Kaplan M.A., Seregin A.V., Leonov A.V., Kozlov V.A., Shkirin A.V., Bunkin N.F., Kolmakov A.G., Simakov S.V., Gudkov S.V. Biocompatibility of new materials based on nano-structured nitinol with titanium and tantalum composite surface layers: experimental analysis in vitro and in vivo // Journal of Materials Science: Materials in Medicine, 2018. Vol. 29. P.33 (https://doi.org/10.1007/s10856-018-6039-3)

[4] Mohsin Shaikh, Ganessan Kichenadasse,Namita Roy Choudhury, Ross Butler, Sanjay Garg. Non-vascular drug eluting stents as localized controlled drug delivery platform: Preclinical and clinical experience. Journal of Controlled Release. Volume 172. Issue 1. November. 2013. p. 105–117

[5] Mazid MA, Scott E, Li N-H. New biocompatible polyurethane-type copolymer with low molecular weight heparin. Clin Mater 1991;8(1–2):71–80

[6] Supper S., Anton N., Seidel N., Riemenschnitter M., Curdy C., Vandamme T. Thermosensitive chitosan/glycerophosphate-based hydrogel and its derivatives in pharmaceutical and biomedical applications. Expert Opin. Drug Deliv. 2014;11:249–267. doi: 10.1517/17425247.2014.867326.

[7] Sevost’yanov M.A., Fedotov A.Yu., Nasakina E.O., Teterina A.Yu., Baikin A.S., Sergienko K.V., Kolmakov A.G., Komlev V.S., Ivanov V.E., Karp O.E., Gudkov S.V., Barinov S.M. Kinetics of the release of antibiotics from chitosan-based biodegradable biopolymer membranes // Doklady Chemistry, 2015. V.465. Part.1. P.278–280.

[8] Kimura H, Ogura Y. Biodegradable polymers for ocular drug delivery. Ophthalmologica 2001;215(3):143–55

[9] Tamai H, Gaki K, Kyo E, Kosuga K, Kawashima A, Matsui S.et al. Initial and 6-month results of biodegradable poly-L-lactic acid coronary stents in humans. Circulation 2000;102(4):399–404

[10] Peres C., Matos A.I., Conniot J., Sainz V., Zupančič E., Silva J.M., Graça L., Sá Gaspar R., Préat V., Florindo H.F. Poly(lactic acid)-based particulate systems are promising tools for immune modulation // Acta Biomater. 2017. V.48. P. 41–57.