Study of the effect of the introduction of heparin on the mechanical properties of polylactide

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Abstract. The paper describes a method for the preparation of polymeric composite films for medical purposes based on polylactide with introduced heparin. The effect of the molecular weight of polylactide and the concentration of the drug on the mechanical properties and thickness of the films obtained was studied. The possibility of creating biodegradable films with the introduced drug with given properties is shown.

1. Introduction

The treatment of many diseases in many cases is accompanied by adverse adverse effects on healthy human organs. Modern medicine has long sought to minimize this possible impact, including from the use of various medicines [1-3].

A large number of studies aimed at creating systems of local controlled drug delivery. Such systems provide therapeutic effects directly in the required area, reducing or completely eliminating the effect on the rest of the body [4-6].

As a basis for creating systems of controlled local delivery, biodegradable polymeric materials of both synthetic and natural origin are used. Polymers such as polylactides, polylactide glycolides, polyethylene glycol, polyanhydrides, polyorthoesters, polysaccharides (starch, dextran, chitosan) have found wide application in this area [7-8].

In this paper, we consider films based on polylactide of various molecular weights. Polylactide is biodegradable, biocompatible and thermoplastic. Polylactide is already used in medicine for the manufacture of surgical sutures and the processing of pins. [9]. The polymer can be obtained with different molecular weights and structure, and can also encapsulate molecules of almost any size. Heparin preparations are chosen as drugs. The created composite material on the basis of polylactide with injected drug can be used to cover medical products of the “kava-filter” type and provide drug therapy during implantation. Thus, using different molecular weights of the polymer, drug concentrations, it is possible to obtain a wide range of coatings with different properties and further selection of the required characteristics. [10]

An important parameter of the resulting composite polymer materials are mechanical properties that must meet the requirements for creating coatings for medical implants.
2. Materials and methods

To create films, we prepared weights of polylactide weighing 2 g (± 0.01 g). 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 polylactide were dissolved to a homogeneous state in chloroform at 800 °C for 1 hour with constant stirring using an electronic top-wheel mixer.

In the resulting homogeneous solution is kneaded the drug 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” indicates the type of polymer from which the film is made: 1 - PLA 45kDa; 2 - 90kDa PLA; 3 - PLA 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 feature 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 using ultraviolet radiation and applying intermediate primer layers, which greatly simplifies the technology for producing films.

Strength studies of polymer films of polylactide under tension were carried out on an INSTRON 3382 universal testing machine 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

The results of the study of the mechanical properties of polymer films for each composition based on polylactide (PLA) with different molecular weight and drug concentration are presented in Tables 1-2.

| Polymer and concentration | Deformation, % | Yield strength, MPa | Ultimate Strength, MPa | Thickness, μm |
|---------------------------|---------------|---------------------|------------------------|---------------|
| PLA 45kDa                 | 7,1±0,4       | 22,9±1,1            | 35,6±1,8               | 42±2          |
| PLA 90kDa                 | 58,1±2,9      | 17,3±0,9            | 20,1±1,0               | 38±2          |
| PLA 180kDa                | 43,9±2,2      | 16,8±0,8            | 19,6±0,9               | 39±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  | PLA 45kDa, 1% heparina    | 2±0,1          | 17,1±0,9            | 17,9±0,8               | 93±5          |
| 1.2  | PLA 45kDa, 2% heparina    | 1,8±0,1        | 15,0±0,8            | 15,7±0,7               | 100±5         |
| 1.3  | PLA 45kDa, 3% heparina    | 1,7±0,1        | 16,4±0,8            | 13,8±1,7               | 110±6         |
| 2.1  | PLA 90kDa, 1% heparina    | 2,4±0,2        | 23,9±1,2            | 33,4±1,6               | 80±4          |
| 2.2  | PLA 90kDa, 2% heparina    | 2,1±0,1        | 34,0±1,7            | 32,1±0,9               | 82±4          |
| 2.3  | PLA 90kDa, 3% heparina    | 1,8±0,1        | 16,2±0,8            | 18,5±1,3               | 100±5         |
| 3.1  | PLA 180kDa, 1% heparina   | 2,5±0,2        | 19,9±1,0            | 25,9±1,2               | 100±5         |
| 3.2  | PLA 180kDa, 2% heparina   | 2,2±0,1        | 22,0±1,1            | 24,3±1,1               | 105±5         |
| 3.3  | PLA 180kDa, 3% heparina   | 1,9±0,1        | 20,6±1,0            | 22,3±                  | 112±6         |
Figure 1. Diagram of deformation depending on the concentration of heparin for PLA

Figure 2. Diagram of the dependence of tensile strength on the concentration of heparin for PLA
Figure 3. The diagram of the dependence of the thickness of polymer films on the concentration of heparin for PLA

With an increase in the concentration of the drug (heparin) in polylactide polymers (PLA) for all molecular weights, the strength and plasticity decrease and the film thickness increases (Figure 1-3). Comparing the results of mechanical tests with a film without a drug, we can conclude that the plasticity of all samples decreases. The tensile strength, on the contrary, increases in all polymers except PLA 45 kDa, but then there was a decrease in the strength characteristic with increasing drug concentration. The increase in strength is associated with 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 the decrease in strength is associated with the accumulation of a large number of these particles and the appearance of fragile zones. In the initial PLA 45kDa (without medication), the tensile strength is 35.63 MPa. With an increase in the concentration of heparin from 1% to 3%, the strength characteristics decrease to 17.9 MPa, 15.03 MPa, 13.75 MPa (49.76%, 57.81%, 61.4%), respectively, which shows a poor correlation between PLA polymer with a molecular weight of 45kDa and heparin.

4. Conclusions
Polymer composite films based on polylactide with introduced heparin were obtained. The dependences of the strength and plastic properties, as well as the thickness of polymeric composite films based on polylactide with heparin injected, on the concentration of the drug and the molecular weight of polylactide were established.

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