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Biodegradable Protection for Medical Devices with Medical Drugs Controlled Separation

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Abstract: With the aim of creating biodegradable materials for medical devices clinical appointments with high hemocompatibility we have developed a new polymer product.The basis of this product is plasticized by polyethylene glycol bacterial copolymer of hydroxybutyrate and oxovalerate. A well-known antithrombotic supplement—acetylsalicylic acid has been added to improve hemocompatibility in the polymer. The results of our studies showed a controlled prolonged separation of acetylsalicylic acid from polymeric material in the blood. We studied in vitro the dynamics of liberation of acetylsalicylic acid from polymeric coatings. It was shown that the concentration of polyethylene glycol and the thickness of the polymer layer can affect the rate of diffusion of acetylsalicylic acid from polymer films.

Key words: Bacterial biodegradable copolymers, poly (hydroxybutyrate-co-oxovalerate), hemocompatible, medical devices for clinical application, polyethylene glycol, acetylsalicylic acid.

1. Introduction

Typically the medical product is prescribed for the diagnosis, prevention, monitoring, treatment, as well as to facilitate the occurrence of disease or trauma. Another field of medical plastic products usage could be replacement of anatomy, physiological processes, or conducting certain studies [1, 2]. Vascular catheters or vascular implant, artificial heart valves, pacemakers, implantable electrical defibrillators, oxygenators are in contact with blood. These products should perform their functions upon contact with the blood, and therefore must be hemocompatible. As materials for these medical products are used as synthetic polymer products and biopolymers [3, 4]. The most promising direction is the creation of environmentally friendly biodegradable materials with the use of copolymers based on poly (hydroxybutyrate-co-oxovalerate) [2, 5]. Medical products have been made of this polymer are biocompatible and are intended for contact with human blood. [6]. Medical biopolymers should not have a negative reaction from the blood and its components. [7, 8].To improve the hemocompatibility of medical supplies one can use antithrombotic drugs [9]. These drugs reduce the negative reaction of the body and increase the service life of the implant [3, 10]. The aim of our work is to provide a hemocompatible materials based on copolymer poly (hydroxybutyrate-co-oxovalerate), for controlled release antithrombotic drug - acetylsalicylic acid.

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2. Materials and Methods

2.1 Objects of the Study

Adsorption of blood proteins is the first stage of the unfamiliar interaction surface with blood [11]. The main reasons for the adsorption of proteins are: dehydration of sorbing surface and the protein molecule, redistribution of charged groups and

structural changes in the adsorbed macromolecule. Blood coagulation is processed by a cascade mechanism, including the stage of generation of thrombin. The resulting blood platelets adhesive on protein layer surface. Contact with enthetic surfaces activates blood coagulation system, leading to conversion of fibrinogen to fibrin. Adhesion of blood platelets is accompanied by the formation of pseudopodia. On the final stage the clot conglomerate of fibrin and cellular elements of blood are formed, which has the risk of separation with emboli or atherosclerotic plaques formation [1, 7].

The main objective of our research is to develop biodegradable materials with high hemocompatible properties. The object of our study is the biopolymer poly (hydroxybutyrate-co-oxyvalerate). This polymer was plasticized with polyethylene glycol with the addition of acetylsalicylic acid for increasing hemocompatibility. Such a system allows controlling release of antithrombotic drugs (acetylsalicylic acid) from polymeric medical devices which come into contact with human blood.

We prepared polymerfilms from the high molecular weight poly (hydroxybutyrate-co-oxyvalerate) (MR = 1 050 000 g/mol). Methods for producing polymer films, plasticized polyethyleneglycol has been developed and has been tested in the Laboratory of Tissue Engineering and delivery systems, Shumakov Federal Research Center of Transplantology and Artificial Organs.Concentration of the plasticizer, and acetylsalicylic acid were varied in a wide range. Methylene chloride was used as solvent in the preparation of films.

2.2 Laboratory Experiment

For the preparation of polymer films to a solution of poly (hydroxybutyrate-co-oxyvalerate) in methylene chloride required amount of polyethylene glycol and acetylsalicylic acid was added. The ratio of plasticizer to polymer was varied from 1: 5 to 1: 1. The addition of acetylsalicylic acid is from 1:10 to 1: 5 to the weight of the polymer. To obtain of polymer films solutions of plasticizer and acetylsalicylic acid were placed in Petri dishes. The solvent was evaporated in air for one hour and then allowed to stand for 24 hours under vacuum at room temperature. Then the polymer film was washed with distilled water and dried in a drying oven at 50^0C for 24 hours.

We have also developed a method of coating a plastic catheter poly (hydroxybutyrate-co-oxyvalerate), modified polyethylene glycol and acetylsalicylic acid. For applying the coating antithrombotic catheters were dipped into a solution of the modified polymer in methylene chloride. Coating was carried out in one, two or three layers. After application of each layer the sample was dried in a drying oven at 50^0C for 24 hours. The surface morphology of a modified catheter was investigated by a standard method using a scanning electron microscope JSM T330 (Japan) at an accelerating voltage of 5 kilowatts, increases 2000 times. To evaluate the effectiveness of an anti-thrombotic coating we studied the dynamics of diffusion of acetylsalicylic acid from the polymer coating into the water. Acetylsalicylic acid extraction was carried out by immersing samples of the same area of polymer films and coated catheters in distilled water. The dynamics of accumulation of acetylsalicylic acid in water was monitored by spectrophotometric method. Statistical analysis was performed using Microsoft Excel.

3. Results and Discussion

Creating biocompatible polymer coatings for medical devices it is necessary that the surface and polymer macrostructure were holistic and homogeneous. By microphotography method we studied the morphology of polymer films with different content of plasticizer (PEG) and an antithrombotic agent (ASA) in details. Visual analysis of the film showed that the best option is to polymer matrices with high (1: 2 and 1: 1) content of the plasticizer in the polymer. At low plasticizer content in the samples of

the films is observed heterogeneous distribution of acetylsalicylic acid, which increases with its concentration.

Microphotographs of the polymer coating also indicate that the smoothest surface and uniform distribution of acetylsalicylic acid were observed in the sample polymer containing 20% PEG and 10% ASA.

We have also studied the dynamic allocation of acetylsalicylic acid from modified polymer film in water at a temperature of 37 ^{0}C (Fig. 1).It is known that acetylsalicylic acid is readily hydrolyzed in aqueous solution to salicylic acid, therefore, for assessing the content of released ASA all analyzed solution was kept at room temperature for 72 hours to complete the hydrolysis of ASA and then spectrophotometrically determined concentration of salicylic acid in this solution (λan. = 295,9 nm).

As it follows from the data presented in Fig. 1, increasing the concentration of plasticizer accelerates ASA allocationfrompolymeric films. The minimum number of acetylsalicylic acid was allocated from the sample without polymeric plasticizer.However, in this case, it is retained better ASA polymer and an antithrombotic agent release time increases substantially. Elevated levels of plasticizer (1: 1) lead to the fact that almost all of acetylsalicylic acid is extracted into solution within the first five hours. Analysis of experimental data showed that the maximum number of ASA (90%) is released from the polymer coating in the first hour. In the next 4-5 hours there is a minor increase in the level of ASA in water and after 5 hours of the allocation of ASA practically stops.

Thus, with increasing content of plasticizer, the porosity of the polymer matrix increases, thereby increasing ASA extraction. The hydrophilic nature of the plasticizer also promotes the release of acetylsalicylic acid.

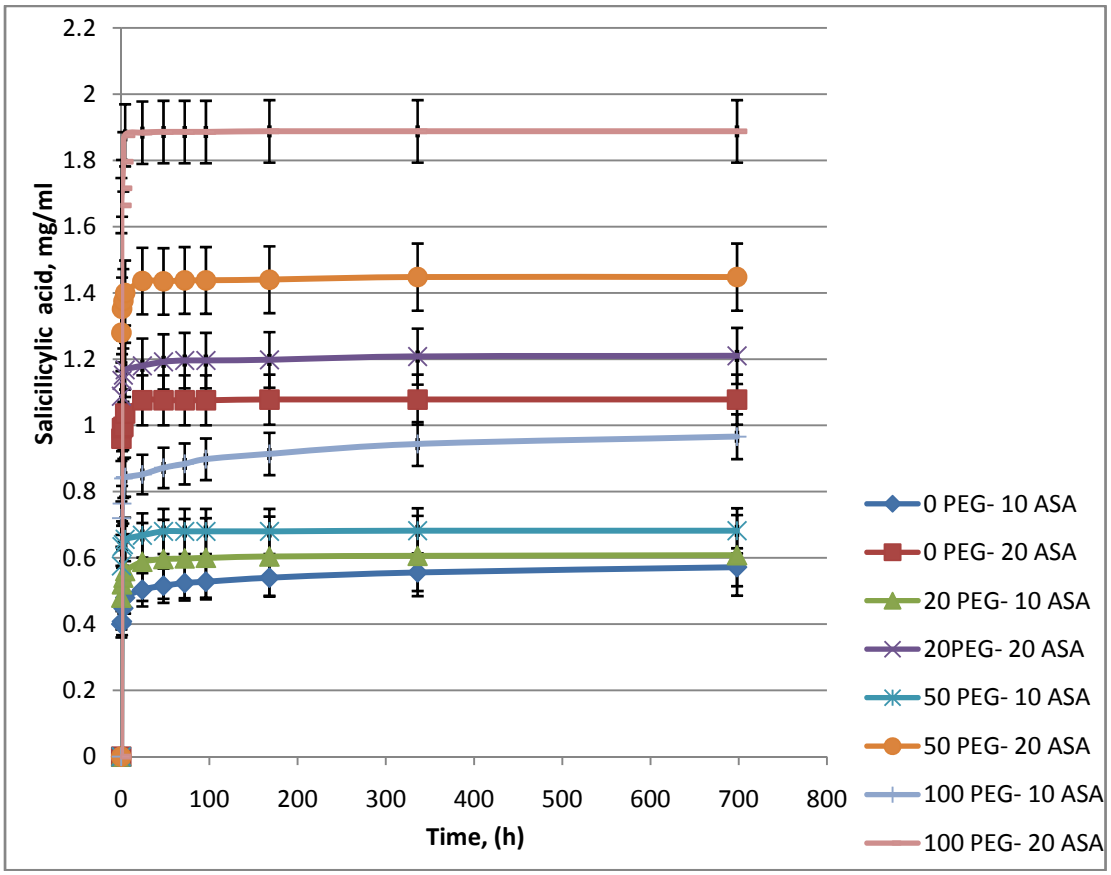

Fig. 1 Dynamic allocation of acetylsalicylic acid from modified polymeric films.

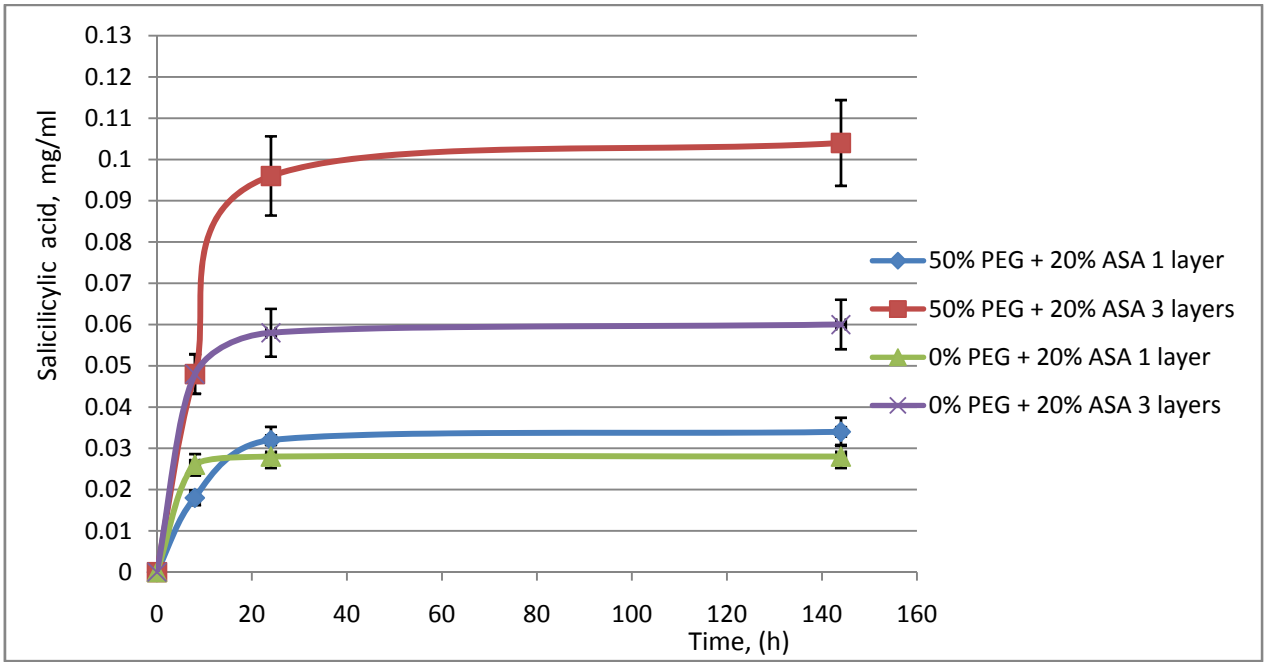

Fig. 2 Dynamic allocation of ASA in water from modified catheters for 144 hours at 37 ^{0}C.

We have also investigated the dynamics of release of acetylsalicylic acid from medical plastic catheter (Fig. 2). Catheter was modified of the poly (hydroxybutyrate-co-oxyvalerate) and acetylsalicylic acid. The polymeric coating is applied to the medical device in one, two or three layers.

A polymer coating with a low content of plasticizer allocates a minimum amount of ASA. The increase of coating thickness due to the three-time application of the polymer solution, double increases the yield of ASA. As expected the increase in the polymer concentration of ASA contributed to its isolation into an aqueous solution. Maximum number of ASA separated from the sample containing 50% plasticizer (PEG) and 20% ASA. From three-layer polymer coating release of ASA was observed for 144 hours.

4. Conclusions

The polymeric compositions for medical purposes on the basis of hemocompatible materials using poly(hydroxybutyrate-co-oxyvalerate), PEG and acetylsalicylic acid were offered to be used at the first time. Procedures of a polymer coating forming controlled release of antithrombotic drug - acetylsalicylic acid. Dynamic of acetylsalicylic acid educing from modified polymeric materials to water has been studied. The choice of polymeric material for a medical device or a coating depends on specific requirements. For quick release of the drug into the bloodstream from the surface of a medical device (catheter) polymers with a high content of acetylsalicylic acid should be used. The case of antithrombotic drug release long period without adverse reactions (implants) has to use compositions with a high content of plasticizer.

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