UDK 678.06:615.45

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DEVELOPMENT OF ARTIFICIAL ESOPHAGEAL PROSTHESES BASED ON SEGMENTED POLYURETHANE

Artificial esophageal prostheses based on segmented polyurethane have been developed. The physical-chemical properties and release of drugs from polyurethane implants were studied. The medical-biological tests of polyurethane implants in vivo experiments at laboratory animals were carried out. The data for application of polymeric implants in esophagus surgery was presented.

Segmented polyurethanes (SPU) are an important class of polymers that have found many applications as biomaterials due to their excellent physical properties and relatively good biocompatibility. Many biomedical devices are made from segmented polyurethanes such as catheters, blood pumps, prosthetic heart valves and insulation for pacemakers, etc. [1,2].

Various prosthetic materials have been experimented with for use as an artificial esophagus. The most commonly used were Celestin tubes made of latex rubber, Atkinson prostheses made of silicone rubber, or Procter-Lewinston tubes made of latex rubber [3]. Some units use polyvinyl chloride tubes which were formed, as needed, from laboratory tubing. A prosthesis with a self-inflating cuff, similar to a cuffed endotracheal tube, has become available and was particularly useful to seal tracheoesophageal fistulae in which traditional prostheses failed [4]. Though various polymers have been used as an material for artificial esophagus, the two main problems that have prevented successful clinical implantation of such a prosthesis were anastomotic leakage and stricture formation of the artificial esophagus.

The perspective and interesting field of polyurethane application is the development biomaterial for implants in the treatment of cancer of esophagus. One of the basic difficulties of anticancer chemotherapy is absence of the directed and controlled transport of drug in cells of tumor. An ideal cancer chemotherapy is to enhance the local concentration of anticancer drugs around the cancer tissue with their reduced total concentration and side effects. The modern chemotherapy of cancer diseases demands application of high dozes of drugs, leading the toxic effects. One of ways of increase of efficiency of chemotherapy of tumor is creation of new implantable anticancer drug delivery system on the basis of biocompatible polymers that allows to create high concentration of drug in a zone of cancer cell during long time. An ideal cancer chemotherapy is to enhance the local concentration of anticancer drugs around the cancer tissue with their reduced total concentration and side effects [5].

The aim of this work is the development of artificial esophageal prosthesis based on segmented on segmented polyurethanes for treatment of damage and cancer of esophagus.

Experimental part

The polyurethanes used in this study was prepared using polypropylene glycol and toluene-2,4-diisocyanate. By varying the ratio of components SPU having different hard and soft segment contents were synthesized. SPU were prepared by means of a prepolymer method as reported elsewhere [6]. The scheme of synthesis is presented below at Fig.1.

Polypropelene glycol (Fluka) with molecular weight of 1500, previously dried in a vacuum at 80°C for 3-4 h, was placed in a three-necked flask equipped with a stirrer, a thermometer and a tube for argon supply, then a toluene-2,4-diisocyanate (Bayer) was added. The molar ratio of polyol and diisocyanate was 1,0:2,5. The reaction proceeded at 100-120°C for 2 h in the argon flow. A prepolymer with isocyanate end groups was obtained. For preparation of polyurethane tubes, prepolymer was placed in special forms made form of the glass or metal

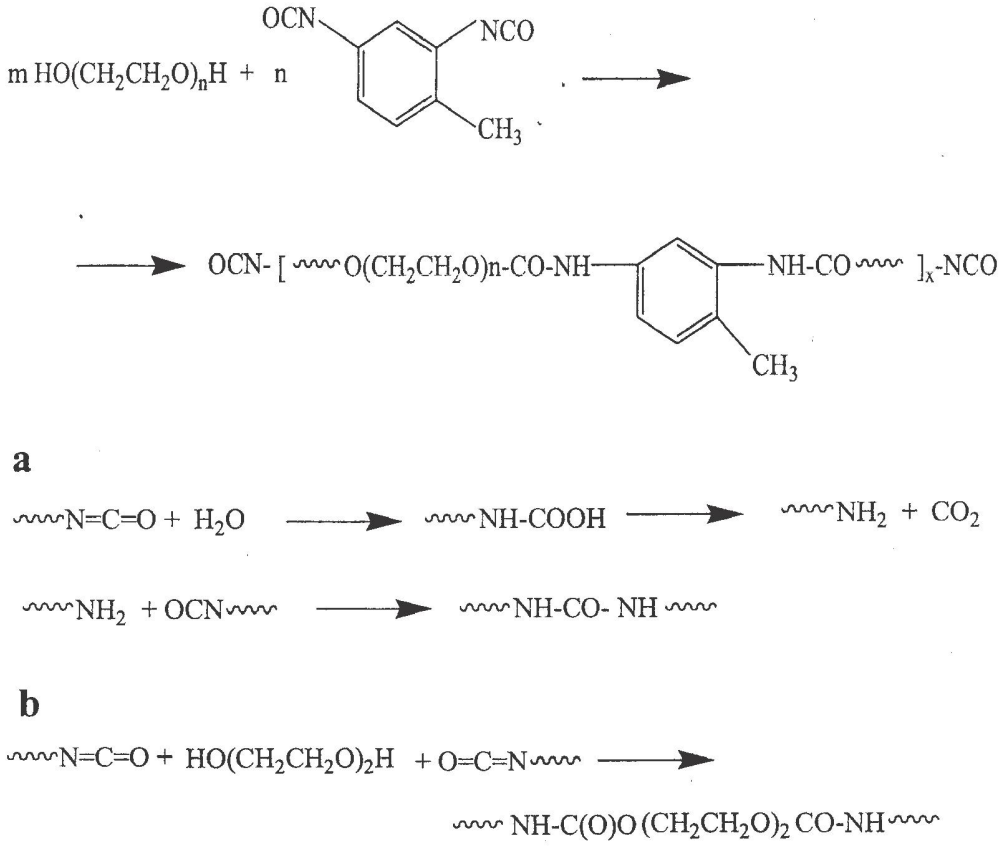

Fig1. Scheme of segmented polyurethane synthesis

cylinders, preliminary processed by paraffin. Then the calculated quantity of water, 1,4-butanediol, a drug (bleocine and vincristine) were added. Antireflux devices, funneled expansions in oral and distal ends of tubes were established in special forms prior to the beginning of process. Received polyurethane implants represented soft porous highly elastic tubes containing various dozes of drugs.

Polymeric films containing anticancer drugs were prepared by solvent cast technique. Briefly, the polyurethane was dissolved in an appropriated solvent and various amounts of anticancer drugs added to the solution. After careful evaporation of the solvent at 60° C in air, the drug containing films were furthermore evaporated for 24 h at reduced pressure to remove solvent completely.

The release behaviour of drugs from SPU films was examined by means of immersing the polymeric samples in a modelling biological medium at 37°C with constant stirring. The amount of drug released was determined by UV spectrometry (Jasco UV/ VIS 7850) by measuring the absorbance maximum characteristic for each drug.

The experiments for anticancer action of polyurethane systems were determined at 120 inbreeded white rats (females, weight 120-125 g, age 2-3 month) infected by malignant Rhabdomyoma strain at the dose of 10 000 cells. On the 10th and 17th days, 20 animals of each group were sacrificed, and the device was removed for morphological/ histological study. The quantity of clones of myoma cells was calculated using magnetic resonance tomography.

Results and discussion

As a material at reconstructive surgery of esophagust the Japanese scientists had been offered tubes from the silicone covered by a thin layer of collagen [7]. At surgical treatment of esophageal defects the tubes made from polyethyleneterephtalate (Dacron), polytetrafluoroethylene, silastic and polyurethane were applied [8]. It was shown, that regeneration of esophageal defects at application of polyurethane goes more quickly, than at use of other polymers. Microporous, compliant biodegradable esophageal prosthesis from polyurethane-polylactide have shown good results in experiment on rabbits [9].

In this study the segmented polyurethanes have been studied as biomaterial for the fabrication of artificial esophageal [10]. These polyurethane prosthesis were used for the treatment of cancer, injures and diseases of esophagus. Implantable artificial esophagus consists of bilayer polyurethane tube, cuff at upper part of tube and original antireflex device in lower part of tube, which avoids the leakage of gastric juices into esophagus. The external layer of tube is porous and contains different anticancer drugs (bleocine and vincristine), the inner layer of tube is monolithic (Fig.2).

Segmented polyurethanes with different content of hard and soft segments were synthesized by a two-step polymerization. The polyether diols were first reacted with two equivalents of the diisocyanate. Subsequent chain extension was obtained by reaction with an equivalent amount of a butanediol. Antitumour drugs bleocine and vincristine were incorporated as solution into the polymeric matrix. The obtained SPU films were contained homogeneously dissolved drugs. The revenant parameters of the drug contained SPU were following: ultimate stress 350-500 kg/cm^{-2}, ultimate strain 460-680%; content of hard segments 14.2-46.4 %.

The anticancer drugs release behaviour from SPU matrix into modelling biological media was studied. In obtained polyurethane films the drugs were dissolved homogeneously throughout the polymeric matrix. In order to estimate the bonding character between bleocine and vincristine and polyurethane matrix, the influence of temperature on the release kinetics of the drugs was studied. The typical example of drug release was shown in Fig.3.

Obviously the release rate of the drugs from the polyurethane increases with an increase of the temperature. All the release data show the typical pattern for a matrix controlled mechanism. The

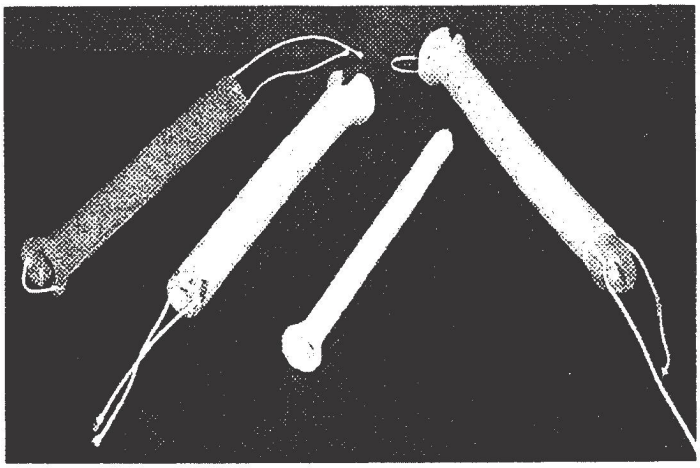

Fig.2. Photos of polyurethane esophageal implants.

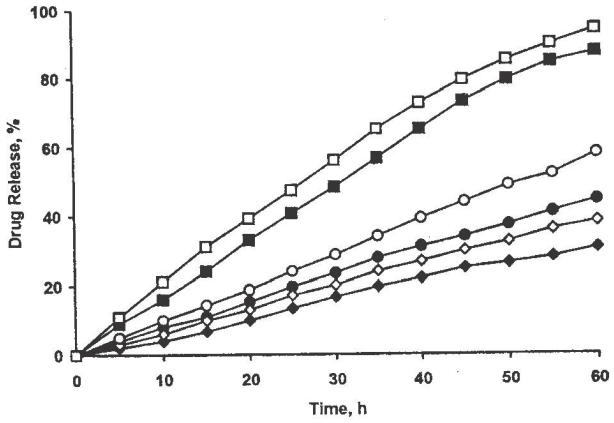

Fig. 3. Release of bleocine (white) and vincristine (black) from polyurethane implants to phoshate buffer at 23, 37 and 58°C

cumulative amount of drug released from the polyurethane was linearly related to the square root of the time and the release rate decreased this time. The process is controlled by the dissolution of the drug and by its diffusion through the polymer. The total amount of bleocine is released in 10–12days and depends of polyurethane structure and contents of high segments in polymer. A determination of activation energy of the drug release has been carried with a graphic method. The thermodynamic parameters (for example, entropy 19,7 cal/moleK and activation energy 3,2 kcal/mole for vincristine) illustrate that the drug release proceeds without hydrolysis of the chemical bonds, but one is likely present the physical interaction (the hydrogen bonds and van der Waals forces) between the drugs and the polymeric carrier. The activation energy values of drug release from SPU correspond to diffuse controlled mechanism.

The supermolecular structure of segmented polyurethane consists of hard segments associated in microdomains with a continuous phase containing soft segments of polyethylene glycol. The most predominant factors behind microdomain formation are the incompatibility between soft and hard segments and intermolecular hydrogen bonding, typical for urethane segments. In the case of drug introduction in SPU, the phase separation between microdomain and continuous phase may be increased, because the proton donors and acceptors of drug molecule may participate in the hydrogen bonding. It has been established that the phase separation in segmented polyurethanes is essentially intensifed by means of both the increase of molecular weight for soft segments and drugs incorporation in the monolithic systems of polyethylene glycol-based polyurethane. Infrared and proton NMR data indicate that drugs are associated with a urethane group of hard segments. It has been determined that the drug-concentrated domains of hard segments are homogeneously dissolved throughout the amorphous soft segments. These results indicate that the supermolecular structure design of segmented polyurethanes allows for control of anticancer drug release from the polymer matrix [11,12].

The anticancer action of polyurethane systems was determined at 120 rats by injection a malignant Rhabdomyoma strain into tail vein of animals. The quantity of tumour clones after 10 and 17 day and the weight of the sensible tissue of spleen was detected for control animals and animals who received anticancer polyurethane implants and drug injection. The strong antitumor action of both forms of bleocine is characterized by a decrease of clone quality, but the lower toxic action of the implant is expressed by the lower reduction in spleen weight. Morphological analysis of the surrounding tissue after 10 days of implantation show that the implant is surrounded by a capsule containing histocytes and fibroblasts, as well as a diffusion accumulation of lymphocytes and plasmocytes. After 17 days of implantation the capsule thickens, but the surrounding tissue shows the usual structure. Thus, the implantation of SPU containing bleocine appears to reduce toxic action of anticancer drug compared with injection.

Clinical tests of artificial esophageal prosthesis have been carried out at children with a deep burn of esophagus, with a cicatricial stenosis and punching of esophagus. Polyurethane tubes entered into the defected esophagus for 2-4 months. We were applied various designs of artificial esophageal implants depending on kind and the sizes of damage. Implants entered through a mouth by means of buzhes-pushers. Children from first days after intubation received usual semi-fluid food, applied it independently.The direct and remote results of treatment have shown that the use of polyurethane tubes at deep burns and stenoses of esophagus allows to improve considerably passableness of esophagus, to exclude necessity of process of buzhation, to provide local medical action and enteral food. The general duration of treatment of children is reduced in 2-3 times and does not exceed 5-6 months whereas at traditional treatment is extended 1,5-2 years.

In comparison with traditional ways of treatment the intubation of polyurethane implants has following advantages: the polymeric tube provides long medical effect directly on a wall of the defected esophagus; the soft elastic consistence of polymeric tubes excludes an opportunity of formation nekroses from squeezing; the microporous structure of prosthesis promotes a rapid growth of tissue; constructional features of tube provide to most patients a normal eating.

Thus, the obtained data testifies to perspectives of using the segmented polyurethane as biomaterials for formation artificial esophageal prostheses for surgical treatment of cancer and damages of esophagus.

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Резюме

Сегменттелген полиуретандар негізіндегі өңештің жасанды протездері алынды. Физика-химиялық қасиеттері және полиуретанды имплантаталардан дәрілік заттардың шығу динамикасы зерттелді. Зертханалық жануарларға *in vivo* тәжірибелерінде полиуретанды имплантаттармен медициналық-биологиялық сынақтар жүргізілді. Өңештік хирургиядағы полимерлі имплантаталар қолдану туралы мәліметтерді берілген.

Резюме

Разработаны искусственные протезы пищевода на основе сегментированных полиуретанов. Исследованы физико-химические свойства и динамика высвобождения лекарственных препаратов из полиуретановых имплантатов. Проведены медико-биологические испытания полиуретановых имплантатов в экспериментах in vivo на лабораторных животных. Приведены данные по использованию полимерных имплантатов в хирургии пищевода.

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Поступила 27.05.09