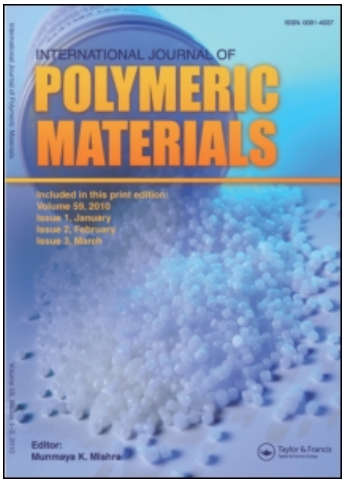

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High-Elastic Blood Compatible Material

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Materials with unique complex of the properties of elasticity and tensile strength processed from the natural rubber latex (NRL) were modified to improve their blood compatibility. ESCA, ATR-IR, UV-spectroscopy and other methods were used for appraisement of the grade of modification, structure and properties of material. Thromboresistancy was studied in *in vivo* and *ex vivo* tests. It was shown that blood compatibility is raised after thorough purification of the material from non-rubber components by means of two-stage extraction changing the physical-chemical parameters of the surface. Two different principles were used in the process of modification: 1) coating by thin polyurethane (PU) coverings with improved thromboresistant properties—thus the problem of providing high adhesion interaction of covering with the latex base was solved; 2) heparin surface immobilization—higher efficiency of modification of latex material in gel-form without preliminary protein adsorption was shown. Modification allows to increase blood compatibility of the latex materials preserving at the same time their elasticity and tensile strength.

KEY WORDS Natural rubber latex material, latex gel, thromboresistancy, polyurethane, heparin.

The blood contact with any polymer surface results in initiating the blood coagulation with thrombosis as the final stage of the process.[1] Elaboration of blood compatible non-thrombogenic materials is the most important problem of the chemistry of medical-biological polymers.

Physical-chemical parameters fully characterize antithrombotic properties of polymer materials. Chemical purity of polymers plays an important role. As a rule in the material are present the components not bonded with the polymer (scarps of catalyst and solvent, non-reacting monomers, technological additions) which can aggravate blood function and even cause hemolisis.[2]

Research in the field of increasing blood compatibility of polymer materials are carried out in two directions: the first one is realized by the modification of well-known polymer materials and improvement of technological processes of their synthesis and processing; the second one is purposeful synthesis of new materials.

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The prevailing methods of the polymer materials modification are: 1—bulk and surface modification by biological-active substances (enzymes, anticoagulants, inhibitors of platelet adhesion) which can influence one or other stage of cascading mechanism of blood coagulation, in order to prevent it; 2—coating by highly antithrombotic synthetic materials (polyurethane, silicons, hydrogels).[3]

The subject of present work is the material which is obtained from natural rubber latex (NRL)—water dispersion of unique isoprene class biopolymer which is produced by plants and contains 97–98% of stereoregular cis-1,4-polyisoprene (natural rubber).[4]

Materials obtained from (NRL) surpass in elasticity all the known polymer materials used for medical purposes. Besides they have high tensile strength, low tensile strain force, are resistant to sterilization and fragmentation caused by puncture and able for autohermetisation.

The NRL concentrates obtained by centrifugation contain about 2% non-rubber components which exist both in the bonded with a polymer form and in the free form. The main non-rubber components of NRL are: proteins and products of their degradation, fetty acids salts and a number of organic and anorganic salts. Besides these, different technological additions (stabilizers, regulators of viscosity, vulcanizing agents and etc.) are introduced into NRL during the processing. Non-rubber components contained in the NRL are transferred into the prepared material. Quantitative and qualitative composition of these components depends on the method of processing of NRL and influence the tissue- and blood compatibility of ready latex material.[2,5]

A number of materials with a high level of biological compatibility is processed on the base of NRL. Different kinds of devices for clinical and diagnostic proposed in different branches of medicine can be prepared out of these materials.[6,7]

In 70-s the NRL materials were considered perspective for production of cardiovascular prostheses, because they imitated elastic properties of living tissue better than any other materials. However, later they were substituted by elastomers of polyorganosiloxanic and polyurethanic classes which possess higher blood compatibility and are resistant to continuous influence of living organism.[8–10]

Nevertheless, from the composition materials prepared on the base of NRL were produced vascular grafts of small diameter which were used successfully in a clinical practice.[11] It was reported recently about use of polyisoprene in construction of vascular grafts.[12] Tubes transfuse, tubes of injection knots for manning system of transfuse, different rubber balloons for embolization and removing of thrombosis are made from NRL.[6,13]

In order to improve thromboresistant properties of NRL materials, the methods of bulk modification by means biological-active substances (proteins, anticoagulants) were proposed.[14,15] However, these methods are not widely used. This fact might be explained by deterioration of some functional properties of the latex materials (decreasing of elasticity, tensile strength, increasing of the degree of water swelling etc.) after modification.

The aim of this investigation is the development of new methods that can raise blood compatibility of NRL materials and retain the complex of their physical and mechanical properties.

MATERIALS AND METHODS

NRL. Preparing of Experimental Samples

Prevulcanized NRL having low modulus (LR Revultex) was used.

Samples in the form of films (thickness 0.5–1.0 mm) and tubes (i.d. 3.0–3.8 mm, wall thickness 1.0–1.5 mm) were obtained on metal former by means of the method of coagulant dipping.[4] 30% alcohol solution of $Ca(NO_3)_2$ $4H_2O$ was used as a coagulant. The scheme of the process is presented below:

Step 1. Dipping of the former into coagulant solution, drying.

Step 2. Dipping of the former into latex—formation of moist, friable latex gel.

Step 3. Air syneresis—fixation of moist latex gel.

Step 4. Water syneresis—compression of moist latex gel.

Step 5. Drying, vulcanization—the end of the film-formation and cross-linking of polymer.

Step 6. Removing ready (control) sample from former.

Since hemolitic activity of polymer material influences negatively on its blood compatibility, the degree of hemolisis was estimated before modification. Preliminary studies were carried out by *in vitro* test and spectrophotometric method was used.[16] It was found out that latex samples do not call forth blood hemolisis, consequently this cannot be the cause of their insufficient blood compatibility.

Methods of Improving Blood Compatibility

1. Purifying from Non-rubber Components. Removing of non-rubber components was carried out by three methods. In accordance with the first one, latex samples were washed for a long time in the flowing water on the stage of compression of moist latex gel (step 4). The second method consists of the extraction of ready latex samples by the mixture of organic solvents (methanol, chloroform, acetone in volumes accordance 1:1,06:1,28) at temperature of boiling (57°C). The third method includes two-stage treatment consecutive by two above mentioned methods.

2. Coating of Thin Polyurethane Layers. Polyurethanes covering (thickness 0.02–0.03 mm) with heightened antithrombogenicity compared to latex material were carried out of their solutions in organic solvents. The higher adhesion interaction between latex support and the covering was the main purpose in working out of this method of modification, and consequently keeping intact the modified latex material in the process of its exploitation. To achieve this result the surface of the latex samples was activated before coating by treatment with the water solution containing active chlorine. It was necessary to work out conditions of modification which can justify high adhesion of covering without changing of functional properties of the latex material for the worse.

3. Immobilization of Heparin. As a starting point the method of surface ion-covalent immobilization of heparin was used.[17] In accordance with this method in the first test ready latex samples were processed in succession by water solution of human serum albumin (HSA) (c = 3 g/l, T = 30°C , t = 1 h), of heparin (c

= 100 ME/ml, T = 30°C, t = 1 h) and glytaric dialdehyde (c = 1%, T = 60°C, t = 40 min).

Similar processing of latex samples was carried out on the stage of compression of moist latex gel (step 4) in the second test.

The method of direct immobilization of heparin—in accordance with this latex samples were processed on the stage of compression of moist latex gel without preliminary activation of surface by albumin or other agents for ionic bonding of heparin by water solution of heparin (c = 150 ME/ml, T = 40°C, t = 1 h), and then by water solution of glytaric dialdehyde (c = 1%, T = 65°C, t = 40 min).

Appraisement of Modification and Functional Properties of Latex Materials

Mechanical, physical-chemical and biological methods of investigation were used. Quality of purification of latex samples from non-rubber water soluble components was estimated by analysis of their water extracts by UV-spectroscopy. Chemical composition of the surfaces of control and modified latex films were studied by ATR-IR and ESCA. Hydrophility of surface was estimated by the value of contact angle defined by the method.[18]

Mechanical properties of films such as modulus at given elongation, tensile strength, elongation at break, and irreversible strain were determined on the Instron testing machine. A peel test was used to measure bond strength between latex film and polyurethane covering.

Thromboresistant properties of control and modified latex samples were estimated in *ex vivo* and *in vivo* tests on dogs under conditions of short- and long-term contacts with blood, correspondingly. In *ex vivo* test the dynamics of near wall clot-formation was studied.[19] With the help of a 12-channel design the tube samples were connected with the blood stream of dogs by the method of artery-vein shunt and the average additional weight per unit of area of their inner surface during various times of exposure was determined. The length of the contact-time of samples with blood depended on peculiarities of blood coagulation system of dogs and reached 21–27 min in different tests. To compare results from different tests, relative index (T) of quantity of precipitated thrombotic masses was used, which was determined as ratio of overweight of modified latex samples to that of control samples. In *in vivo* tests the thromboresistant properties were estimated by measuring the bulk blood stream in tubular latex samples and by the visual of inner surface of the tubes after removing it from the blood stream.

RESULTS AND DISCUSSION

Influence of Removing Non-Rubber Components on Blood Compatibility of NRL Materials

It is well known that washing of latex material in a gel form is more effective than after the consummation of film-formation and complete drying of it.[20] Therefore the removing of water soluble components was carried out by prolonged washing of latex material in gel form in the running water (step 4). The kinetics of washing

is presented in Figure 1. After quick decrease of the mass of samples which agrees with the process of gel compression at the expense of contraction of dispersive medium (serum) a very slow decreasing of mass is observed which is caused by removing the non-rubber water soluble components. However even after a long washing the constant mass of samples is not achieved. Analysis of UV-spectrum of water extracts of latex films after long washing in the running water reveals the presence of a fragments of soluble substances which are extractable from control films (Figure 2). The longer washing was not expedient because it might lead to the deterioration of polymer materials properties.[21] By extraction of mixture of organic solvent the constant mass of latex samples and therefore the highest possible

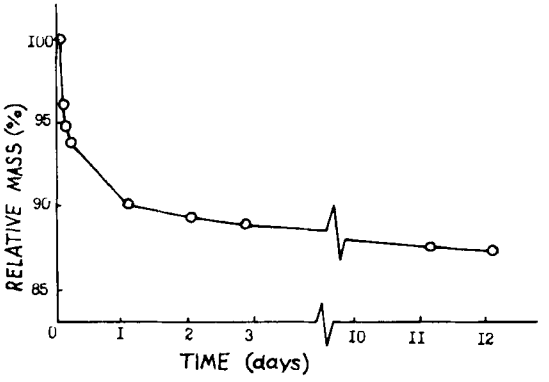

FIGURE 1 Kinetics of running water washing of the latex films in gel form.

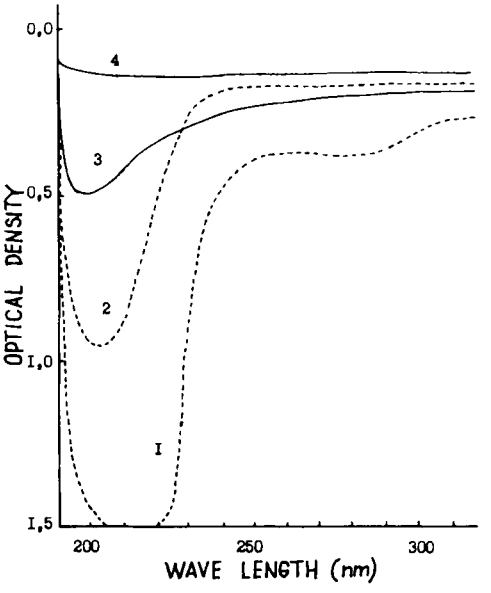

FIGURE 2 UV-spectra of water extracts of the latex films: 1) control; 2) after washing in running water; 3) after extraction by the mixture of organic solvents; 4) after two-stage purification.

degree of purification of the material by this method is achieved within 10 h. In this case the purification is more complete, the mass loss is 4.23%. But UV-spectrum of water extract of the films which was prepared after their organic solvents extraction shows the presence of some water soluble components.

After two-stage working up of latex films with a prolonged washing by running water and consequent extraction by mixture of organic solvents all water soluble components are characteristic for NRL materials are absent in water extract. The change of film masses after such working up is the highest and is equalized 4.81%.

Thus, the most effective purification of latex materials from non-rubber components is achieved by two-stage purification with water and organic solvents. It was shown that this purification does not deteriorate tensile properties of latex films and does not change their crosslink density.

Since thromboresistant properties of the polymer materials are essentially determined by physical-chemical characteristics of their surface estimating of the change of chemical composition and the structure and hydrophilic properties of the surface of latex films after the two-stage purification was carried out. Analysis of the elemental composition of surface layer thickness about 10 nm by ESCA method showed that after purification the content of such elements as O, N, S which are not contained in the polymer structure considerably decreases (Table I). The surface of the film is enriched by non-polar polyisoprene, its hydrophobic increases which is confirmed by increasing of water contact angle.

The studying of the surface macrostructure of latex films by the method of SEM shows that after purification the surface becomes more homogeneous.

Thromboresistant properties of latex material purified from non-rubber components by the two-stage method were estimated in *ex vivo* test. Index "T" for purified latex samples after maximal time of the contact with blood was 66 ± 6%. This result shows that purified latex material is less thrombogenic than the initial material.

Thus, the removing of non-bonded with the polymer non-rubber substances allows to improve the blood compatibility of NRL materials.

Coating of Thin Polymer Films with a Heightened Thromboresistancy

One of the methods of improving functional properties of latex material including blood compatibility is the covering with the synthetic polymers such as segmental polyetherurethane and polyetherurethanurea with a higher thromboresistant properties.

As the consequence of low thermodynamic compatibility of polyisoprene and polyurethane composite materials from NRL with the covering constructed on the base of polyurethanes are characterized by low adhesion interaction (bond strength varies from 0.001 to 0.01 kN/m). After the contact with the water solutions it decreases 10 times which leads to the breach of integrity of the composite material.

So at the time being the central problem of the investigations is elaboration of the method of preliminary activation of the surface of latex material which provides high adhesion interaction with a polyurethane covering. It is achieved by the working up of the latex material surface by chlorination.

In order to preserve the initial properties of latex materials the duration time of

TABLE I

Influence of removing of non-rubber components on some physical-chemical properties of the latex material surface

Type of film	Elemental composition, (%)				Contact angle (grad.)
	O	N	S	C	
Control	5.8	2.3	0.2	91.7	82.5±1.4
Purified	2.8	0.4	0.1	96.7	86.0±1.3

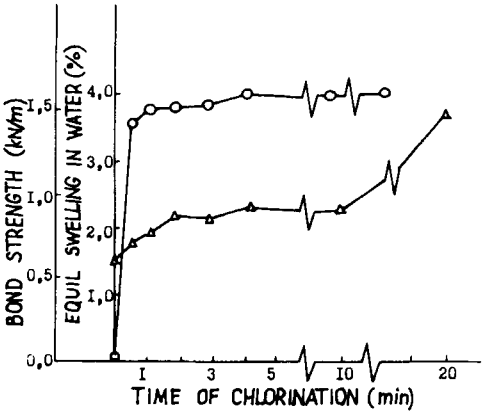

FIGURE 3 Plots of bond strength of the latex films with polyurethane covering (○) and their equilibrium swelling in water (△) versus time of chlorination.

working up was limited to early steps of chlorination. By analogy with reaction of chlorination of cis-1,4-polyisoprene in organic solution[22] it might be expected that reaction of substitution of α-methylen hydrogen atoms will take place. Further transformations in reactions of cyclization and joining of chlorine to double bonds might lead to undesirable changes of the properties of latex material.

Optimum conditions of processing (temperature, time, concentration of active chlorine) were estimated by the change of physical-chemical, tensile properties of latex material and its bond strength with a polyurethanic covering. It was determined by tests, that solution of active chlorine with a concentration 0.015–0.025% is the most suitable one for activation of latex samples surface. Using of solutions with higher concentration leads to the deterioration of functional properties of latex materials. That is: increasing of friability of the surface, hardness and water swelling and decreasing of their tensile properties. The duration of chlorination was determined by comparing the dependencies of changing of water swelling of the films and bond strength with a polyurethanic covering from time of chlorination (Figure 3). Optimal time of chlorination was 1 min; further processing does not increase

adhesion interaction while the level of water swelling of films is growing. The absorption peaks in the region of the chlorinated functional groups were observed in ATR-IR spectrum of latex films treated by the optimum regime. The tensile properties of latex film were not changed while the bond strength was increased approximately 100 times.

Estimating of thromboresistant properties of latex samples, modified by polyurethanic covering was carried out in *ex vivo* test and showed that they completely correspond with the thromboresistant properties of polyurethane used as covering. It should be noted, that besides the improvement of thromboresistancy latex materials acquired rising their oil-, ozone-, and wear resistance.

Adding Anticoagulant Properties to the Latex Materials

In order to prevent the clot-formation during the prolonged contact with blood surface of latex material must possess a higher anticoagulant activity. This can be provided by the immobilization of the natural anticoagulant of blood heparin.

The chosen method of surface immobilization of heparin[17] includes three steps of treatment: 1) uninversive adsorption of natural hydrophilic surface-active substances—proteins of the surface of polymer material; 2) formation of ionic complex of protein-heparin; 3) formation of covalent bonds by the interaction of complex with the glytaric dialdehyde.

The process of human serum albumin (HSA) adsorption was studied on dry and gel latex samples. The formation of layer of uninversive adsorbed HSA on the surface of the dry latex film led to the decrease of water contact angle and to the change of elemental composition of surface layer (increasing of contents of nitrogen, oxygen, sulphur and decreasing of contents of carbon) (Table II).

Characteristic absorption peaks of protein Amid-11 on 1550 cm^{-1} appears in ATR-IR spectra (Figure 4).

Kinetics of HSA absorption on dry latex film was studied by the method of

TABLE II

Change of physical-chemical parameters of materials after biopolymer immobilization

Type of film	Elemental composition, (%)				Contact angle (grad)
	O	N	S	C	
Control	5.8	2.3	0.2	91.7	82.5±1.4
Modified by HSA	11.8	3.8	0.3	84.1	67.6±2.8
Modified by HSA, heparin glytaric dialdehyde	10.0	3.6	0.5	85.9	61.9±2.9

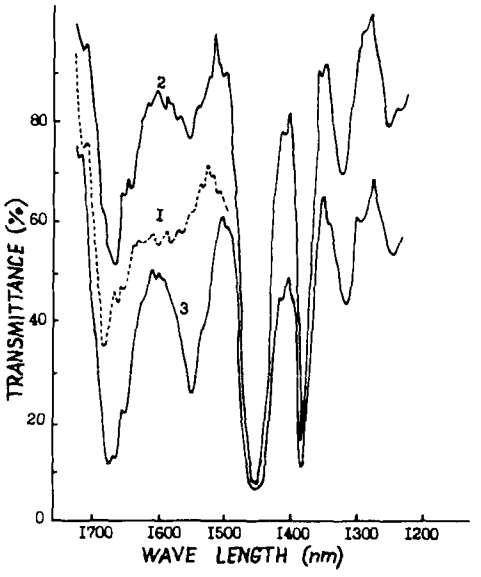

FIGURE 4 AIR-IR spectra of the latex films: 1) control; 2) treated by the HSA solution; 3) treated in gel form by the HSA solution.

pyrolitic mass-spectroscopy. Concentration of uninversive adsorbed HSA was estimated as 0.63 mkg/cm.[2,23]

The amount of surface adsorbed HSA was increased during the treatment on a stage of moist latex gel. It is revealed in the increasing of the Amid-11 peaks in ATR-IR spectra of the processed films (Figure 4).

The formation albumin-heparin conjugate in the process of treatment by solutions of heparin and glytaric dialdehyde of latex film activated by proteins was confirmed by the increase of sulphur content in surface layer, the appearance of characteristic violet coloring of the surface of processed samples by the contact with a water solution of toluidine-blue pigment, and decreasing of water contact angle.

Index "T" estimated in *ex vivo* test was 48 ± 8% for the maximal time of contact for latex samples which were modified in ready dry form, but for samples in gel form which were modified the same way, it was 40 ± 5%. The rise of effectiveness in the last case can be explained by the fact that the friable gel structure with a higher water content lightens the interaction agent of modification in a surface layer and so leads to increase of their surface concentration.

In *in vivo* test the blood flow in tube samples, modified by biopolymers, remained constant while the test was taking place (105 min). After removing the tubes from the flow only insignificant amounts of deposits of thrombotic masses were found out. The blood flow in the control samples was interrupted in a 15–20 min owing to their complete occlusion.

It is known NRL materials contain protein components. They possess high reaction activity and influence notably the reactions of cis-1,4-polyisoprene in processes of modification and technological processing of NRL and NR.[4] Since, one of protein components is bonded with polymer and should not be extracted by

water solutions, it was supposed that these protein components were capable of ionic bonding with heparin and of the possibility of immobilization of anticoagulant without preliminary activation of latex material by adsorbed HSA. In order to make the contact easier the treatment was carried out on stage of friable moist latex gel. The complex of NRL-protein with heparin was fixed by glytaric dialdehyde. The presence of bonded heparin was confirmed by coloring of samples in toluidine-blue solution.

The biological tests showed that the method of direct immobilization of heparin on latex material was effective. Index "T" was 35 ± 7% in *ex vivo* tests. In *in vivo* tests visible deposits were not observed on the surface of modified samples after 130 min contact with blood. The blood flow was constant during all the test.

It is found out that the modification of latex materials by biopolymers do not influence their tensile properties and crosslink density.

So, the immobilization of heparin on NRL material surface allows to add the hinger anticoagulant activity and makes possible their functioning during prolonged contact with blood. The most simple and effective for the latex material is the method of direct immobilization of heparin at the expense of the protein components of NRL.

CONCLUSIONS

In this study the method of increasing the blood compatibility of NRL materials are proposed. These methods are based on the purification of NRL materials from free non-rubber components and on the surface chemical modification preserving at the same time their tensile and elastic properties.

Using of these methods gives the chance on the base of NRL the materials of hinger elasticity which possess thromboresistant properties and which can be used for devices functioning both during prolonged and short-term contact with blood.

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