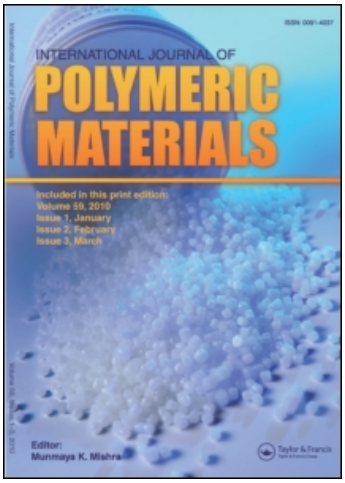

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Stability of cis-1,4-Polyisoprene and Its Vulcanizates in Aqueous and Biologically Active Media

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The biological stability of natural and synthetic cis-1,4-polyisoprene is investigated with the objective to develop new highly elastic materials for biomedical applications.

KEY WORDS Biological stability, elastomers, cis-1,4-polyisoprene, vulcanized elastomers

INTRODUCTION

Biological resistance and biocompatibility are the important properties of polymers intended for the production of medical goods and devices. Biological resistance means the ability of the polymer to retain its initial structure and properties for a long time under the conditions of the simultaneous action of the biologically and chemically active media of the body (water being the base of living tissues) and at a moderate temperature of about 40°C. Biological stability depends not only on the polymer chain's resistance (for example to hydrolysis) but on the polymer macrostructure (crystallinity, crosslink density, surface texture, etc.), which limits in many respects their diffusional characteristics as well. If the polymer contains certain additives both their nature and distribution in the polymer matrix influence its biological resistance. Mechanical strains occurring due to complicated configurations or specific application conditions decrease the polymer's stability to surrounding actions, including biological ones. The term "biocompatibility" implies favourable interaction and acceptable coexistence of the polymer material and the living tissues. Specifically, it depends on the purpose of the article.

Polymer materials based on cis-1,4-polyisoprene, natural rubber (NR) and natural rubber latex (NRL) are widely used in consumer goods such as surgical and

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examination gloves, prophylactics, various catheters, etc. Only a few references have been reported concerning the use or testing of the rubber and latex materials in prolonged contact with living tissues or biological media.[1-5] Their results are conflicting. It is well known that polyisoprene is not a highly resistant polymer because of its tendency to various types of ageing (see, e.g. Reference 6). However, on the other side NR has been called "the longest serving polymer"[7] when it was discovered that after very long contact (from 23 to 102 years) with seawater, sewage and soil the structure and properties of several rubber goods did not change notably.

The effect of water and aqueous solutions on the rubber and latex materials was studied in many papers.[8-10] It should be noted (without detailed discussion) that all the authors emphasize the definite influence of the presence and distribution of hydrophilic impurities and of the degree of water absorption. Therefore the notion that the stability of various materials processed from the same polymer might be rather different.

This paper describes a study of polyisoprene's behaviour in long term contact with a biological medium, blood serum. The aim is to estimate biological resistance, to find out what kind of factors are of major importance to stability, and finally, to develop some methods of improving their biological resistance and biocompatibility.

EXPERIMENTAL

The objects of the present study were: 1) non-cured raw rubbers—NR (Pale crepe) and synthetically analogous SKI-5PM; 2) their non-filled vulcanizates and 3) the latex films obtained by the coagulant dipping method from prevulcanized NRL (Revultex LR) and post-vulcanized latex films obtained from the latex mixture with curing ingredients. The basic formulation of both dry rubber and latex mixtures was one of the so-called semi-effective (semi-EV) curing systems (parts by weight: sulphur, 0.5; tetramethylthiuramdisulphide (TMTD), 1.8; zinc ethylphenyldithiocarbamate (Zn-EPhC), 0.3; ZnO, 1.5; AO-2246, 1.0).

All samples in the form of thin sheets (0.2–0.5 mm) were sterilized for an hour in boiling water before immersion into the test media. The primary medium was blood serum. In order to understand the specific action of the biological components the samples were kept not only in serum but also in a salt solution (0.9% NaCl), in a protein solution (0.3% human serum albumin (HSA)), in distillated water and in air. All experiments were carried out at 40°C.

Periodically the samples were tested by various methods. The viscosymmetric method (in toluene solution at 30°C) was used to measure the average molecular weight—$\bar{M}v$—of non-cured rubber. The medium absorption of samples was assessed by mass uptake measurements. The methods of ESCA, ATR-IR and water contact angle measurement were used for an estimation of the changes in the structure of the surface layer. Vulcanizates and latex films were tested for physical/mechanical properties according to standard procedures and UV-spectra of their aqueous extracts were obtained.

RESULTS AND DISCUSSION

Non-cured Rubber

The mass uptake measurements are presented in Table I. As would be expected NR absorbs much more water than SKI due to the presence of natural hydrophilic substances in it. Water saturation of NR is reached only after 9–10 months of storage while in SKI one month is enough. The degree of absorption in both polymers in salt solution and in blood serum is reduced significantly (by 5–7 times) in accordance with well known data about the behaviour of rubber om electrolyte solutions.[11]

Estimation of molecular weight changes was sufficiently correct only in the case of SKI which, contrary to NR, retained full solubility in toluene during the whole

TABLE I

Mass uptake (%) of non-cured NR and SKI-5PM during storage in distillated water, 0.9% NaCL solution and blood serum at 40°C

	NR			SKI-5PM		
Months	H_2O	NaCL	Serum	H_2O	NaCL	Serum
1.0	21.0	—	—	15.0	—	—
3.7	44.4	9.6	9.5	15.1	3.0	2.6
9.5	75.7	10.8	11.3	14.7	3.4	2.3
13.5	74.4	10.2	10.5	17.2	3.7	2.7

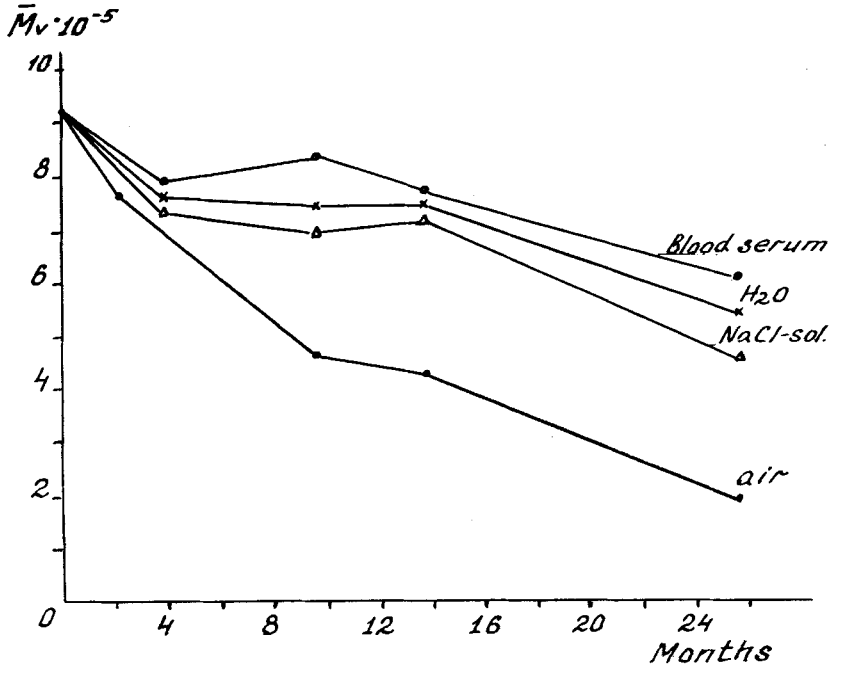

FIGURE 1 Effect of storage at 40°C in various media on the molecular weight of cis-1,4-polyisoprene.

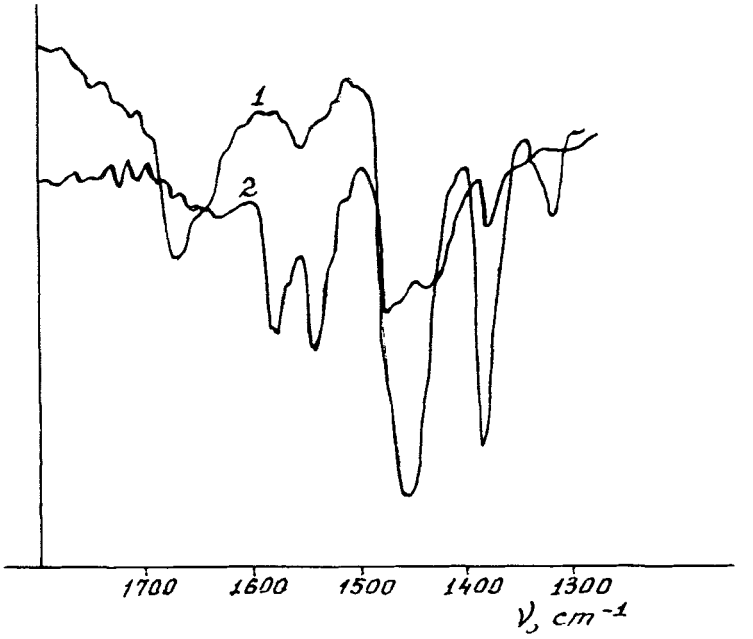

FIGURE 2 ATR-IR spectra of an NR-sheet's surface. 1 = control sample; 2 = the same sample after 2 hours' immersion in blood serum and subsequent washing in water. Characteristic lines in the 1500–1600 interval belong to the serum protein (Amid II-lines).

experimental period. Results are shown in Figure 1. It can be seen that the fastest decrease of Mv occurred if the sample was kept in air at 40°C (polymer did not contain an antioxidant). In aqueous media, thermal oxidative processes are slowing down. Blood serum protects polymer more effectively than water and salt solution. It has been found that the serum proteins adsorb onto the rubber surface (Figure 2) and probably play the role of amine antioxidants.

So, it appears that cis-1,4-polyisoprene does not undergo specific biodegradation. The main cause of its destruction is thermal oxidation which is quelled significantly if the polymer is isolated by one aqueous medium from direct contact with atmospheric oxygen.

Unfilled NR and SKI-5PM Vulcanizates

Dry rubber samples optimally vulcanized at 130°C by a semi-EV system have good physical/mechanical properties which even increase after sterilization in boiling water. Their equilibrium absorption in salt solution and in blood serum after 3–4 months of storage averages 2.5% for NR and 1% for SKI.

It is shown in Table II that network density (1/Mc) and stress-strain properties of both vulcanizates have not changed notably during nearly two years of storage in air. The semi-EV system has formed a network structure which is highly resistant to thermal oxidation at moderate temperature. The same behaviour is observed in blood serum where tensile strength retention is nearly 90%.

It seems to be helpful to compare these results with those obtained from a similar

TABLE II

Effect of storage during 22 months at 40°C in air and blood serum on the properties of unfilled vulcanizates

Sample, medium	$1/Mc \cdot 10^5$ mol/ccm	TS, MPa	EB, %
NR, init.	12.9	32.8	880
NR, air	12.5	29.8	750
bl. serum	15.6	29.8	890
SKI, init.	10.8	25.7	1030
SKI, air	14.6	21.5	840
bl. serum	11.2	23.0	980

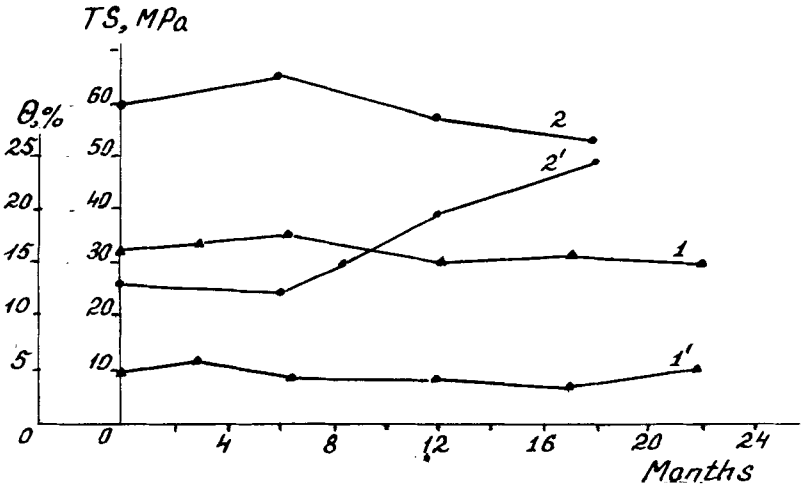

FIGURE 3 Effect of storage in blood serum at 40°C on tensile strength (TS) and residual elongation (θ) of NR vulcanizates (1,1') and polyurethane Biomer (2,2').

experiment for the segmented polyetherurethane Biomer, one of the best biomedical polymers (Figure 3). Contrary to expectations there is no essential difference between the plots of the two curves (1 and 2) which show the dependence of tensile strength of the NR vulcanizates and Biomer on the time of storage in blood serum. The first retain their elasticity as well (residual elongation does not practically change) while Biomer becomes less elastic i.e., the value is increasing (curves 1' and 2').

Latex Films

The behaviour of latex film in biological media is more intricate. Overall they are less resistant to different types of ageing than dry rubber vulcanizates and that is valid for their biological stability as well.

Macrostructure, composition and network structure are the main factors influencing the resistance of latex films in aqueous media at moderate temperature. Films obtained from prevulcanized NRL have a so called "open" structure formed

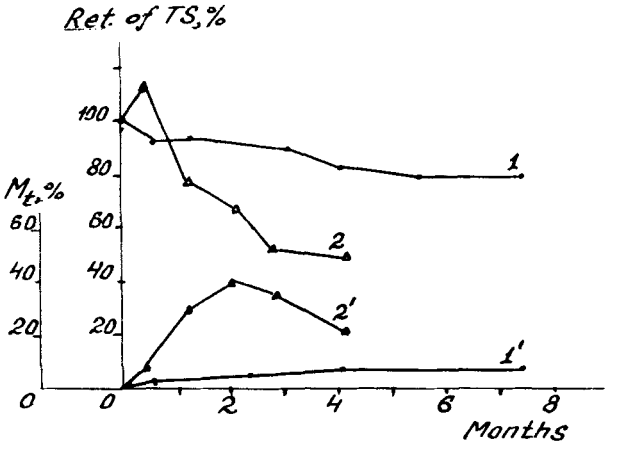

FIGURE 4 Percentage retention of tensile strength (1,2) and mass change (1',2') versus the time of water immersion at 40°C on prevulcanized (1,1') and post-vulcanized (2,2') films from NRL.

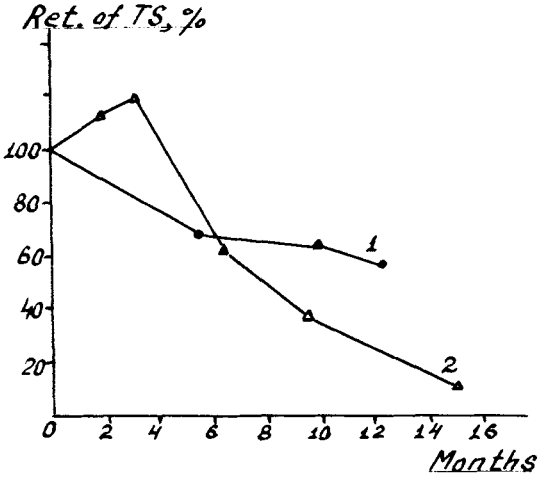

FIGURE 5 Percentage retention of tensile strength versus time of immersion in blood serum at 40°C on prevulcanized (1) and post-vulcanized (2) films from NRL.

by precrosslinked particles. Post-vulcanized latex films have a more "close" structure, crosslinked after the latex particles have coalesced to form a continuous film.[12] Composition and network structure depend on the type of curing system and on processing conditions. Revultex LR is prepared using a conventional sulphur-accelerated system and purified by centrifugation to remove excess ingredients. So, the films contain a small amount of impurities and have mainly polysulphidic crosslinks. Post-vulcanized latex films were produced from NRL mixture with the semi-EV curing system. In this case almost all non-rubber substances remain in the finished film.

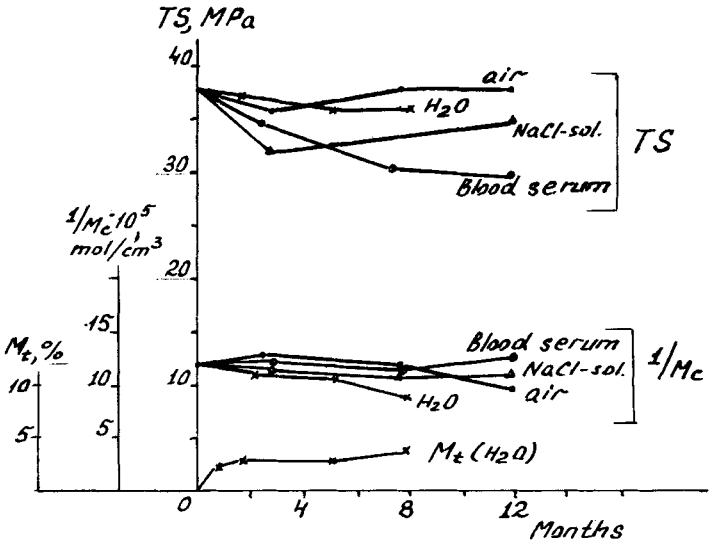

FIGURE 6 Behaviour of structurally modified latex films in various media. Changing of tensile strength (TS), network density (1/Mc) and mass (Mt) versus time at 40°C.

After careful washing and boiling of the latex films having "open" macrostructure, they become more compact and strong, have a low level of water absorption and high resistance to the action of water (Figure 4, curves 1 and 1'). Post-vulcanized films are characterized by a higher level of water absorption due to the presence of non-rubber impurities and this is the main cause for the reduction of tensile strength during long-term storage in water (Figure 4, curves 2 and 2').

Another situation is observed when the same films are kept in blood serum. Here the films with "open" structure turn out to be less resistance than those with "close" structure. We suppose that the fact may be explained by the following reasoning. Several components of the serum, such as proteins and salts, promote extraction of non-rubber natural substances which provide the particles' catenation in film (it has been shown in a special experiment). Because of the absence of interglobular chemical crosslinks such a film loses its strength quicker than the post-vulcanized one, where these crosslinks are present (Figure 5).

So, it has become obvious that the biologically resistant latex material is to be specially designed. Such a material must contain a small amount of curatives. It is necessary to create a film with a quite "open" macrostructure but the particles should be chemically cured. The water absorption ability of such a film must be low and the network structure has to be stable to oxidative breakdown at 40°C.

We have designed latex films possessing all these properties and called them "structurally modified" films. We used a curing system similar to semi-EV, but with a much lower content of sulphur, accelerators and zinc oxide. To provide a high level of physical/mechanical properties and the required macrostructure, curing reactions were carried out first in the latex mixture at 50°C and then in the ready

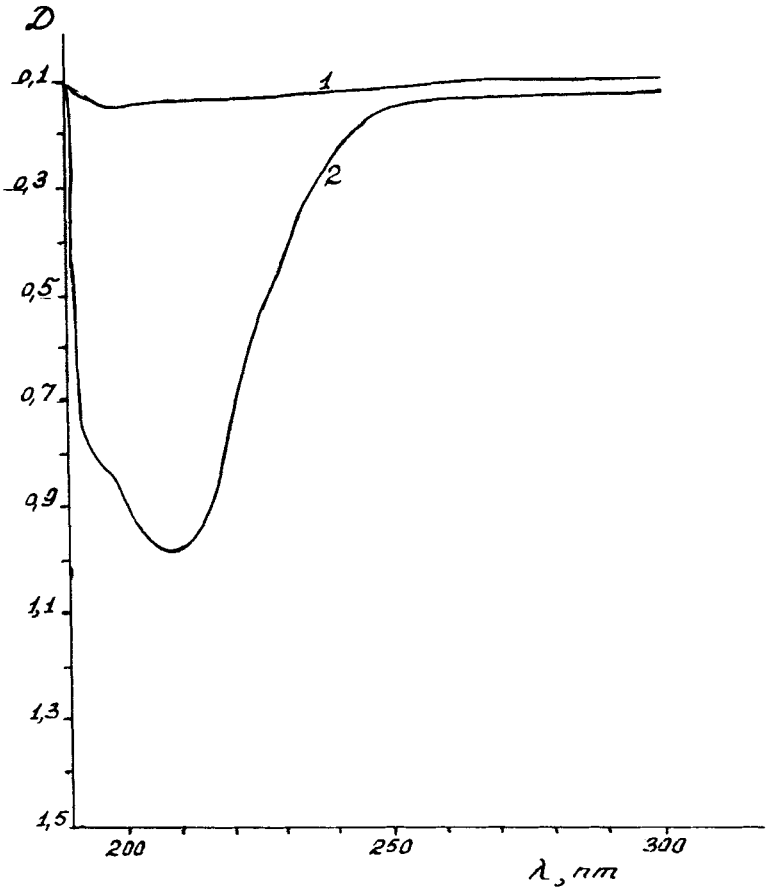

FIGURE 7 UV-spectra of the 25-days' water extracts of NRL films: 1 = structurally modified; 2 = post-vulcanized by semi-EV system.

film at 120°C. Owing to this method, optimal correlation between the intraglobular and post-vulcanized crosslinks was obtained.

Figure 6 shows the behaviour of the structurally modified films in all media for nearly a year. It can be seen that these films are much more resistant than the others. They are much cleaner as well. No characteristic lines appear in the UV-spectrum of their water extracts, contrary to the spectrum for films of the basic formulation (Figure 7).

Further investigations were carried out to create highly elastic blood compatible materials from NRL. All experimental details have been presented in our previous paper.[13] It has been found possible to modify the latex film's surface by immobilization of heparin. Some special features of latex material allowed us to simplify this method and make it more effective. We have used the possibility to carry out the modification of the latex films in gel form and have shown that the NRL's own proteins are capable of bonding heparin. High thromboresistant properties of modified latex devices have been confirmed in tests "ex vivo" and "in vivo."

SUMMARY

Studies in the area of the biological stability of natural and synthetic cis-1,4-polyisoprene and their vulcanizates have been undertaken in connection with the development of highly elastic materials for biomedical applications.

Natural rubber, its synthetic analogous SKI-5PM, and their unfilled rubber vulcanizates and films of various composition and structure obtained from natural rubber latex were kept in blood serum at 40°C during 1 to 2 years. The molecular weight of non-cured rubbers, (their physical/mechanical properties as well as their absorption of media), of vulcanizates and latex films have been tested through certain periods of time. The control samples were kept in a physiological solution, in distilled water and in air at 40°C.

It was shown that cis-1,4-polyisoprene does not undergo specific degradation by the action of the biological components of the serum. Thermal oxidation is quelled significantly due to the effect of isolation by the aqueous media. The unfilled NR and SKI-5PM vulcanizates (if the choice of curing system is correct) have high resistance to thermal oxidative ageing at 40°C and to the action of aqueous biological media. The macrostructure of latex films is most important to their stability in water and blood serum. It may be regulated by compounding and by the conditions of processing.

Some methods for structural and surface modification have been developed to improve the biological stability and blood compatibility of highly elastic biomedical materials based on polyisoprene.

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