Russian Chemical Reviews **63** (10) 853–867 (1994)
©1994 Russian Academy of Sciences and Turpion Ltd

UDC 615.462.011

Macrokinetic aspects of the biocompatibility and biodegradation of polymers

K Z Gumargalieva, G E Zaikov, Yu V Moiseev

Contents

I.	Introduction	853
II.	Reaction of the organism on the polymer	853
III.	Biocompatibility of polymers	854
IV.	Catalytic activity of biological media	855
V.	Products of the degradation in the organism	858
VI.	Biocompatibility and biodegradation of polymers of different classes	859
VII.	Conclusion	865

Abstract. We review the quantitative relationships between the degradation kinetics of the main classes of polymers (polyolefins, polyesters, polyamides, elastomers) used as implants. Their biocompatibility criteria and the reactions of the organism on the implants are considered, and the catalytic activity of biological media (water, salts, enzymes) are discussed together with problems in the metabolism and conjugation of the degradation products. The bibliography includes 127 references.

I. Introduction

The problem of producing special synthetic polymers to be used in contact with biological media first arose in the 1950s. It was created by the need by biology and medicine for synthetic polymeric materials to be used in the manufacture of various endoprostheses. This led to the development of a completely new area in technology: the production of polymers for medical applications.[1–3]

Both in the case of testing existing polymers for medical applications and when modified materials are used, the minimisation of the undesirable interactions between the material and the tissue of the living organism in implants of short or long duration as a function of the properties of the material is the most urgent problem.

Bioengineers who produce articles from these materials and doctors who use them in practice are interested in the biocompatibility of the polymers and in the retention time of desirable properties (mechanical, diffusional, optical, etc.).

When in contact with biologically active media (tissues) most polymers undergo two mutually related processes: degradation under the influence of the biologically active substances and interaction of the degradation products with the biological media responsible for the degradation (i.e. an influence of the metabolic and of the conjugation products on the life processes of the organism).

K Z Gumargalieva, G E Zaikov, Yu V Moiseev N N Semenov Institute of Chemical Physics, Russian Academy of Sciences, 4 ul. Kosygina, 117334 Moscow, Russian Federation. Fax (7-095) 938 21 56

Received 28 April 1994
Uspekhi Khimii **63** (10) 905–920 (1994); translated by J I Carasso

The study of the macrokinetic aspects of these processes ultimately allows the prediction of the lifetime of the polymer under stated operating conditions.

II. Reaction of the organism on the polymer

1. Initial reaction of the organism

A polymer in contact with the tissues of a living organism not only undergoes changes in its physical and chemical properties but also stimulates (as a foreign body) a corresponding reaction from the organism.

As a result of the damage produced in the tissues, the implantation of polymers into a living organism is accompanied by an inflammatory process.[4] This reaction consists, in the first stage of damage to the tissues, in a decrease in pO_2 and in pH, a decrease in the concentration of potassium, sodium, calcium, and magnesium ions, an accumulation of physiologically active substances resulting from the breakdown of the cell membranes and the evolution of circulating lymphocytes, and an increased accessibility of the microvessels.

In the second stage of the inflammatory process different forms of cell (neutrophils, monocytes, basophils, macrophages, etc.) are accumulated as a result of the directed motion of cells towards the inflammation region stimulated by the chemical irritants (chemotaxis). Chemical irritants include the physiologically active substances released by damaged cells and tissues (Table 1, see over), and also substances released by the polymeric materials (degradation products, residues of catalysts, stabilisers, fillers, etc.).[5]

Thus in this stage polymers can actively influence the progress of the inflammatory process.

If the process is not complicated by the onset of infections this stage of the inflammatory process is completed (on average) in three days, and the neutrophils (which were the predominant species initially) are replaced by monotcytes, plasma cells, lymphocytes, and macrophages.[6]

2. Formation of capsules round the polymer

After 4 to 5 days of contact the macrophages begin to predominate round the polymer, but lymphocytes, plasma cells, and fibroblasts are also present.[7]

If the polymer is biocompatible the number of macrophages decreases steeply after 1 or 2 weeks, and the fibroblasts form a collagen-like capsule on the surface of the polymer (Fig. 1). If the polymer is only partially biocompatible the microphages can

Table 1. Physiologically active substances contributing to inflammation reactions.

Substance	Chemical nature	Origin	Special features of the action
Histamine	β-Imidazolylethylamine	Fat cells, basophils, thrombocytes	Increased penetrability of the microvessels
Serotonin	5-Oxytryptamine	"	"
Catecholamines	Noradrenaline	"	"
Kinins	Polypeptides (metabolic products)	Plasma	Increased penetrability of the microvessels, pathogenic reactions
Hageman factor	Protease, globulin	"	"
Plasmin	Protease	"	"
Complement	Plasma proteins and metabolic products	Endothelium cells	Chemotaxis
Leucokinins	Polypeptides	Leucocytes	Increased penetrability of the microvessels
Lysosomal enzymes	Within-cell proteins	Neutrophils, macrophages, fat cells	Chemotaxis, phagocytosis
Lymphokinins	"	Lymphocytes	Immune reactions in the organism
Low-molecular regulators	Prostaglandins	Precursors present in all cells except erythrocytes	Increased penetrability of the microvessels, modulation of the inflammation, chemotaxis

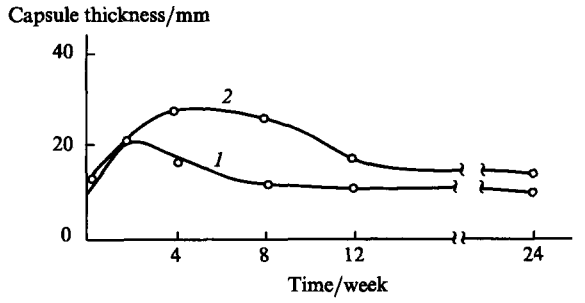


Figure 1. Plots of the thickness of the capsule against implantation time.[14] (*1*) Polydimethylsiloxane; (*2*) polystyrene coated with polydimethylsiloxane.

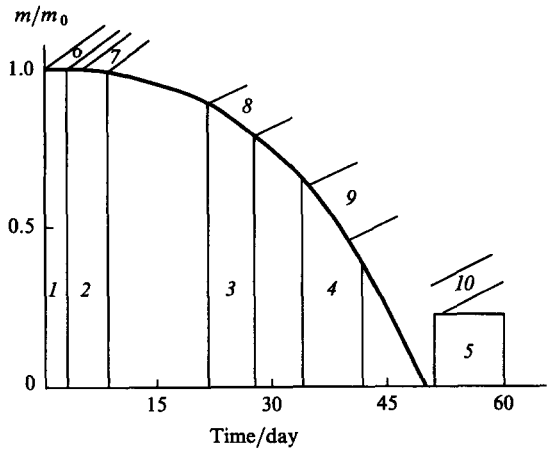


Figure 2. Dependence of the mass of the implant on time, and on its histoformological surroundings during the degradation of a polymer with satisfactory compatibility (polyglactin). (*1*) Macrophages round the implant: (*2*) macrophages containing phagocytes, fibroblasts; (*3*) giant cells and active macrophages; (*4*) macrophages and giant cells surrounding the polymer filaments with mitochondrial regions; (*5*) macrophages and giant cells surrounding the residues of the polymer fragments; (*6*) reaction on the polymer structure; (*7*) reaction to an operational trauma and healing, synthesis of collagen; (*8*) participation in the hydrolysis of the implant through the enzyme system; (*9*) participation of the cells in the metabolic process (increase in the respiratory functions); (*10*) complete resorption.

survive for longer times round the implanted polymer, and under these conditions giant cells can be formed.[8]

The thickness of the capsule depends on the biocompatibility of the polymer.[9] If the species responsible for the inflammation (for example, the degradation products) are produced at steady state we observe a chronic inflammation leading, after a long period, to the complete degradation of the polymer.

Being the main phagocyte cells of the organism the macrophages actively contribute to the degradation of most polymers. The macrophages contain lysosomes, which act as the 'alimentary canal' of the cell.[10] The lysosomal enzymes, mainly hydrolases, can destroy the polymer (phagocytosis) by two mechanisms. The first is exocytosis, in which liposomal enzymes are produced by the macrophage and the degradation takes place on the polymer surface. The second is endocytosis, in which the degradation process within the cell is preceded by the absorption of polymer particles by the macrophages. For example, Winter[11] detected metal particles within the macrophages by spectroscopic methods.

The dynamics of the morphological changes taking place on the surface of the polymer after implantation are illustrated in Fig. 2.

III. Biocompatibility of polymers

1. General definitions

We shall examine in general terms the response of the organism to a polymer after implantation, with special emphasis on the problems of biocompatibility.

When implanted into the organism polymers used in medical applications can fulfil special prosthetic or other functions (diagnostic, surgical or therapeutic) without undesirable interactions with the surrounding tissues or with the organism as a whole. At present we have no clear definition of biocompatibility, since there are no material parameters or biological tests which could be used as a quantitative measure of this property of polymers.[12]

Biocompatibility means that the polymer can exist in contact with blood and enzymes without undergoing degradation or causing thrombosis, breakdown of the tissues, or harmful immunological, toxicological, or allergenic effects.

Pure polymers with a high molecular mass usually have a low toxicity.[13] The degradation of the macromolecules produces fragments of lower molecular mass, down to the final degradation products (which could be the pure monomers). We know that the toxicity of the polymers of a given homologous series is inversely proportional to their molecular mass.[13]

Depending on the rate of degradation of the polymeric implant in the biological medium, its biocompatibility is found to change. In general the biocompatibility of the polymeric material is defined not only by the initial interactions but also by its chemical stability towards the surrounding biological medium.

2. Methods of determining the biocompatibility

A group of papers describing quantitative tests of the biocompatibility in various series of polymers has been published in the last few years.[14-18]

The in vitro experiments were mostly done by the 'tissue culture' method, which consists in growing cells on the surface of the experimental material. Two forms of the method are known: (1) depositing a layer of agar on the polymer, and observing the multiplication of the cells in the medium;[18-21] (2) depositing cells (usually fibroblasts) on the polymer and immersing the polymer inoculated with cells in the feed medium.[22,23]

The effect of the polymer on three functions of the cells is usually studied: their adhesion, survival, and multiplication.

Eleven phenomena were observed in a microscopic study.[15] Table 2 lists the polymers, the phenomena which were observed, and the doubling parameter (P_D) of the resulting fibroblast cells:

$$P_D = \frac{\lg(N/N_0)}{0.69}, \quad (1)$$

where N is the number of cells after 48 h incubation and N_0 is the initial number of cells deposited on the polymer.

From the results obtained in vitro all the polymers were divided into three arbitrary toxicity classes.

The in vivo measurements included 6 tests of the biocompatibility: (1) the extent of damage to the cells; (2) the thickness of the capsule; (3) the total number of cells; (4) the number of multinuclear leucocytes and erythrocytes; (5) the number of eosinophils, lymphocytes, and giant cells; (6) the number of fibrocytes from mononuclear phagocytes.

The number of cells is usually determined microscopically by defining a standard area.

An eight-point scale was adopted for each test.[16] The average index for each test (M) was found by adding the data obtained after two implantation cycles:

$$M_{STS} = (STS_{7\,\text{days}} + STS_{28\,\text{days}}) \times 10^{-1}, \quad (2)$$

where STS is the average sum of the marks on the scale for the tests.

The M_{STS} values for various polymers determined after implantation in the subcutaneous cellular tissues of the rat and their arbitrary assignment to the toxicity classes are shown in Table 3.

Table 2. Cytotoxicity of polymers in vitro.

Polymer	Phenomenon[a]	P_D	Toxicity class
Polypropiolactone	1	2.7	I
Polyhexamethylenediamine	1	1.9	I
Teflon	1	2.1	I
Polylactide	1	1.6	I
Poly(ethylene oxide)	1	2.1	I
Polyacrylamide	1	2.0	I
Polycaprolactone	1	2.1	I
Polyacrylonitrile	1	2.1	I
Polyglycollide	1	2.0	I
Poly(methyl methacrylate)	1, 11	–	II
Polymethyllactyl-2-cyano-acrylate	7, 8, 10	–	II
Polyisobutyl-2-cyanoacrylate	1	2.0	II
Poly(1,2-isopropylidene)-glycerolcyanoacrylate			
high-molecular	4	0.4	II
low-molecular	2, 5, 6, 7	–	III
Poly(acrylic acid)	5, 8, 9	–	III
Polydimethyl-2-cyanoacrylate	5, 7, 8	–	III

[a] The numbers refer to the following phenomena: 1, normal adhesion and multiplication of cells; 2, adhesion of a small number of cells; 3, normal growth of a small number of adhering cells; 4, the number of cells adhering after 48 h is negligible; 5, all cells in the medium have died; 6, all cells adhered to the growing surface have died after 48 h; 7, cells form a clump; 8, cells are not attracted to the surface; 9, sudden change in pH to 5.2; 10, there are some changes in the cells in the medium after 48 h; 11, the polymer adheres to the cells.

Table 3. Toxicity of polymers.

Polymer	M_{STS}	Toxicity class
Gelatin	2.1	I
Polyacrylamide	10.3	I
Polyglycollide	19.6	I
Polyacrylonitrile	52.0	I
Poly-α-lactide	34.7	I
Poly-β-propyllactone	69.1	I
Polycaprolactone	37.3	I
Poly(ethylene oxide)	21.8	I
Polymethyl-α-lactylcyanoacrylate	56.7	II
Poly(methyl methacrylate)	49.2	III
Polydimethyl-2-cyanoacrylate	59.1	III
Polyisobutyl-2-cyanoacrylate	49.7	III

IV. Catalytic activity of biological media

At the contact between polymers and biological media the latter usually show a catalytic activity towards the chemically unstable bonds in the polymers. Biological media contain a large number of low-molecular and high-molecular mass substances of different chemical nature, which interact with different polymers to different extents.

An analysis of published papers showed that the following substances should be considered from the standpoint of catalytic activity: water, salts, and enzymes. The choice of these substances was made partly because they are the most widespread and partly because their catalytic activity is now generally accepted.

1. Water

The water content of biological media is high. For example, the human organism contains approximately 75% of water, mainly in the intracellular fluid of the tissues and in the plasma. Thus polymers implanted into any part of the organism must be in contact with water.

Abundant information on the sorption and diffusion of water in various polymers is available. In Table 4 we show accepted data for the polymers used in medicine. As can be seen, water readily diffuses in all the polymers, but the amount of sorbed water varies widely as between the polymers. Three characteristic features can be noted.

In amorphous-crystalline polymers the sorbed water is located mainly in the amorphous regions. A dual sorption takes place in hydrophobic polymers at temperatures below the glass transition: volume filling of the micropores and dissolution in the polymer matrix.[28,29] Heterochain polymers and some carbon-chain polymers with heteroatoms in the side radicals are unstable towards water. Carbon-chain polymers without heteroatoms in the side chains are stable towards water.

Table 4. Values of the sorption ($c^0_{H_2O}$) and of the diffusion coefficient (D) of water in various polymers used in medicine.

Polymer	T/°C	$c^0_{H_2O}$/ g (100 g)$^{-1}$	10^9D/ cm^2 s^{-1}
Segmented polyurethanes			
Avcotan-51	37	1.2	400
Biomer	37	1.0	700
Polyacrylonitrile [a]	25	7.5	
Poly(vinyl alcohol) [a]	25	4.0	0.051
Poly(vinyl chloride) [a]	30	0.5	23
Polydimethylsiloxane [a]	35	0.07	70000
Polydodecaneamide [b]	30	2.0	3.9
Poly(2-hydroxyethyl methacrylate), hydrone	37	40	100
Polyglycollide	37	8	5.0
Polycaproamide [b]	35	8	1.2
Polycarbonate	37	0.3	66
Polyglactin (copolymer of lactic and glycollic acids)	37	8.0	7.0
Poly(methyl methacrylate) [a]	50	1.2	130
Polypropylene [a]	25	0.007	240
Polytetrafluoroethylene [a]	20	0.01	–
Polyethylene (ρ = 0.923) [a]	25	0.006	230
Poly(ethylene terephthalate)	25	0.3	3.9

[a] Data from Ref. 26.
[b] Data from Ref. 27.

In the majority of polymers water diffuses relatively fast, and is sorbed in quite large quantities. Thus, in filaments and thin plates we can expect the degradation processes to take place in the inner kinetic region.

Table 5 shows the $k_{eff}c^0_{H_2O}$ values at 37 °C (where k_{eff} is the effective rate constant of the polymer degradation), and also the activation energy of the degradation for different heterochain polymers.

Partially cross-linked polydimethylsiloxane sorbs very small amounts of water, and its degradation takes place mainly in the outer diffusion-controlled kinetic region. The k_{eff} value at 37 °C and the activation energy are 2×10^{-5} g cm^{-2} day^{-1} and 14 kcal mol^{-1} respectively for this material.[35]

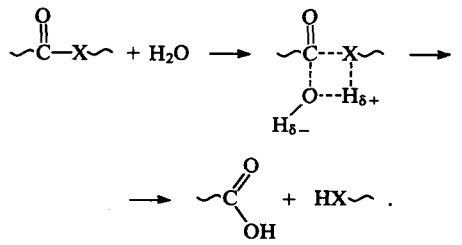
Thus in many polymers [for example polyglycollide, polygalactin, and poly(dimethylsiloxane)] degradation in water is relatively fast, and this must be allowed for when considering the overall kinetics of the resorption of these polymers in biological media, and also when choosing a sterilisation procedure (these polymers cannot be sterilised in steam).

Table 5. Values of $k_{eff}c^0_{H_2O}$ at 37 °C and activation energies for the degradation of various heterochain polymers.

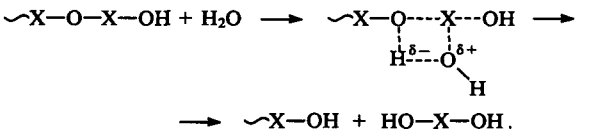
Polymer	$k_{eff}c^0_{H_2O}$/ min^{-1}	E_{H_2O}/ kcal mol^{-1}	Ref.
Polydodecaneamide	4.0×10^{-11}	–	see [a]
Polyglycollide	9.0×10^{-4}	–	
Polycaproamide	1×10^{-10}	–	32, 33
Polycarbonate	3.3×10^{-6} (at 70 °C)	23 ± 1	34
Polyglactin	1.5×10^{-3}	–	see [a]
Poly(ethylene terephthalate)	1×10^{-10}	25 ± 2	

[a] Reviewers' experimental results.

The hydrolytic degradation of carbonyl-containing polymers (polyamides, polyesters, polycarbonates) takes place by the bifunctional catalytic mechanism



The hydrolytic degradation of polymers containing oxygen (for example, polydimethylsiloxane) takes place only at the end of the chain (depolymerisation), and apparently by the following mechanism:[36]



2. Salts

Salts are found in large quantities in biological media. In Table 6 we show the ionic composition of liquids in the human organism.[37] The plasma and the intracellular liquid contain proteins present in the anionic form, because they include carboxylate groups. Detailed studies of the diffusion and sorption of salts in various polymers have been carried out in our laboratory.[24,38] We shall mention only some of the most characteristic results.

In the diffusion of electrolytes in hydrogels [poly(2-hydroxyethyl dimethacrylate), poly(vinyl alcohol), etc.] the kinetic parameters (for example, the diffusion coefficient D) are close to the corresponding values for solutions. In hydrophilic polymers with only a moderate solubility for water the sorbed water does not form a continuous aqueous medium in the polymer matrix, and the ions diffuse by activated jumps between polar groups. This leads to a large decrease in the c^0 and D coefficients of the electrolyte as compared with the same parameters for the solution.

Electrolytes diffuse in hydrophobic polymers by a mechanism analogous to the transport of gases and vapours. Therefore in the case of electrolytes with a high vapour pressure (for example, hydrochloric acid) the c^0 and D values are close to the corresponding values for water in these polymers. For electrolytes with a low vapour pressure (for example, chlorides and phosphates) we find very low values of c^0 and D, i.e. these electrolytes are not sorbed on hydrophobic polymers to a significant extent.

Table 6. Ionic composition of the liquids in the human organism, mequiv l^{-1}.

Ion	Plasma	Liquid in tissues	Intracellular liquid
Na^+	138	141	10
K^+	4	4.1	150
Ca^{2+}	4	4.1	40
M^{2+}	3	3	40
Cl^-	102	115	15
HCO_3^-	26	29	10
PO_4^{3-}	2	2	100
SO_4^{2-}	1	1.1	20
Organic acids	3	3.4	–

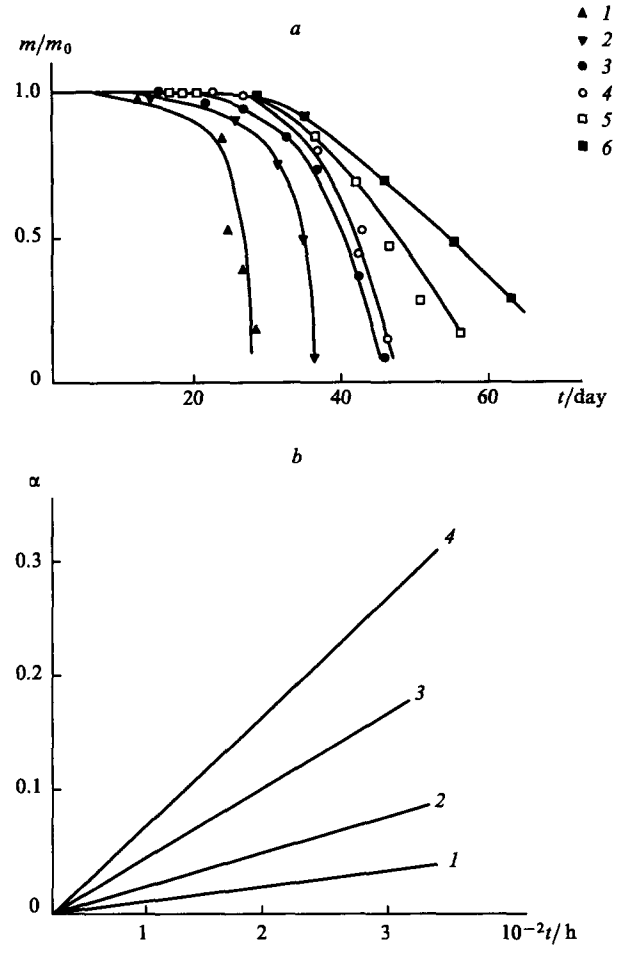


Figure 3. Plots of the relative mass of polyglycollide filaments against time since implantation and of exposure to model media (*a*) and change in the degree of conversion of the molecular mass of polycaproamide filaments incubated in a phosphate buffer solution (*b*). (*a*) pH 7.4, $T = 37$ °C; (*1*) 1 M phosphate buffer; (*2*) organism (subcutaneous tissue of rabbit): (*3*) 0.5 M phosphate buffer; (*4*) 0.1 M phosphate buffer; (*5*) 1 M salt solution; (*6*) water; (*b*) $M_{PCA} = 15000$, pH 7.4, $T = 37$ °C; concentration of phosphate buffer, M, (*1*) 0.1; (*2*) 0.3; (*3*) 0.6; (*4*) 0.1.

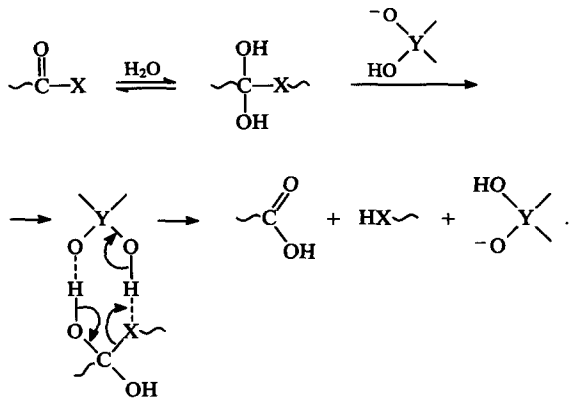
Thus all polymers can be nominally classified into two groups: those that dissolve water and those that do not. Polymers with $c^0_{H_2O} > 1\%$ are assigned to the first group; those with $c^0_{H_2O} < 1\%$ are assigned to the second.

Studies of the catalytic action of salts towards polymers are only just beginning. The effect of the salts listed in Table 6 on some polymers has been examined in our laboratory.

The degradation of moderately hydrophilic polymers (polyglycollide and polycaprolactam is markedly accelerated by an increase in the concentration of acid phosphates, bicarbonates, and bisulfates in buffer solutions of constant pH (Fig. 3). On these same polymers the salts of monobasic acids have a much smaller catalytic effect.[39]

Thus the ions so far examined can be arranged in the following sequence: the anions of polybasic acids are potentially catalytically active, the anions of monobasic acids and the cations listed in Table 6 are catalytically inactive.

The following overall scheme can be suggested for the catalysis by salts of the processes leading to the degradation of polymers containing carbonyl groups:[24]



Clearly, this bifunctional catalysis is impossible in polymers not containing carbonyl groups: for example polydimethylsiloxane.[35]

Thus salts (especially phosphates) have a strong catalytic influence on the degradation process in polymers containing carbonyl groups.

3. Enzymes

Enzymes play an active role in the degradation of polymers implanted in the organism. However, until very recently there was no clear experimental evidence of the reality of these effects. Typical results reported for medical polymers are shown in Table 7. Similar results have been obtained for some other polymers.[42]

Table 7. Rate of change of the relative intensity of the IR absorption bands ($10^2 W/\text{day}^{-1}$) of the polyurethane adhesive KL-3 in model media and in the subcutaneous tissue of rats.[40]

Medium	1110 cm^{-1}	1230 cm^{-1}	1730 cm^{-1}
Physiological solution	0.13	0.05	0.04
Ringer–Lock solution	0.13	0.04	0.03
Rabbit liver extract	0.10	0.04	0.02
Rabit muscle extract	0.10	0.02	0.03
Rabbit kidney extract	0.12	0.02	0.02
Trypsin solution (0.01%)	0.11	0.01	0.02
Chymotrypsin solution (0.01%)	0.12	0.01	0.02
Living organisms	0.59	0.39	0.34

We may conclude from these figures that the chosen media do not adequately model the high rate of degradation of polymers in the living organism. This can be explained by noting that the enzymes which catalyse the degradation are dissolved in a capsule and are essentially lysosomal enzymes produced by macrophages and other cells.

Salthouse[6] determined by quantitative histoenzymology the activity of various enzymes in a capsule on the surface of materials after implantation for different times into rats (Table 8, see over). An increase in the enzyme activity takes place in all the materials after 14 days, associated with an increased phagocytosis in the implantation region. After the healing of the surgical incision and the formation of a capsule from the connective tissue a stationary concentration of enzyme is apparently reached on the polymer surface.

Enzymes diffuse easily in the capsule, and are adsorbed on the surface of polymers in different concentrations. The surface concentration of catalytically active enzymes is determined not only by the number of enzyme species in the bulk of the capsule but also by the competitive adsorption of other proteins (catalytically inactive plasma proteins), lipids, etc. The mechanism of the action of enzymes on polymers is

Table 8. Activity of enzymes in the capsule on the surface of various materials.

Group of materials	Time after implantation	Activity		
		acid phosphatase	aminopeptidase	oxyreductase[a]
Polypropylene,	7	+	±	+
polyethylene,	14	+ +	+	+
polyurethane, poly-	28	±	±	±
tetrafluoroethylene	42	–	–	±
Silicone resin,	7	+ +	+	+
poly(vinyl chloride),	14	+ + +	+ +	+
polyethylene	28	+ +	+	+
(technical)	42	±	–	±
Poly(vinyl chloride),	7	+ +	+	+
plasticised with	14	+ + +	+	+
di-n-propyl and	28	+ +	±	±
decyl phthalates	42	±	–	±
Poly(vinyl chloride)	7	+ + +	+ +	+
plasticised with	14	+ + + +	+ +	+ +
di-n-amyl phthalate	28	+ + +	+ +	+
	42	+	+	+
Poly(ethylene	7	+	±	+
terephthalate)	14	+ +	±	+
	28	±	–	±
	42	–	–	–
Silk	7	+ +	+	+
	14	+ +	+ +	+ +
	28	+	+	+
	42	+	+	+
Polycaproamide	7	+	±	+
	14	+	+	+
	28	±	±	±
	42	±	±	±
Catgut	7	+ +	+	+
	14	+ + +	+ +	+
	28	+ +	+ + +	+
	42	+	+	+
	63	+	+	±
Polyglactin 910	7	+	+	+
	14	+	+	+ +
	28	+ +	+	+ +
	42	+	+	+
	63	–	–	–

Notes. The following symbols are used: – no activity; ± very low activity; + moderately high activity; + + substantial activity; + + + high activity; + + + + abnormally high activity.

[a] Combined activities of succino- and lactodehydrogenase and of cytochromeoxidase.

extremely complex because the majority of polymers are not specific substrates for the enzymes.

We have the results of experiments in vitro which confirm the action of enzymes on polyglycollide. Fig. 4 shows the kinetic curves for the evolution of glycollic acid during the degradation of polyglycollide fibres in solutions with different activities of β-glucouronidase.[43] The initial rate of degradation increases in proportion to the activity of the enzyme; if an inhibitor (iodoacetamide) is added to these solutions the catalytic effect of the β-glucouronidase is almost totally suppressed. Williams[44–46] studied the stability of polyglycollide filaments in solutions of various enzymes, and showed that carboxypeptidase A, physin, and leucineaminopeptidase can strongly accelerate the degradation of this polymer. In the case of other polymers catalytically active enzymes have not been identified beyond doubt, though they are often suggested as a possibility in published papers.

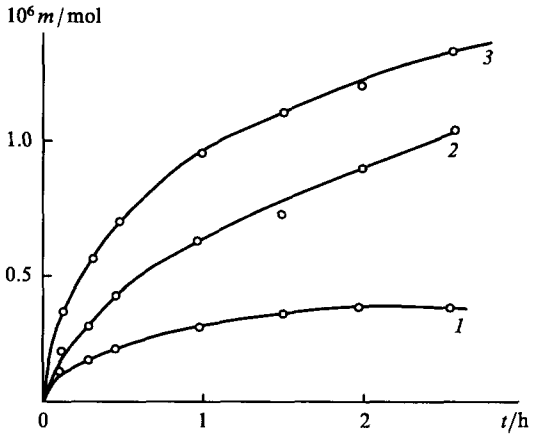


Figure 4. Kinetics of the production of glycollic acid during the incubation of polyglycollide filaments in a solution of the enzyme β-glucouronidase at a concentration of 1 mg ml^{-1} without inhibitor (*1*) and in the presence of the inhibitor iodoacetamide at concentrations 0.5 (*2*) and 1.8 mg ml^{-1} (*3*).

Thus enzymes, like water and the phosphates, are important catalytic agents in the degradation of polymers in biological media.

V. Products of the degradation in the organism

The degradation products are removed from the organism by a two-phase process: metabolic transformation and conjugation. This produces metabolites and conjugates, which are excreted with the urine and the bile or breathed out into the air.[47]

Metabolic transformations are reactions as a result of which the degradation products undergo one or more conversions (oxidative, hydrolytic, etc.) leading to the formation of functional groups which increase the polarity of the molecules.

Conjugation is a reaction which allows the degradation products or their metabolites to combine with biologically active substances in the organism, making the molecules more polar and less fat-soluble and therefore easily eliminated.

Table 9 shows the main heterochain medical polymers, the degradation products identified in model media, and their characteristic properties.

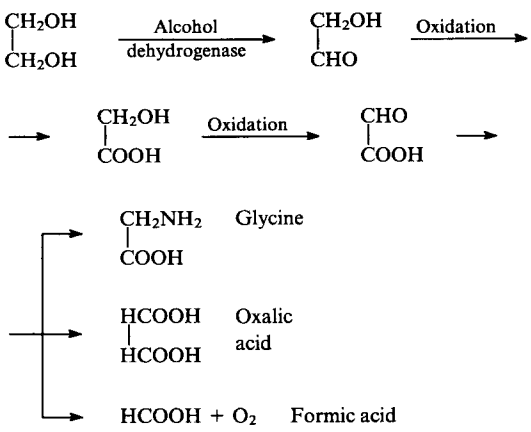
All the degradation products can be divided into three groups.

(1) Degradation products which contribute directly to the metabolic processes (cycles) of the organism: for example, lactic acid in the Corey cycle. These degradation products are almost nontoxic.

Table 9. Heterochain polymers used in medicine, their degradation products, and their characteristics.

Polymer	Degradation products	$10^5 k_{dis}$	Solubility in water
Polyglycollide	Glycollic acid	15	Good
Polyglactin	Glycollic and lactic acid	14	"
Polydodecaneamide	Aminoundecanoic acid	14	Poor
Polycaproamide	α-Aminocapronic acid	14	Good
Polydimethylsiloxane	Mixture of silols and their cyclisation products	–	–
Poly(ethylene terephthalate)	Terephthalic acid, ethylene glycol	29 35	Poor Good

(2) Degradation products able to undergo metabolic or conjugative transformations. For example, ethylene glycol is transformed in the organism by the scheme[47]



The toxic effect of the ethylene glycol is seen first of all in the kidneys, where oxalates are deposited in the channels.

(3) Degradation products eliminated from the organism in an unchanged form. For example, terephthalic acid ($k_{diss} \approx 3 \times 10^{-4}$) has a fairly high polarity and cannot easily penetrate into the tissues, and is therefore rapidly eliminated through the kidneys. It should not be forgotten that terephthalic acid can form a complex with albumin through the amino group of aspartic acid, and in this form it can be carried by the blood circulation system of the organism. Metabolically inert and nonpolar compounds such as vinyl chloride are eliminated with difficulty and tend to accumulate in the fatty tissues.

VI. Biocompatibility and biodegradation of polymers of different classes

Work on the biocompatibility and biodegradation of the main classes of polymers of medical importance is being currently reported. Various approaches to the study of these processes and the most important results obtained by various workers will be discussed below.

1. Polyamides

a. Polycaproamide

Polycaproamide (PCA) is one of the polymers first used for medical purposes. Its structure is similar to that of a polypeptide chain. At present this polymer has only limited applications, mainly as suture filaments (produced by the Ethicon Company, USA: a similar filament is produced in Russia as A122). Polycaproamide can be considered to be biocompatible as a polymer: histological data suggest a very slight inflammation round the implant.[48,49]

PCA has a moderately high resolution time in the organism. From this standpoint it can be used as a model for in vitro studies. For this reason detailed data are now available on the microkinetics of the decomposition of PCA not only in the organism but also in model media.[39,40,42] It follows from those data that the degradation of PCA takes place by a mixed mechanism: both on the surface and in the bulk of the polymer. The catalytic action of water and salts (phosphates, carbonates) on the degradation process should be examined first. In the organism the degradation of PCA takes place with a change in weight and in the molecular mass, due to the dissociation of the accessible amide bonds in the amorphous regions of the polymer (Fig. 5).

A remarkable feature of the degradation of PCA is the fact that the total surface of the polymer remains practically constant during the degradation as a result of the compensation of the normal decrease in diameter of the filaments by the increase in surface area produced by roughness and cracks on the surface.

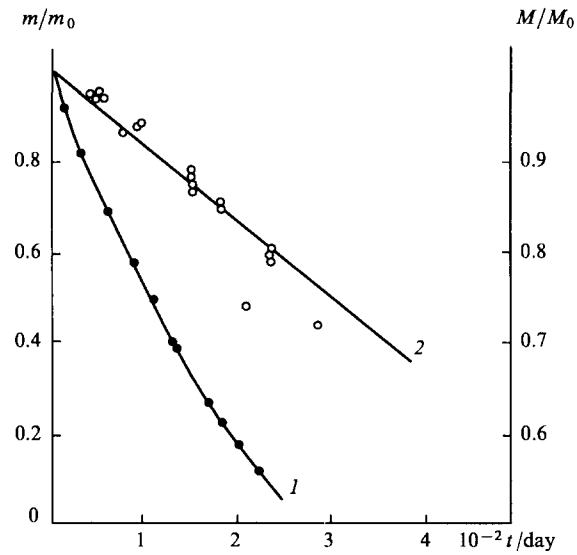


Figure 5. Change in the mass (*1*) and in the molecular mass (*2*) of PCA A122 (diameter = 24±2 μm, M = 15 000) after implantation for various times in the subcutaneous tissues of rabbits.

The change in mass of the polymer is described by the equation

$$m = m_0 - k_{eff}^S t .$$

Here m_0 and m are the initial and final mass respectively, and k_{eff}^S is the rate constant for the degradation of the polymer on the surface,

$$k_{eff}^S = kc_{cat} S ,$$

where c_{cat} is the concentration of catalyst and S is the area of the polymer surface.

The constant k_{eff}^S was determined by experiments on rabbit, and found to be $(1.6 \pm 0.2) \times 10^{-3}$ g day^{-1}. The rate constant of the decomposition of the amide linkages in the polymer matrix, determined by the law of chance [$k_{eff(l.ch.)}$] from data on the titration of the terminal amido groups in the implanted samples, was $(5.4 \pm 0.5) \times 10^{-5}$ day^{-1}.

An analysis of the action of catalytic agents showed that the bulk degradation of PCA takes place under the influence of water, whose solubility in PCA is 5.5% ± 0.5%. The large water content of the polymer allows the penetration of salts into the PCA with a diffusion coefficient[51] of 10^{-9} cm^2 s^{-1}. The rate constant of the decomposition of the amide bonds in the amorphous region in the presence of water at 37 °C is 1×10^{-7} day^{-1}; with this value of the rate constant only 0.5×10^{-4} of the amide bonds are dissociated in a year, which is much less than the rate constant for the decomposition in the organism.[32] This shows the important contribution made by salts to the degradation of polymers in the bulk. Model experiments in 0.1 M NaH_2PO_4 (the concentration of the liquid within the cells) at 37 °C gave

$$k_{eff(l.ch.)} = (0.5 \pm 0.1) \times 10^{-5} \text{ day}^{-1} .$$

Special experiments have shown that enzymes cannot penetrate effectively into films of PCA of thickness equal to the diameter of the filaments even over a period of 100 days. It is assumed that enzymes can contribute to the degradation process only from the surface. Thus the decomposition in the bulk of the polymer (V-type) takes place under the influence of water and salts, whereas the decomposition on the surface (S-type) takes place under the influence of enzymes in the organism.

These quantitative results allow us to predict the stability of PCA in the organism. In spite of the satisfactory compatibility with the tissues of the organism the use of PCA in suture threads is not very widespread; the prospects of using this material as rapidly resorbed threads have suffered from the more recent development of materials such as Dexon and polyglactin.

b. Polydodecaneamide

Polydodecaneamide (polyamide 12) is used as an endoprosthesis. This polymer is fairly stable in terms of its rate of resorption in the tissues of the organism, and therefore it is of interest as the foundation of various structural modifications aimed at preparing new materials for endoprosthetic purposes.[52-55]

The mechanism of the degradation of polyamide 12 was shown to be similar to the mechanism found in polycaproamide: implantation results in a decrease in molecular mass, in mass of the sample, and in the stability and diameter of the elementary filament, accompanied by the appearance of cracks on the polymer surface. As could have been expected the degradation mechanism is identical to that of the decomposition of PCA in the organism, i.e. the degradation takes place in the amorphous regions of the polydodecaneamide (according to IR spectroscopy and to X-ray structural analysis data[54]) under the influence of the same catalytic agents as in the case of PCA: salts and enzymes.

2. Polyesters

a. Polyglycollide

Polyglycollide (PGL), the polycondensation product of glycollic acid, was the first polymer specially synthesised for medical applications (in the late 1960s) by the American Cyanamid Company (USA). The principles of the synthesis and the structural features of PGL have been widely studied.[56-60] Polyglycollide is used in various fields of medicine: in orthopaedics and traumatology (pins, plates, pegs, needles, bone replacements), and in opthalmology as threads, fibre materials, sponges, and powders for wounds and burns. The principal advantage of PGL is its suitability for use in two-component systems as the resorbed member of the prosthesis.

The widespread use of PGL is explained by the good compatibility of the polymer at the initial implantation irrespective of its form (blocks, powders, filaments), and also by the fact that the only decomposition product, glycollic acid, contributes actively to the metabolism in the organism, breaking down[6] to H_2O and CO_2. Histological studies of this material (see Tables 2 and 3) in the initial, intermediate, and final stages of the implantation failed to detect any trend towards an increase in the size of the cells, characteristic of specific inflammation reactions. A well-formed capsule of connective tissue is found round the implant.[61-63]

Since the synthesis of PGL many studies of its degradation have been reported. The most detailed studies were made of suture threads of PGL commercially available under the name of Dexon produced by the firm Chek and Devis Cyanamid (USA).[8,46,64-66]

Some recent papers[43,46,67-71] discuss the kinetics of the decomposition of PGL in the organism and in model media. They include studies of the macrokinetics of the decomposition in the organism and in vitro and determinations of the main catalytic components of the medium in the living organism, and also of the relative contribution of each component to the degradation process.

Studies of the macrokinetic features of the degradation of the material in the living organism and in the separate components of the biological medium, coupled with quantitative studies of the contribution of each component of the medium allowing for the structural properties of the PGL filaments (established by electron microscopy and by X-ray diffraction analyses), led these workers[68,70] to propose a mechanism for the decomposition of PGL in the organism. The most significant results of this work are the following.

The filaments decompose by an unusual mechanism in the organism. After 15-18 days implantation the micrographs show a transverse distribution of the filaments on regions ~1 mm wide, without any change in the diameter of the elementary threads. However, a loss in mechanical strength of the PGL is observed.

The curves describing the loss in mass (Fig. 6) have a complex form: a slight change in the initial stages of the implantation followed by a rapidly increasing loss of mass after 20 days.

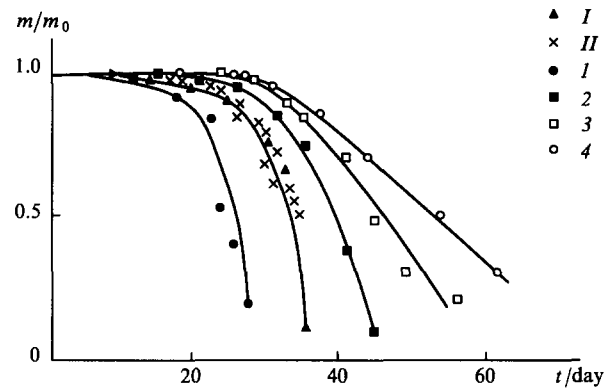


Figure 6. Changes in the relative mass of PGL filaments against time of implantation in the subcutaneous tissues of rabbits and time of treatment in a phosphate buffer of pH 7.4 at 37 °C. (*I*) In the organism, (*II*) theoretical curve for the organism as a medium; concentration of phosphate buffer, M: (*1*) 1; (*2*) 0.3; (*3*) 0.1; (*4*) water.

The kinetic weight loss curves in water, in phosphate buffer, and in carbonate buffer at pH 7.4 and 37 °C are similar to those observed in the organism, the salts of strong monobasic acids having practically no effect on the kinetic parameters whereas in the presence of phosphates we find a marked increase in the rate of degradation (curve *1* of Fig. 6).

In buffer solutions of pH 4.05 and 2.01 the PGL filaments are degraded at a rate close to that observed in water, i.e. in this range of pH the acid medium does not markedly affect the hydrolysis of the ester bonds.

In vitro experiments on the incubation of PGL in proteolytic enzyme solutions showed that the enzyme β-glucouronidase is active towards this reaction. The following values of the effective decomposition rate constant for the dissociation of esters bonds in PGL under the influence of the main components of the medium in the organism at 37 °C were reported.

Constant	$k \times 10^2$
$k^{V}_{H_2O}$	5.0
$k^{S-V}_{H_2O}$	4.2
$k^{V}_{H_2PO_4}$	5.0
$k^{S-V}_{H_2PO_4}$	4.2
k^{S-V}_{enz}	1.0

Here k^V is the effective rate constant for the decomposition of the ester bonds in PGL in the amorphous regions of the polymer under the influence of water and salts; k^{S-V} is the effective constant for rate of dissociation of ester bonds on the surface of the crystallites, depending on the type of decomposition of the fragments of the PGL macromolecule on the crystallite surface and on the adhesion and solubility in the surrounding medium of the decomposition products.

An analysis of these results suggests a two-stage mechanism for the degradation of PGL (a highly crystalline polyester, with an amorphous fraction of ~0.2 and a crystalline fraction of 0.8). In the initial period of the implantation water is sorbed in the amorphous regions, and the polymer degrades slowly, mainly under the influence of water. Then, after a conversion of the polymer of 0.2, the rate of degradation in the organism increases rapidly. This can be attributed to the breakdown of the crystallites on the surface under the influence of the sorbed water, salts, and enzymes. From in vitro experiments we can obtain the effective rate constants for the dissociation of the ester bonds under the influence of water, salts, and enzymes.

The general equation for the change in mass, obtained from the above results, is

$$\frac{m}{m_0} = 0.2 - v_i[1 - \exp(-k^V_{H_2O}\, c^V_{H_2O}\, t)]^2 + (1 - v_i)\left(1 - \frac{k^{S-V}_{H_2O}\, c^{S-V}_{H_2O}\, t}{Nb_0\rho}\right)^2 - v_i[1 - \exp(-k^V_{H_2PO_4^-}\, c^V_{H_2PO_4^-}\, t)]^2 + (1 - v_i)\left(1 - \frac{k^{S-V}_{H_2PO_4^-}\, c^{S-V}_{H_2PO_4^-}\, t}{Nb_0\rho}\right)^2 + (1 - v_i)\left(1 - \frac{k^{S-V}_{enz}\, c^{S-V}_{enz}\, t}{Nb_0\rho}\right)^2,$$

where m_0 and m are the initial and the time-dependent mass of the polymer, N is the number of crystallites in the transverse section, ρ is the density of the polymer, b_0 is the transverse dimension of the crystallites, $c^V_{H_2O,\,H_2PO_4^-}$ is the average concentration of water and of phosphate ions in the amorphous part of the polymer, 0.2 is the volume fraction of amorphous regions in the PGL, $c^{S-V}_{H_2O,\,H_2PO_4^-}$ is the average concentration of water and of phosphate ions on the side surface of the crystallite.

A computer solution of the inverse problem which used the above rate constants and a range of enzyme concentrations in the subcutaneous tissue of rabbits, undertaken because of the lack of accurate published data, gave a satisfactory agreement with the experimental curve for the weight loss in the organism.

The above quantitative analysis allows the kinetic curves for the decomposition and lifetime of PGL filaments of various diameters to be predicted for different parts of the organism (containing different enzymes and salts). The prospects for the application of this polymeric material in medicine are exceptionally good because of its good mechanical properties and biocompatibility and of its controllable resorption times.

b. Polyglactin

Polyglactin (PGLA) is a copolymer of glycollic and lactic acid produced by the Ethicon Company (USA). The decomposition products of this polymer in the organism are glycollic and lactic acid, which take part in the metabolic processes. Histomorphological tests on PGLA items in the form of suture threads or tablets show a good compatibility with the tissues of the organism.[6,72-76]

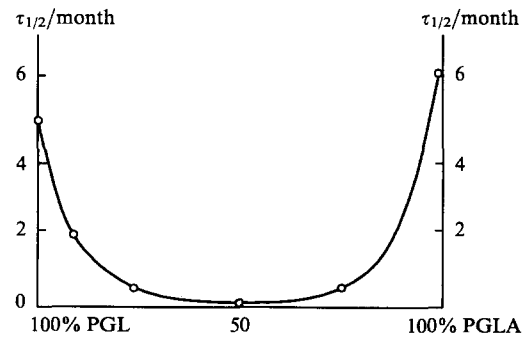


Figure 7. Plot of the time of half-decomposition of tablets of the copolymers PGL and PGLA implanted in rats.

The decomposition mechanisms and the rates of degradation of PGLA and its copolymers are identical. The homopolymer of lactic acid decomposes more slowly than PGL in the subcutaneous tissue of rats, evidently because of the lower solubility of water in the polylactide.[77] Tablets of the copolymer with different concentration ratios of glycollic and lactic acid have different half lives (measured from the concentration of ^{14}C in the organs of the rats), ranging from several months for the homopolymers to one week for the polymer with a concentration ratio of 50 : 50 (Fig. 7).

Salthouse and Matlaga[78] published a detailed study of the degradation of PGLA 910 in the subcutaneous tissues of rats, aimed at clarifying the role of cell enzymes in the resorption of the polymer. They concluded that in the initial stages the enzymes do not contribute to the degradation. A slight increase in the dehydrogenase and cytochrome oxidase activity after 40 days is explained by the participation of these enzymes in the breaking down of the dissociation products to metabolites by the scheme

PGLA 910 + water ⟶

⟶ Lactic and glycollic acids $\xrightarrow{\text{Oxyreductase}}$

⟶ $CO_2 + H_2O$.

We should stress that PGLA is the only polymer for which the decomposition kinetics and the metabolism of the degradation products have been investigated.

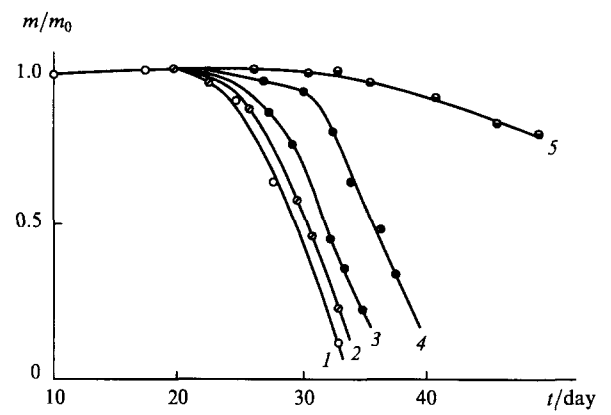


Figure 8. Changes in the relative mass of PGLA filaments with time of implantation in the subcutaneous tissues of rabbits and with the time of treatment in buffer systems of pH 7.4 at 37 °C. (*1*) 1 M carbonate buffer; (*2*) organism; (*3*) 1 M phosphate buffer; (*4*) 0.5 M phosphate buffer; (*5*) water.

The weight loss curves in the organism, in water, and in various buffer solutions are similar to the kinetic curves for PGL (Fig. 8).[68] We note a slight acceleration of the decomposition of PGLA as compared with the PGL filaments.[77] This can be explained by a slight disordering of the crystalline regions of the polymer due to the difference in the parameters of the unit cell of the copolymer.

Copolymers of this type have good prospects of applications in medicine because suture materials made from them offer a wider spectrum of resorption times than the materials made from PGL.

c. Poly(ethylene terephthalate)

Items made of poly(ethylene terephthalate) (PETP) as gauzes, suture threads, and vessel prostheses have a well established place in surgical practice because of their ability to retain their functional prosthetic properties over long implantation times as well as because of their good biocompatibility.[79-82]

Abundant information is available on its histological compatibility: it is well established that PETP implants always produce the smallest reaction from the tissues, consisting of a thin capsule and a normal connective tissue round the prosthesis for extended time periods (up to 5 years).[83-85] However, macrophages have been detected after long implantation times, apparently due to the influence of terephthalic acid on the surrounding tissues.[86]

There are reports of macroscopic observations of differences in the properties of vessel prostheses in the human organism implanted for different times, and it has been shown that periods in the organism of up to 5 years make effectively no difference to these properties.[81] After 8 and 11.5 years of residence in the organism cracks appears on the surface of the polymeric prosthesis, and the filaments becomes thinner.

Systematic studies of the degradation processes in PETP gauzes produced in Russia and implanted in the muscle tissues of rabbits, dogs, and humans have been aimed at establishing the lifetimes of the prostheses.[87-89]

As was pointed out above, at 37 °C PETP is stable towards hydrolysis in water, but it undergoes *S*-type decomposition in basic media (when the reaction rate is much greater than the rate of diffusion of the aggressive medium) and *V*-type decomposition in acid media (when the reaction rate is much smaller than the rate of diffusion of the aggressive medium). An analysis of data on the degradation of prostheses made from PETP used in soft tissues showed that both types of degradation can take place, depending on the conditions existing in the organism.

When the pH of the surrounding medium is between 7.0 and 7.4 the breaking load can be determined by the formula

$$P = P_0\left(1 - k_{\text{eff}}^{S}\,\frac{t}{r_0\rho}\right)^2,$$

where P_0 and P are the initial and the final breaking loads and r_0 is the radius of the elementary filaments. The linear dependence of $P^{1/2}$ on the time t allows the time for a 50% loss of strength under these conditions to be predicted (Fig. 9*a*).

The *V*-type decomposition of PETP was first detected in an analysis of the properties of prostheses implanted in the organism under conditions of strong inflammation. The medium had a pH of 4.8–6.8, and it appeared that these values were controlled by the action of bacteria observed on the prostheses and near them.[80] Under these conditions the samples completely lost their strength after 2 or 3 months in the organism, and their molecular mass fell steeply as a result of the dissociation of the ester bonds in the amorphous regions (Fig. 9*b*). The change in the molecular mass is described by the equation[90]

$$\frac{1}{M} - \frac{1}{M_0} = k_{\text{eff}}^{V}\,t,$$

where M_0 and M are the initial and the time-dependent number-average molecular masses, and k_{eff} is the effective rate constant of the dissociation of the bonds in the amorphous regions of the polymer.

As regards the participation of the catalysts present in the organism water does not appear to have any catalytic effect in the case of PETP: k_{eff} for water in PETP at 37 °C is 10^{-9}–10^{-10} min^{-1}, and after 10 years 0.1% of the ester bonds are decomposed.[24] Phosphate ions penetrate into the polymer matrix to a negligible extent, and therefore the degradation induced by these species is confined to the surface. The enzymes found in the organism should contribute (as in the case of PGL and PCA) to the degradation starting from the surface. Therefore under the conditions normally experienced by the prosthesis (pH 7.0–7.4) the degradation of the PETP will take place from the surface under the influence of salts and enzymes.

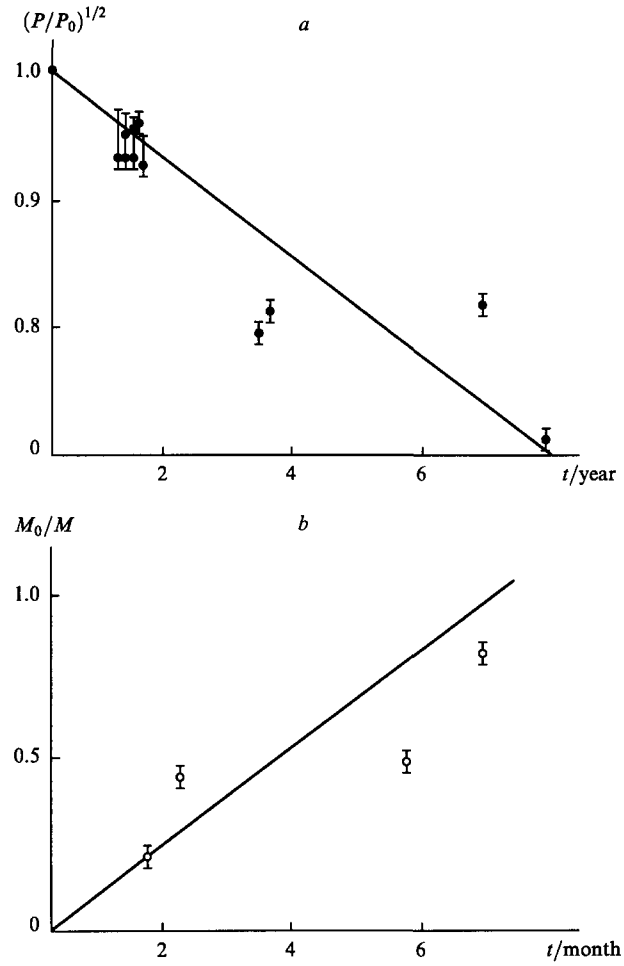


Figure 9. Changes in the breaking strength of elementary filaments of PETP recovered from the human organism for different times of residence of the prosthesis in the organism at pH 7.0–7.4 (*a*) and dependence of the relative molecular mass for samples of prostheses of PETP recovered from the human organism under infectious conditions, pH 4.8–6.8 (*b*).

In the case of a prosthesis in pathological surroundings (acidic medium) enzymes and acids can become catalytically active. Acids are the only really active substances able to induce degradation in the volume of the PETP because of the ability of volatile acids to diffuse in the polymer matrix. In this case the effective rate constant for the degradation of PETP in the organism[91] is 1.1 ± 0.5 year^{-1}.

These observations can explain the report[46] that PGL is degraded in the presence of bacteria. In fact, PGL (unlike PETP) dissociates in an acid medium at a rate close to its rate of decomposition in water (see Fig. 6). As reported,[89,92] the active degradation agents in a bacterial medium are mainly the enzymes produced by the bacteria, and various low-molecular products (mainly acids) which lower the pH of the medium. In the light of the main parameters of this material (biocompatibility and biodegradation) we may suggest that PETP will achieve a wide exploitation in medical practice for the fabrication of prostheses and other articles and materials.

3. Polyolefins

a. Polypropylene

Polypropylene (PP) was first used in medical practice because of its high chemical stability and favourable mechanical properties. In the early 1970s it was used for lining the valves of artificial hearts, and for ball joint prostheses. It is now commercially available as suture threads from the Ethicon Company (USA).

Histological results show that PP of 'medically pure' grade stimulates only a moderate reaction from the tissues of the living organism [6, 8, 93] as compared with PP containing traces of catalysts and stabilisers.[94]

Polypropylene can undergo only oxidative degradation. Therefore in the tissues of the living organism PP should be stable, and decompose slowly only under the influence of oxidative enzymes and oxygen dissolved in the living medium.

The overall picture of the degradation of PP filaments and films in the organism is characterised by the following phenomena: a worsening of the mechanical properties (a decrease in the breaking load and in the relative elongation);[84] crack formation in the initial stages of the implantation and fragmentation of the polymeric implant at longer times (the fragmentation being observed sooner in PP samples without an antioxidant);[84] constant molecular mass at all times during the implantation; appearance in the IR spectra of the PP samples after implantation of an absorption band corresponding to the C=O group;[95] an increased activity of oxyreductase and cytochrome oxidase in the capsule surrounding the implant.[6]

It follows from the above experimental observations on the degradation of PP in the organism that this polymer undergoes the *S*-type of degradation under the influence of oxidising enzymes, which cannot penetrate into the polymer matrix. As is well known, oxidative degradation is accompanied by the breaking of the main chain of the polymer and should lead to a decrease in the molecular mass, but since the catalytic agents are unable to penetrate into the bulk of the polymer the surface bond breaking produces a negligibly small decrease in the molecular mass of the whole article. The accumulation of carbonyl compounds as a result of oxidation also takes place on the surface of cracks rather than over the whole volume of the sample.

Special experiments with PP incubated in a solution of cytochrome oxidase did not produce the expected result because of the rapid inactivation of this enzyme in experiments in vitro. Therefore experiments with bacteria which produce oxidative enzymes able to open the C–C bond are needed to account for the role of these enzymes in the oxidation of this polymer.

b. Polyethylene

Articles made of polyethylene (PE) have been used in surgery for the past 30 years: for example, high-pressure polyethylene (HPPE) is used for fabricating pelvic joint prostheses. As a stable, undecomposed polymer this material has been used in emergency medical technology as packing and as circulatory vessels.

Histomorphological studies of PE have attracted extensive interest. It has been reported that the overall reaction of the organism to this polymer is favourable.[98–100]

The biodegradation of PE was established by solving the inverse problem with the aim of exploiting the polymeric by-products with the aid of microorganisms and bacteria. It was found that commercial polyethylenes (especially HPPE) undergo practically no biodegradation by the radical mechanism.[101, 102]

The following features of the biodegradation of PE have been established.

(1) The main condition for the biodissociation is an increase in the specific surface of the polymer (for example by using powders).[103]

(2) The dissociation process takes place with a decrease in mass, accelerating during the initial stages of incubation and then slowing down.

(3) Samples of low-pressure polyethylene (LPPE) incubated with microorganisms are found to include carbonyl groups, especially in the presence of fillers, which are sensitive to oxidases and esterases.[104, 105]

PE specially labelled with ^{14}C was used in studies of the rate of biodegradation of slowly decomposed PE.[105] Samples incubated with microorganisms for different times (up to 3 years) were irradiated with UV light in order to accelerate the degradation, and the weight loss caused by the action of the bacteria and microorganisms was determined. Extrapolation to zero time of irradiation gave the weight loss due to the biodegradation. The loss of mass of the powders determined by this method was 0.5% in 3 years.

It follows from these data that PE (like PP) is degraded by the *S*-type of mechanism, and that the decomposing species can be oxidative enzymes generated by bacteria and microorganisms, for which the PE acts as a carbon feed medium.

By combining the data for the degradation of PP and PE we may conclude that although these polymers decompose slowly the rearrangement of their structure during the oxidation process can lead to undesirable consequences for the organism.

4. Elastomers

a. Polydimethylsiloxane

Articles made from polydimethylsiloxane (PDMS) are used successfully in medicine. Its inertness, its favourable mechanical properties, and the ability to produce articles of almost any shape for introduction into the organism opened a wide range of applications for polyorganosiloxanes in various fields of medicine (in surgery as prostheses for various bone structures and for soft tissues, and as auxiliary items such as tubes, catheters, bypasses, medicine carriers). In the 1960s this polymer was industrially adopted for the production of various articles, now available under the trade name Silastic, by the Dow Corning Corporation (USA).

The good biocompatibility of PDMS is confirmed by the results of many quantitative studies. Histological and histochemical data obtained for silicone polymers are often used as tests for the biocompatibility in the evaluation of new polymers.[106–110]

In spite of the extensive studies and experimentation aimed at the practical application of siloxane polymers very few quantitative data on their degradation in the organism have been published. Systematic studies of the degradation of

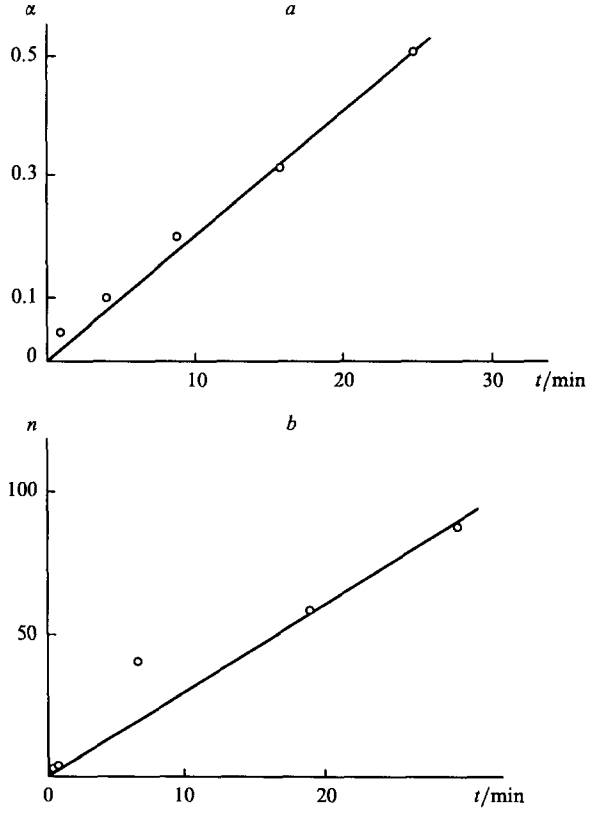


Figure 10. Plots of the extent of mass conversion of PDMS (*a*) and of the number of broken silanol bonds (*b*) against time during hydrolysis at 300 °C.

vulcanisates from dimethylsiloxane rubber of low molecular mass (SKTN) in living tissues have been carried out during the last 20 years at the Vishnevskii Surgery Institute.[109,111,112]

Fragments containing Si–O bonds can decompose in water.[113,114] Reported data [115] on the decomposition of SKTN at high temperatures in water vapour (Fig. 10) can be analysed quantitatively by postulating two simultaneous processes:
(1) decomposition by the laws of chance (with a rate constant $k_{l.ch.}$) with formation of silanol end groups

$$\frac{dn}{dt} = k_{l.ch.}(n_0 - n),$$

where n_0 is the initial concentration of silanol bonds, and n is the concentration of broken bonds at time t;
(2) depolymerisation at the silanol bonds (with a rate contant k_{dep}), resulting in loss of mass of the polymer

$$\frac{dm}{dt} = k_{dep}\, n .$$

On the assumptions that these two processes take place with comparable rates, that the decomposition by the laws of chance proceeds only to a small extent, and that the reaction itself is under activation control, the overall change in mass can be described by the equation

$$\Delta m = k_{dep} k_{l.ch.} t^2 .$$

Data on the degradation of PDMS are shown in Fig. 11.

The degradation of PDMS at temperatures below 100 °C has been discussed.[35] At these temperatures we can expect, in addition to the decomposition in the inner activation-controlled region, an active contribution from decomposition at the surface, since the concentration of water in the bulk of the polymer is extremely small. These types of degradation can be identified as follows. If a change in strength is observed the process is taking place mainly in the bulk, and conversely if the strength remains unchanged the surface decomposition is predominant. It was found that at high temperatures, when the water is in the vapour phase, the reaction is of the *V*-type, whereas at lower temperatures it is of the *S*-type.

Experiments on the degradation of PDMS in a phosphate buffer failed to detect a catalytic influence from the phosphate ions, thus excluding the possibility of a bifunctional catalysis reaction under the influence of the ions present in the organism.

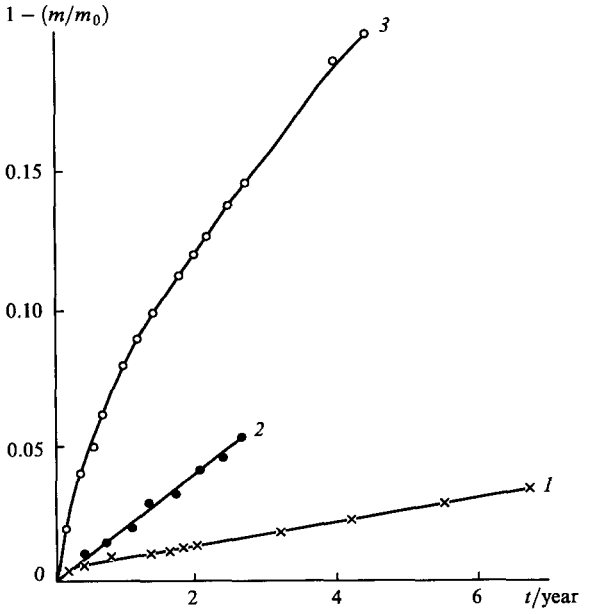


Figure 11. Plots of the extent of mass conversion of PDMS at 37 °C against time. (*1*) air; (*2*) water; (*3*) organism (subcutaneous rabbit tissue).

Therefore the contribution of water to the degradation of PDMS in the organism should manifest itself in the activation of the reaction leading to the depolymerisation of the end groups on the surface of the PDMS. However, the rates of degradation in the organism and in water are very different (see Fig. 11). This difference can be ascribed to the contribution from the enzyme component to the surface depolymerisation reaction. Unfortunately enzymes capable of breaking siloxane bonds have not so far been identified, and it is difficult to attempt a quantitative analysis of the contribution from enzymes.

The thinning of a PDMS plate owing to loss of mass (for example, during degradation in the organism) amounts to ~ 40 μm year^{-1}. Therefore the fabrication from PDMS of articles having a strictly prescribed form for long-term implantation is not recommended.

The prospects of articles based on polyorganosiloxane polymers in medicine are assured, especially in the solution of medical technology applications. Polydimethylsiloxane is also often used as an essential component for the modification of other polymers.

b. Polyurethanes

Polyurethane materials have found applications in medical practice because of their physicochemical properties, which can be varied over wide limits.

The polymer chain of polyurethanes (PU) contains the urethane group, whose structure is close to that of the peptide group in proteins: this may account for the successful application of this class of synthetic materials as biological plastics. Articles based on segmented PU with ether bonds are used as clot-resistant materials, catheters, intra-aortal bulbs, and components of artificial hearts.

Widely used items made from PU foam with ester bonds include adhesives and various alloplasts. Extensive studies have been devoted in our country as well as abroad to problems of biocompatibility and biodegradation in articles made from PU, especially adhesive compositions.[41,116–118] This work led to the conclusion that the main reaction is the hydrolysis of esters bonds, which results in the degradation of adhesives and other PU items in the tissues of the living organism.[119] These workers deny the involvement of enzymes in the degradation process on the basis of model experiments in solutions of trypsin, chitotrypsin, and elastase. Their results showed that in every case there was no difference between the rates of decomposition of PU in these media and in a physiological solution (the rates being determined from the change in molecular mass and from the strength of the IR absorption bands).

Enzymes which are found in a capsule of the given polymer must be used for experiments in vitro. In particular, aminopeptidase and acid phosphatase were found in the PU capsule.[6] This explains the negative effect reported [119] when using proteolytic enzymes, which often have an inhibiting action.

An analysis of kinetic data for PU with ester bonds showed that the degradation is caused by the hydrolytic dissociation of these bonds in water over the whole volume, as shown by the change in molecular mass of the polymer. The difference in the rates of decomposition can be explained by the participation of enzymes in the degradation from the surface of the polymeric material theough the breaking of the urethane bonds under the laws of chance, as was shown in the case of PGL.[68]

A systematic study of the degradation of low-molecular polyurethanes labelled with ^{14}C under the influence of a range of enzymes (from esterase to oxidative enzymes) also indicated a nonspecific degradation, mainly dependent on the molecular mass of the polymer. This work was done at a qualitative level.[120]

The role of the cell components in the degradation of PU foams from the surface (the so-called 'cell participation') has also been reported.[121,122] The cell involvement in the degradation of polymers is specially striking in polymers with a developed surface, such as PU, but nevertheless the active groups are the ultimate degradation agents.

Table 10. Main parameters of biocompatibility and biodegradation of polymers.

Polymer	Toxicity class of polymer	Toxicity of decomposition products	Type of decomposition and main catalyst	Notes
Polycaproamide	–	Moderately high	*S*, enzymes *V*, salts	$m/g = m_0/g - 1.6 \times 10^{-3} t/day$; a filament 24 ± 4 μm in diameter decomposes in 500 ± 50 days in the subcutaneous tissues of rabbits
Polydodecaneamide	–	Moderately high	*S*, enzymes *V*, salts	$m/g = m_0/g - 1 \times 10^{-3} t/day$
Polyglycollide	I	Very low	*S*, enzymes *V*, salts, water	$m/m_0 = 0.2 - 0.2[1 - \exp(-k_{H_2O}t) - \exp(-k_{salt}t)] + 0.8[(1 - k_{H_2O}t/A)^2 + (1 - k_{salt}t/A)^2] + (1 - k_{enz}t/A)^2$, where $A = Nb_0$. For a filament with a diameter of 18 ± 1 μm $P = 0$ after 20–25 days (subcutaneous rabbit tissues)
Polyglactin	I	Very low	*S*, enzymes *V*, water, salts	Similar equations apply to PGL
Poly(ethylene terephthalate)	–	Moderately high	*S*, enzymes, salts	$m/g = m_0/g - 4.0 \times 10\,(t/day)(S/cm^2)$ $P = P_0[1 - 4.0 \times 10\,(t/day)(S/cm^2)]^2$ After 30 ± 7 years a filament with a diameter of 19 ± 2 μm is completely decomposed and $P \approx 0$ (clinical data)
Polypropylene	–	Not determined	*S*, enzymes	–
Polyethylene	–	"	*S*, enzymes	$m/g = m_0/g - 2 \times 10^{-6} t/day$
Polydimethylsiloxane	I	"	*S*, water, enzymes	$m/g' = m_0/g - 1.5 \times 10^{-5} (t/day)(S/cm^2)$

5. Cyanoacrylate adhesives

Synthetic adhesive compositions based on cyanoacrylates have found wide applications in surgery for the sutureless connection of tissues. Cyanoacrylates, including the well known ethyl ester of α-cyanoacrylic acid, were first used in medical technology, but they were then modified for applications in medicine. At present adhesives based on alkyl(aryl)-α-cyanoacrylates are generally used in experimental and clinical surgery. A recent review[120] listed the main conclusions on the properties of cyanoacrylate adhesives. In general, according to a large group of results, cyanoacrylate adhesives are degraded rapidly (~60%–80% by weight in the first few months).[120] It is pointed out that the degradation products do not cause toxic of allergenic reactions in the organism,[120] and that the adhesives based on n-alkyl-α-cyanoacrylates are nontoxic, nonimmunogenic, biodegradable polymers.[121,122] According to other workers (for example, Lipatova and Pkhakadze[123]) the degradation products of cyanoacrylate adhesives can induce local toxic reactions.

Unfortunately many studies of the biodegradation of cyanoacrylate adhesives do not include a quantitative analysis. Some interesting results were obtained[124] for the heterogeneous in vitro degradation of poly(n-alkyl-α-cyanoacrylates) of different molecular masses at 37 °C and different pH values (6–8). Under these conditions the degradation proceeds from the surface, and the experiments were made with films of sample having identical surface areas. The main product of the degradation is formaldehyde, and the dependence of the mass dissociation constant on the pH, molecular mass, and nature of the radicals (ethyl, butyl, hexyl) is linear.

Salts present in the organism catalyse the degradation, and therefore we expect the degradation of cyanoacrylate adhesives in the tissues of the living organism to proceed mainly from the surface.

Other polymers, such as polytetrafluoroethylene, poly(vinyl chloride), polycarbonate, poly(methyl methacrylate), cyanoacrylates, poly(vinyl alcohol), and poly(ethylene oxide) are used in medicine in addition to those mentioned above. The possibility of medical applications has been examined for polymers such as polydodecaneamide, polyglycollide, polyglactin, hydrogels, and segmented polyurethanes.

VII. Conclusion

At present polymers used in medicine cannot (unfortunately) be fully characterised in terms of their biocompatibility and biodegradation parameters (see Table 10). For PGL, PETP, and PDMS the lifetime and the mass durability in the organism can be determined with adequate precision. For PP and PE accurate data are not available at present, and must be obtained in the current research. Biocompatibility problems are the less well understood. With the exception of polymers specially synthesised for medical purposes, for which we may confidently expect that the degradation products cannot cause any complications in the organism, unambiguous and well founded conclusions on the biocompatibility of other polymers should become possible in the near future from a generalisation of the results of implantations and of experiments now in progress in many medico-biological research centres.

References

1. *Polymeric Biomaterials* (Eds S E Piskin, A S Hoffman) (Dordrecht: Martinus Nijhoff, 1986)
2. N A Plate, L I Valuev *Zh. Vses. Khim. O-va im. D I Mendeleeva* **30** 402 (1985)
3. *Fundamental Aspects of Biocompatibility* (Ed. D F Williams) (Boca Raton, FL: CRS Press, 1981)
4. A M Chernykh *Vospalenie* (Inflammation) (Moscow: Meditsina, 1979)
5. B Monis, T Weinberg, G J Spector *Br. J. Exp. Pathol.* **49** 302 (1968)
6. T N Salthouse *J. Biomed. Mater. Res.* **10** 197 (1976)
7. P A Ward, in *Principles of Pathobiology* (Eds M F Lavis, R D Hill) (New York: Oxford University Press, 1971) p. 115
8. T N Salthouse, B F Matlaga *J. Surg. Res.* **19** 127 (1975)
9. R E Wilsnack, D V M Bernadyn, B S Huntington *Biomater. Med. Devices Artif. Organs* **7** 527 (1979)
10. G M Frank (Ed.), in *Structure and Functions of the Cell* (Translated into Russian; Moscow: Mir, 1964) p. 90
11. G D Winter *J. Biomed. Mater. Res.* **5** 11 (1974)
12. D Bruck *J. Biomed. Mater. Res.* **11** 1 (1977)
13. R Lefaux, in *Chimie et Toxicologie des Matières Plastiques* (Ed. Y Champetier) (Paris: Compagnie Fran d'Éditions, 1964) p. 57

14. W L Guess, J Autian *Am. J. Hosp. Pharm.* **21** 261 (1964)
15. R M Rice, A F Hegyeli, C W R Wade, J G Dillon, H Jaffe, R K Kulkarni *J. Biomed. Mater. Res.* **12** 43 (1978)
16. S J Courlay, R M Rice, A F Hegyeli, C W R Wade, J G Dillon, H Jaffe, R K Kulkarni *J. Biomed. Mater. Res.* **12** 219 (1978)
17. M F Nichols *J. Biomed. Mater. Res.* **13** 299 (1979)
18. Y S Yeh, Y Iriyma, Y Matsuzawa *J. Biomed. Mater. Res.* **22** 795 (1988)
19. R F Wilsnack, D V M Bernadyn, B S Huntingdon *Biomater. Med. Devices Artif. Organs* **4** 235 (1976)
20. S A Rosenblath, G R Weddington, W L Guess, J Autian *J. Pharm. Sci.* **54** 156 (1965)
21. W L Guess, S A Rosenblath, J Autian *J. Pharm. Sci.* **54** 1545 (1965)
22. R I Johnsson, A F Hegyeli *Ann. N. Y. Acad. Sci.* **146** 66 (1968)
23. A Weninberg, G Haselgren, L Tronstad *J. Biomed. Mater. Res.* **13** 109 (1979)
24. Yu V Moiseev, G E Zaikov *Khimicheskaya Stoikost' Polimerov v Agressivnykh Sredakh* (Chemical Stability of Polymers in Aggressive Media) (Moscow: Khimiya, 1979)
25. M Shen, M B Bever *J. Mater. Sci.* **7** 741 (1972)
26. J A Barrie, in *Diffusion in Polymers* (Eds J Crank, G S Park) (London: Academic Press, 1968) p. 259
27. V I Lebedev, G P Andrianova, A E Chalykh, in *Difuzionnye Yavleniya v Polimerakh, Riga 1977 (Tez. Dokl.)* [Diffusion Phenomena in Polymers, Riga 1977 (Abstracts of Reports)] (Riga, 1977) Part 2, p. 323
28. W R Vieth, K J Sladek *J. Colloid Sci.* **20** 1014 (1965)
29. W R Vieth, K J Frangoulis, J A Rionda *J. Colloid Sci.* **22** 454 (1966)
30. G E Zaikov *J. Macromol. Sci. Chem. Phys.* **25C** 551 (1985)
31. A L Iordanski, G E Zaikov, in *Diffusion of Electrolytes in Polymers* (Utrecht: VSP, 1988) p. 385
32. Z Rogovin, E Khait, I Knunyants, Yu Rymashevskaya *Zh. Obshch. Khim.* **17** 1316 (1974)
33. V A Burshtein, L M Egorova, V V Solov'eva *Mekh. Polim.* (5) 854 (1977)
34. A A Khokhlov, Candidate's Thesis in Chemical Sciences, Mendeleev Chem. Technol. Inst., Moscow, 1980
35. N V Trostenyuk, B A Zhubanov, A A Adamyan, O S Voronkova *Vestn. Akad. Nauk Kaz. SSR* (1) 27 (1989)
36. L V Ivanova, Yu V Moiseev, G E Zaikov *Vysokomol. Soedin., Ser. A* **14** 1057 (1972)
37. E Laifut *Transfer Phenomena in the Living System* (Translated into Russian; Moscow: Mir, 1977)
38. A L Iordanskii, A D Shterenzon, Yu V Moiseev, G E Zaikov *Usp. Khim.* **48** 1460 (1979) [*Russ. Chem. Rev.* **48** 781 (1979)]
39. Yu V Moiseev, T T Daurova, O S Voronkova, K Z Gumargalieva, L G Privalova, in *17th Microsymposium on Medical Polymers, Prague, 1977* p. 113
40. K Z Gumargalieva, Yu V Moiseev, T T Daurova, O S Voronkova, I B Rozanova *Biomaterials* **1** 214 (1980)
41. E Lipatova, G A Pkhakadze, in *Primenenie Polimerov v Khirurgii* (Application of Polymers in Surgery) (Kiev: Naukova Dumka, 1977) p. 7
42. O S Voronkova, Candidate's Thesis in Chemical Sciences, Mendeleev Chem. Technol. Inst., Moscow, 1971
43. S Ya Karpukhina, E Z Gumargalieva, T T Daurova, V A Mironova *Vysokomol. Soedin., Ser. B* **25** 209 (1983)
44. D F Williams, in *Proceedings of the ASTM Conference, Kansas City, 1978;* ASTM Special Publ., 1979 (Eds B Syrett, A Acharya) p. 215
45. D F Williams *J. Biomed. Mater. Res.* **14** 329 (1980)
46. D F Williams, in *III International Conference on 'Plastics in Medicine and Surgery'* Netherlands, 1979
47. D V Park *Biokhimiya Chuzherodnykh Soedinenii* (Biochemistry of Alien Compounds) (Moscow: Meditsina, 1978)
48. D F Williams, R Roaf *Implants in Surgery* (Translated into Russian; Moscow: Meditsina, 1978)
49. K Schwertassek *Faserforsch. Textiltech.* **11** 125 (1960)
50. O V Voronkova, T T Daurova, M V Shablygin, L P Mil'kova, N M Mikhailov *Vysokomol. Soedin., Ser. A* **13** 677 (1971)
51. Yu V Moiseev, V S Markin, G E Zaikov *Usp. Khim.* **45** 510 (1976) [*Russ. Chem. Rev.* **45** 246 (1976)]
52. G E Titova, in *Fiziologicheski Aktivnye Sinteticheskie i Drugie Polimery Meditsinskogo Naznacheniya (Tez. Dokl. Simp.)* [Physiologically Active Synthetic and Other Medical Polymers (Abstracts of Reports)] (Leningrad: Nauka, 1975) p. 15
53. G E Titova, M S Akutin *Plast. Massy* **1** 73 (1976)
54. G E Titova, Candidate's Thesis in Chemical Sciences, Mendeleev Chem. Technol. Inst., Moscow, 1976
55. D J Heikens *J. Polym. Sci.* **35** 277 (1959)
56. V A Savin, O G Fortunatov *Promyshlennost' Meditsinskogo Stekla,* N 2 (Medical Glass Industry, N 2) (Moscow: TsBNTImedprom, 1976)
57. M N Noryan *Br. Med. J.* **1** 308 (1969)
58. T P Nuquid *Philipp. J. Surg.* **21** 215 (1969)
59. Y Chuja, K Suchiro, Y Okita, H Todokoto, K Chuio *Makromol. Chem.* **103** 215 (1968)
60. K Chuio, H Kobayaski, J Suzuki, S Tokuhara *Makromol. Chem.* **100** 267 (1967)
61. H Zilch, W Kleengel *Schwester* **10** 34 (1971)
62. R K Kulkarni, K C Pani, C Neuman, F Leonard *Arch. Surg.* **93** 839 (1966)
63. J M Brady, D E Cutright, R A Miller, G C Battistone, E E Hunsuck *J. Biomed. Mater. Res.* **7** 155 (1973)
64. D E Cutright, E E Hunsuck *J. Oral Surg.* **31** 134 (1971)
65. D E Cutright, E E Hunsuck, J D Brady *J. Oral Surg.* **29** 39 (1971)
66. D E Cutright, B Peres, J Beasley, W J Larson, W R Rasey *Oral Med., Oral Pathol.* **37** 142 (1974)
67. N S Snegireva, K Z Gumargalieva, L G Privalova, in *Starenie i Stabilizatsiya Polimerov, Tashkent 1976 (Tez. Dokl. IV Konf.)* [Ageing and Stabilisation of Polymers, Tashkent, 1976 (Abstracts of Reports at the Fourth Conference)] p. 64
68. Yu V Moiseev, T T Daurova, O S Voronkova, K Z Gumargalieva, L G Privalova *J. Polym. Sci., Polym. Symp.* **66** 269 (1979)
69. L L Razumova, T T Daurova, A A Veretennikova, L G Privalova, K Z Gumargalieva, O S Voronkova *Polim. Med.* **9** 119 (1979)
70. L G Privalova, K Z Gumargalieva, O S Voronkova, Yu V Moiseev, T T Daurova, L L Razumova, G E Zaikov *Vysokomol. Soedin., Ser. A* **22** 1891 (1980)
71. J Hermann, R I Kelly, G A Higgins *Arch. Surg.* **100** 486 (1970)
72. J D Bankroft *An Introduction to Histochemical Technique* (New York: Appleton Crofts, 1967)
73. R K Kulkarni, E G Moore, A F Hegueli, F Leonard *J. Biomed. Mater. Res.* **5** 169 (1971)
74. P H Craig, J A Williams, K W Davis, A D Magoun, A S Levy *Surg. Gynecol. Obstet.* **141** 1 (1975)
75. T N Salthouse, G K Kaminska, M L Murphy *Investig. Ophthalm.* **9** 844 (1970)
76. J Philippa, J Hocking *J. Macromol. Sci., Chem. Phys.* **32C** (1) 35 (1992)
77. R M Robert, J M Brady, D E Cutright *J. Biomed. Mater. Res.* **11** 711 (1977)
78. T N Salthouse, B F Matlaga *Surg. Gynecol. Obstet.* **142** 544 (1976)
79. K Schwertassek, J Dvorak *Faserforsch. Textiltech.* **24** 2 (1970)
80. K Schwertassek, J Dvorak *Textil. Praha* **26** 196 (1971)
81. K Schwertassek, J Dvorak *Faserforsch. Textiltech.* **25** 2 (1972)
82. H H Harrison *Am. J. Surg.* **95** 3 (1968)
83. R W Postlethwait *Ann. Surg.* **171** 892 (1970)
84. R W Postlethwait *Ann. Surg.* **190** 10 (1979)
85. Y Noishica *J. Biomed. Mater. Res.* **10** 759 (1976)
86. T T Daurova, S M Degtyareva *Byull. Eksp. Biol. Med.* **64** 366 (1977)
87. T T Daurova, O S Voronkova, S D Andreev, T E Rudakova, Yu V Moiseev, L L Razumova, G E Zaikov *Dokl. Akad. Nauk SSSR* **231** 919 (1976)
88. T E Rudakova, G E Zaikov, O S Voronkova, T T Daurova, S M Degtyareva *J. Polym. Sci., Polym. Symp.* **66** 277 (1979)
89. O S Voronkova, T T Daurova, Yu V Moiseev, K Z Gumargalieva *Vysokomol. Soedin., Ser. A* **24** 1412 (1982)
90. Z A Rogovin, in *Osnovy Khimii i Tekhnologii Khimicheskikh Volokon* (Fundamentals of the Chemistry and Technology of Chemical Fibres) (Moscow: Khimiya, 1964) p. 140
91. D A Ravens *Polymer* **1** 375 (1960)
92. J V Maxham, W J Maier *Biotechnol. Bioeng.* **20** 865 (1978)
93. N C Liebert, R P Cherthoff, S L Cosgrofe, R McCuskey *J. Biomed. Mater. Res.* **10** 939 (1976)

94. T I Vinokurova, I B Rozanova, S M Degtyareva, in *Sinteticheskie Polimernye Materialy Meditsinskogo Naznacheniya, Belgorod-Dnestrovskii 1977 (Tez. Dokl. III Simp.)* [Synthetic Polymer Medical Materials, Belgorod-Dnestrovskii, 1977 (Abstracts of Reports at the Third Symposium)] p. 32
95. J Dolezel *Plasty Kaut.* **13** 257 (1976)
96. N Grassie, in *Chemistry of High Polymer Degradation Processes* (Translated into Russian; Moscow: Izd. Inostr. Lit., 1959) p. 96
97. S N Levine *Ann. N. Y. Acad. Sci.* **146** 3 (1968)
98. Z Neuman *Br. J. Plast. Surg.* **9** 195 (1957)
99. N E Stinson *Br. J. Exp. Pathol.* **46** 135 (1965)
100. J Charniey, A Kamangar, M D Longfield *Med. Biol. Eng.* **7** 31 (1969)
101. A C Albertson, O A Svek, K Sigbritt *Polym. Degrad. Stability* **18** 73 (1987)
102. N B Nykvist *Plast. Polym.* **42** 195 (1974)
103. I P Fisher, in *First Biomaterials Congress* (Vienna: Hüthig, 1980) p. 20
104. M Mlinac, I Munjko, in *Second International Symposium on Degradation and Stabilization of Polymers, Dubrovnik, 1978* p. 8
105. A C Albertson, B Ranby, in *Proceedings of the 3rd International Symposium on Biodegradation, Kingston, RI, 1975* p. 743
106. R W Marck, Ch R H Wildevuur *J. Biomed. Mater. Res., Symp.* **1** 43 (1973)
107. J Autian *Ann. N. Y. Acad. Sci.* **146** 251 (1968)
108. E J Frazz, E E Schmidt *J. Biomed. Mater. Res., Symp.* **1** 43 (1973)
109. N I Ostretsova, Candidate's Thesis in Chemical Sciences, Mendeleev Chem. Technol. Inst., Moscow, 1980
110. W F Agnew, E M Todd, H Richmond, W S Chronister *J. Surg. Res.* **2** 357 (1962)
111. N I Ostretsova, A N Neverov *Vysokomol. Soedin., Ser. B* **16** 55 (1974)
112. N I Ostretsova, T T Daurova, A N Neverov *Polim. Med.* **6** 122 (1976)
113. M G Voronkov *Geterotsiklicheskie Reaktsii Rasshchepleniya Siloksanovykh Svyazei* (Heterocyclic Reactions in the Splitting of Siloxane Bonds) (Moscow: Khimiya, 1961)
114. D K Thomas, B B Moor *Polymer* **13** 109 (1972)
115. I A Metkin, K K Piotrovskii, Yu A Yuzhelevskii *Zh. Prikl. Khim.* **48** 1108 (1975)
116. J W Boretas, W S Pierse, R E Baier, A F Leroy, H I Donachy *J. Biomed. Mater. Res.* **9** 327 (1975)
117. D A Ulsen, H D Kletschka, E H Rafferty *Polym. Eng. Sci.* **13** 241 (1973)
118. H Hernauer *Plasty Kaut.* **10** 413 (1963)
119. T E Lipatova, T T Alekseev, L A Bakalo, T L Tereshchenko *Polim. Med.* **10** 19 (1980)
120. R Smith, D F Williams, C Oliver *J. Biomed. Mater. Res.* **21** 1149 (1987)
121. G A Pkhakadze, E L Tereshchenko, N A Galatenko, A K Kolomiitsev *Biosovmestimost'* **1** 33 (1994)
122. T E Lipatova, G A Pkhakadze *Primenenie Poliuretanov v Endoprotezirovanii* (Application of Polyurethanes in Endoprosthesis) (Kiev: Naukova Dumka, 1983)
123. T E Lipatova, G A Pkhakadze *Meditsinskie Klei* (Medical Glues) (Kiev: Naukova Dumka, 1979)
124. H Stricher *Arch. Pharm.* **300** 289 (1967)
125. V C Smith *J. Biomed. Mater. Res., Symp.* **1** 189 (1979)
126. R Lehman, G S Hays, F Leonard *Arch. Surg.* **93** 441 (1964)
127. W R Werin, A T Florence *J. Biomed. Mater. Res.* **14** 93 (1980)